NOVEL STRATEGIES FOR THE CONSTRUCTION OF MACROCYLIC RESORCYLATE NATURAL PRODUCTS

A Thesis Submitted by

Sarah Margaret Major

In partial fulfilment of the requirements for the degree of

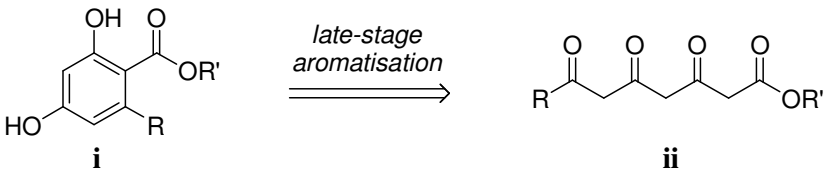
DOCTOR OF PHILOSOPHY

Department of Chemistry
Imperial College
South Kensington
London
SW7 2AZ
United Kingdom

December 2007

Abstract

A novel strategy for the construction of macrocyclic resorcylate natural products is currently under investigation. Our strategy, to construct the aromatic resorcylate units from poly-β-carbonyl precursors with late aromatisation, constitutes a biomimetic approach towards these targets, as consistent with the polyketide pathway[1] (Scheme I).



i Resorcylate

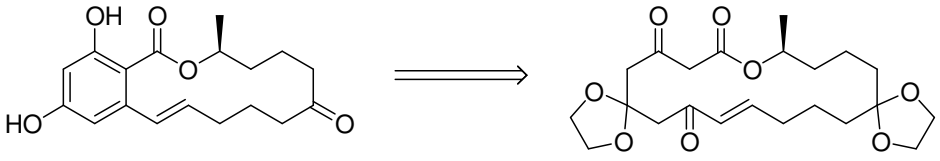
ii poly-β-carbonyl precursor

Scheme I. *Late-Stage Aromatisation Strategy for Resorcylate Construction.*

This thesis will discuss our first attempts to apply the late-stage aromatisation strategy to the construction of a macrocyclic resorcylate natural product target.

(*S*)-Zearalenone (**iii**) is potent anabolic and estrogenic mycotoxin which was first isolated in 1962 from the microfungus *Fusarium graminearum.*[2] (*S*)-Zearalenone (**iii**) belongs to the resorcylic acid lactone (RAL) family of natural products and was our initial target chosen to demonstrate the strategy.

The first two results and discussion chapters will outline our initial attempts to synthesise (*S*)-zearalenone (**iii**) from protected β-triketo ester, diketone **iv**, firstly *via* a RCEYM strategy followed by selective oxidative scission of the *exo*cyclic double bond of the product diene, and secondly *via* a RCM reaction (Scheme II).

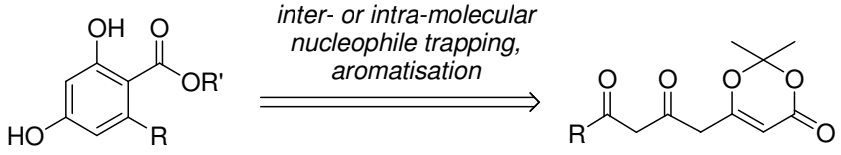


iii
(*S*)-Zearalenone

iv

Scheme II. *Strategy for (S)-Zearalenone Synthesis.*

Difficulties encountered in these investigations prompted the search for a more general and selective method for resorcylate and poly-β-carbonyl synthesis, in order to introduce an element of control into the aromatisation step. The final chapter of the results and discussion section will summarise our revised strategy, employing dioxinone analogues **v** as masked β-triketo ester equivalents and hence resorcylate precursors. General methods for their construction, their use in the total synthesis of (*S*)-zearalenone (**iii**) and in addition, their potential use in the synthesis of other resorcylate natural products will be examined (Scheme III).



i

v

Scheme III. *Strategy for Resorcylate Construction from Dioxinone Analogues* **v**.

---

1) Birch, A. J., *Proc. Chem. Soc.* **1962**, 3.

2) Stob, M.; Baldwin, R. S.; Tuite, J.; Andrews, F. N.; Gillette, K. G., *Nature (London)* **1962**, *196*, 1318.

Acknowledgements

I would like to first say a big thank you to Professor Anthony G. M. Barrett, without whom I would not be in this position today: for penning the original idea for this fascinating and challenging PhD project, encouraging me to develop my own ideas and the opportunity to present my work at Steamboat Springs in Colorado.

Particular thanks to Catherine Atkinson at Novartis, for not only being an exceptional industrial supervisor but also being the original pioneer of the late-stage aromatisation work. Thanks to Novartis for the Graduate Fellowship award and to the EPSRC for funding.

Thanks to Mickie Sahrle and Sam DeMello for running of the Barrett group, wine receptions, trips and becoming good friends along the way. Also thanks to Pete Sulsh for technical support and constantly reminding me that my lab should have been condemned years ago. Other technical thanks to Dick Sheppard and Pete Haycock for NMR; John Barton for mass-spec and Andrew White for X-ray.

Alice, Gill, Greg, Matt and Robert: thanks for fulfilling the horrible proof-reading tasks and doing a pretty fine job! Also thanks to all the Barrett group members past and present who have helped make my PhD time fun and memorable: the good times at beer parties, the Cornwall/Devon trips and general lab entertainment.

Paula, you're pretty much responsible for me still being (relatively) sane after 3 years of PhD and have been through all of it with me! Jon, you've supported me through the worst and the best of the last two years: thank you.

To my family, for their patience and support over the last 21 years of education. Lets hope its finally over!

Table of Contents

Abbreviations

$[\alpha]_D$	optical rotation
Ac	acetyl
AIBN	2,2'-azobisisobutyronitrile
Alloc	allyloxycarbonyl
Anal.	analysis
app.	apparent
aq.	aqueous
Ar	aryl
atm.	atmosphere (pressure)
Bn	benzyl
b.p.	boiling point
br.	broad
Bt	benzotriazole
Bu	butyl
BuLi	butyllithium
Bz	benzoyl
c.	concentrated
°C	degrees Celsius
ca.	*circa*
CAL-B	*Candida antarctica* lipase B
CAN	ceric ammonium nitrate
cat.	Catalytic
Cbz	benzyloxycarbonyl
$CDCl_3$	chloroform
CDI	carbonyldiimidazole
CI	chemical ionisation
CM	cross metathesis
COD	cyclooctadienyl
cp	cyclopentadienyl
δ	chemical shift
d	doublet
DBU	1,8-diazabicycloundec-7-ene

dd	doublet of doublets
DDQ	dichlorodicyanoquinine
DHP	3,4-dihydro-2H-pyran
DIAD	di*iso*propyl azodicarboxylate
DIPA	di*iso*propylamine
DIPEA	di*iso*propylethylamine
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethylsulfoxide
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	enantiomeric excess
EI	electron ionisation
eq.	equivalent
ES	electrospray
Et	ethyl
Et_3N	triethylamine
Et_2O	diethyl ether
EtOAc	ethyl acetate
Fur	2-furyl
GCMS	gas chromatography mass spectrometry
h	hour
HMDS	hexamethyldisilazane
HRMS	high-resolution mass spectrometry
Hz	Hertz
i	*iso*
IBX	*o*-iodylbenzoic acid
Imid.	imadazole
IR	infrared spectroscopy
J	coupling constant
L	litre
LDA	lithium di*iso*propylamine
L_n	ligand

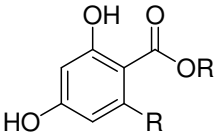
M	molar
m	multiplet
m	*meta*
MAP kinase	mitogen activated protein kinase
Me	methyl
MeOH	methanol
MIC	minimum inhibitory concentration
min	minute(s)
mL	millilitre(s)
mol	mole(s)
MOM	methoxymethyl
mmol	millimole(s)
m.p.	melting point
MS	mass spectrometry
m.s.	molecular sieves
m/z	mass to charge ratio
n	*normal*
N_3	azide
NaH	sodium hydride
NCS	*N*-chlorosuccinimide
NHPI	*N*-hydroxyphthalimide
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance spectroscopy
o	*ortho*
p	*para*
P	general protecting group
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
PhH	benzene
PhMe	toluene
Ph_3PO	triphenylphosphine oxide
PPh_3	triphenylphosphine
PKS	polyketide synthase

ppm	parts per million
PPTS	pyridinium *para*-toluene sulfonate
Pr	propyl
*p*TSA	*para*-toluenesulfonic acid
pyr.	pyridine
q	quartet
quint.	quintet
R	general substituent
RAL	resorcylic acid lactone
RCEYM	ring-closing enyne metathesis
RCM	ring-closing metathesis
R_f	retention factor
s	singlet
sat.	saturated
S.M.	starting material
t	tertiary
t	triplet
TBADH	*Thermoanaerobium brokii* alcohol dehydrogenase
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TDS	thexyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl (triflic)
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	tri*iso*propylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
Ts	para-toluenesulfonyl (tosyl)
µL	microlitre(s)
µM	micromole(s)
UV	Ultra-violet

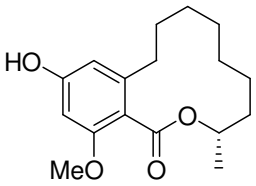
Chapter One: Introduction to Resorcylates and Polyketide Synthesis

1.1 Examples of Macrocyclic Resorcylate Natural Products

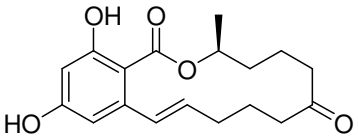
The 6-alkyl-2,4-dihydroxybenzoic acid or β-resorcylate unit (**1**) can be found as part of macrocyclic lactone ring systems in a number of biologically active natural products. The biosynthesis of these compounds arises from the polyketide pathway (see Section 1.2), hence they are included in the rare macrolide polyketide natural product class. Examples include lasiodiplodin (**2**),[3] zearalenone (**3**),[2] monocillin I (**4a**),[4] radicicol (**4b**),[5] 15G256-α (**5a**) and 15G256-β (**5b**)[6] (Figure 1).



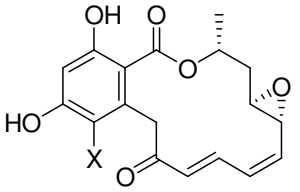
1
6-Alkyl-2,4-dihydroxybenzoic acid unit



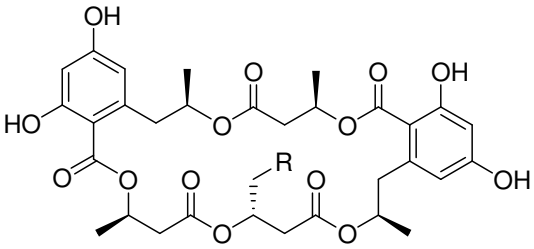
2
Lasiodiplodin



3
Zearalenone



4a: X = H, Monocillin I
4b: X = Cl, Radicicol



5a: R = OH, 15G256-α
5b: R = H, 15G256-β

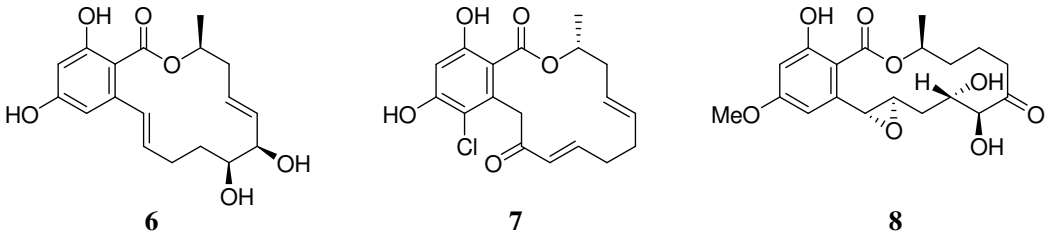
Figure 1. *Examples of Bioactive Resorcylate Natural Products*

The biosyntheses of macrocyclic resorcylate natural products are catalysed by polyketide synthases (PKSs), which are prevalent in fungi. This has resulted in the re-isolation of the same macrolide resorcylates from different fungal strains. For example, radicicol (**4b**) was first isolated from the fungus *Monocillium nordinii* and

accordingly named monorden.[7] The same compound was later independently isolated from the fungus *Nectria radicicola* and given the name radicicol,[5] which has prevailed.

1.1.1 β-Resorcylic Acid Lactones (RALs)

Zearalenone (**3**) is a potent anabolic and estrogenic mycotoxin[8, 9] isolated in 1962 from the microfungus *Fusarium graminearum* which colonises maize, barley, wheat and oats. Urry *et al*. confirmed the structure and the natural (*S*)-configuration of (*S*)-zearalenone (**3**) by mass spectrometric and NMR studies[10] and it is considered the primary member of a biologically important naturally occurring class of 12- and 14-membered macrolides called the β-resorcylic acid lactones (RALs). In addition to (*S*)-zearalenone (**3**), monocillin I (**4a**) and radicicol (**4b**) (Figure 1), other examples of RALs include agialomycin D (**6**),[11] pochinon D (**7**)[12] and hypothemycin (**8**).[13] These examples reflect the diversity of functionality exhibited around the macrocycle as well as the differing biological activities (Figure 2).[14]



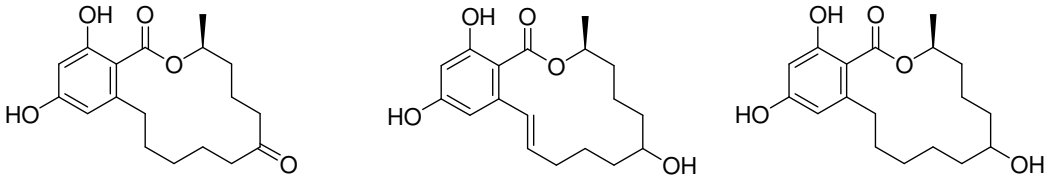
6
Agialomycin D
anti-malarial (18mM)
CDK 1 & 5 inhibitor (6 mM)

7
Pochinon D
HSP-90 inhibitor (80 nM)

8
Hypothemycin
MAP kinase inhibitor (17-90 nM)

Figure 2. *Examples of β-Resorcylic Acid Lactones*

Today, (*S*)-zearalenone (**3**) is manufactured industrially *via* fermentation and is thence utilised in the synthesis of its derivatives zearalanone (**9**), zearalenol (**10**) and zeranol (**11**), the latter of which is marketed as Ralgro®, an anabolic growth stimulant for cattle (Figure 3).[9]



9
Zearalanone

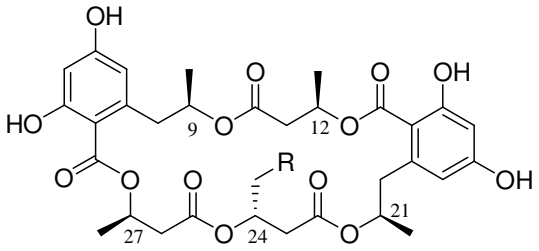
10
Zearalenol

11
Zeranol

Figure 3. *Further Derivatives of (S)-Zearalenone* (**3**)

1.1.2 Antifungal Macrolides from LL-15G256

A novel class of macrocyclic polyesters, including 15G256-α (**5a**) and 15G256-β (**5b**), were isolated by Abbanat and co-workers in 1998 during the screening of fermentation extracts of *Hypoxylon oceanicium* (LL-15G256) for chitin biosynthesis inhibitors (Figure 4).[6, 15, 16]



5a: R = OH, 15G256-α
5b: R = H, 15G256-β

Figure 4. *Macrolides Isolated from LL-15G256*

These antifungal macrolides were shown to be identical to some natural products previously isolated from different fungal cultures by Breinholt and co-workers, named BK223-A and BK223-C.[17] The absolute stereochemistry was assigned by degradation and shown to be (9*R*, 12*R*, 21*R*, 24*S*, 27*R*) for 15G256-α (**5a**), and (9*R*, 12*R*, 21*R*, 24*R*, 27*R*) for 15G256-β (**5b**) and in turn it was found that the same compounds had previously been isolated by Ito *et al.*,[18, 19] and Kondo *et al.*[20]

These macrolides are of interest due to their potent, broad spectrum activity against a number of pathogenic fungi. They act by inhibiting fungi cell wall (formed mainly of chitin) biosynthesis and hence fungal growth. 15G256-β (**5b**) is the most active of the family, having an MIC (minimum inhibitory concentration) of 0.5 μg/mL against *Neurospora crassa* (OS-1) for example. [17]

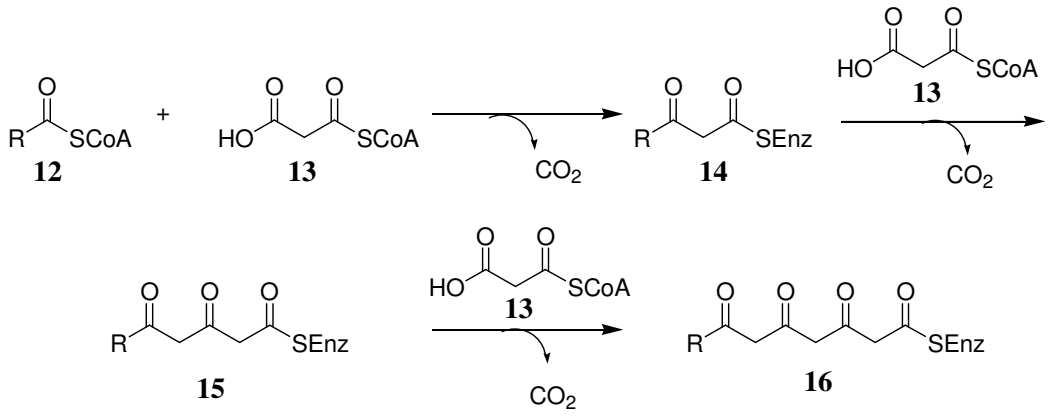
To date there are no reported chemical syntheses of either 15G256-α (**5a**) or 15G256-β (**5b**).

1.2 Biosynthesis of Polyketides

Biomimetic synthesis has long been of interest within the field of organic chemistry, not only to probe in detail the biosynthetic pathway of natural products but also to provide alternative solutions to conventional synthetic problems.

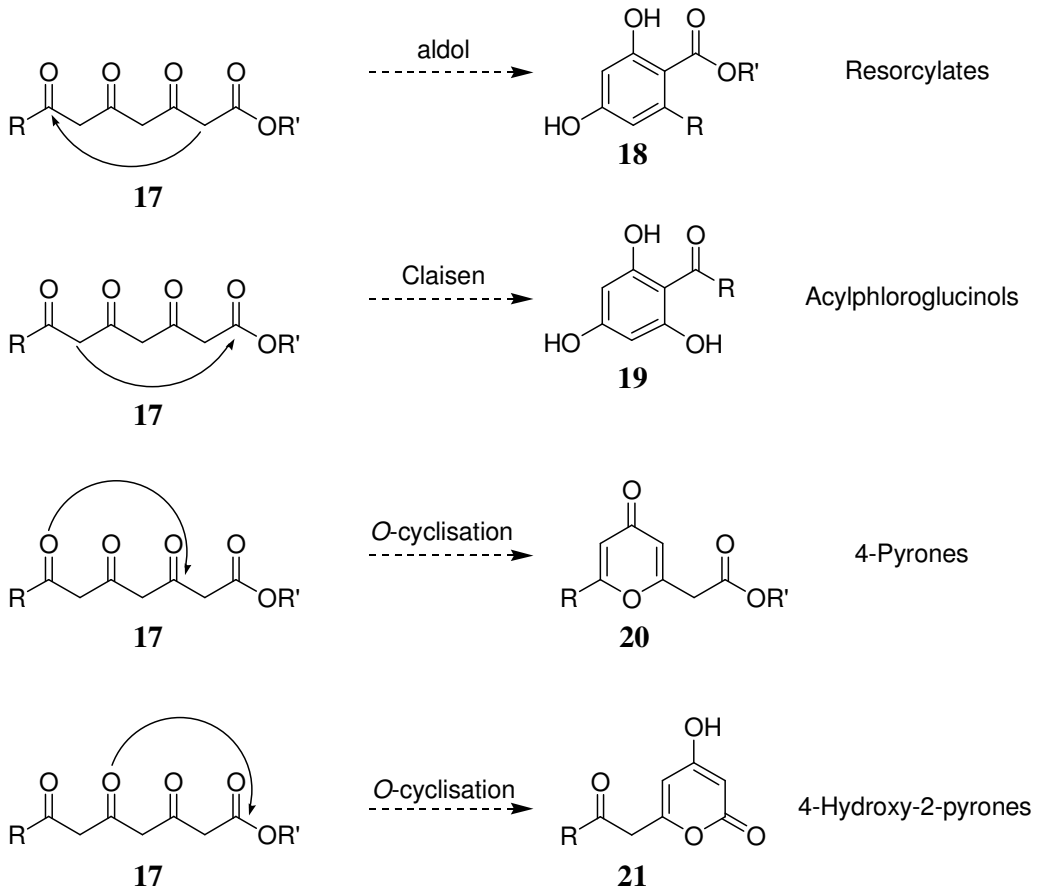
The biosynthesis of many aromatic units found in nature involves the condensation of acetate and malonate units. This concept was pioneered by Collie at the start of the 20th century,[21] however, lack of available technology at this time meant there was little supporting evidence for his theories. He first coined the phrase 'polyketide' which was used to loosely describe a molecule or structure made up of repeating "CH_2CO" units. These included derivatives such as lactones, pyrones, benzenoids and other aromatic or non-aromatic compounds built from acetate *via* the 'polyketide route'.[21-27]

Interest in the biosynthesis of polyketide compounds was revived in the late 1940's and early 1950's firstly by Robinson[28, 29] and then Birch.[1, 30, 31] This resulted in a revision of the hypothesis, culminating in the theory still believed today: polyketide chains are constructed by the condensations of coenzyme A esters **12** with malonyl coenzyme A ester (**13**) which, following decarboxylation, produce β-keto thiol esters **14**. These can then undergo further Claisen-type condensations with malonyl coenzyme A ester (**13**) to give thiol esters of 3,5-diketo acids **15**, then thiol esters of 3,5,7-triketo acids **16** and so on, thus building poly-β-carbonyl chains (Scheme 1).



Scheme 1. *Biosynthesis of Poly-β-carbonyl Chains*

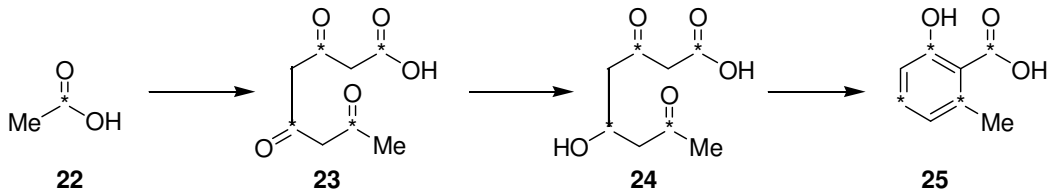
An array of further biocatalysed transformations, such as reductions, deoxygenations, halogenations or alkylations, can then be undertaken to create a diverse set of natural products. Intramolecular condensations to give non-aromatic or aromatic systems may also occur. For example, β-triketo acid derivatives **17** can undergo four possible condensations: aldol condensation-dehydration to generate resorcylates **18**, Claisen (Dieckmann) cyclisations to produce acylphloroglucinols **19**, or two different *O*-cyclisations to give 4-pyrones **20** or 4-hydroxy-2-pyrones **21** (Scheme 2).



Scheme 2. *Possible Intramolecular Condensations of β-Triketo acid Derivatives* **17**

As well as resorcylates **18**, 4-hydroxy-2-pyrones **21** (sometimes called polyketide lactones)[32] and Claisen-type products **19** can also occur naturally, but the natural occurrence of 4-pyrones **20** have not as yet been reported.

Birch *et al*. provided evidence for the polyketide hypothesis primarily by demonstrating that ^{14}C-labelled 6-methyl salicylic acid (**25**) could be produced biosynthetically from *Penicillium griseofulvum* fed 1-^{14}C-acetic acid (**22**). The product acid **25** was shown to have four alternating ^{14}C labelled sites, as predicted by the polyketide route from intermediates **23** and **24** (Scheme 3).[1, 33]



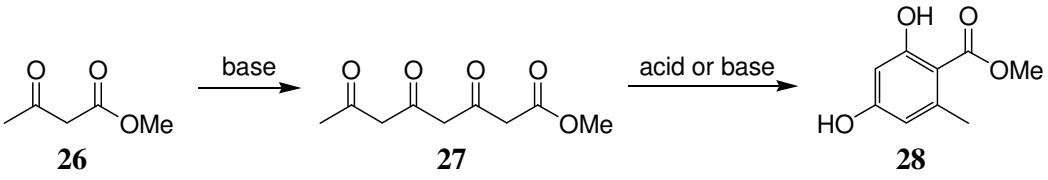
Scheme 3. *Biosynthesis of 6-Methyl Salicylic Acid* (**25**)*, * indicates ^{14}C labelling*

At least 3000 polyketide compounds have been identified, often using similar ^{14}C tracer techniques. Indeed, the distribution of ^{14}C in zearalenone isolated from *Fusarium roseum* cultures fed 1-^{14}C-enriched acetate has been examined and the alternating labelling of the carbon skeleton provided evidence for condensation of nine acetate units.[34-36] The upper limit of the polyketide pathway is thought to be poly-β-carbonyl compounds containing approximately ten carbonyl groups, which is sufficient to produce tetracyclic systems.[37]

1.3 Brief Review of the Biomimetic Synthesis of Polyketides

Following Birch's revival of the polyketide hypothesis, in the early 1960's and late 1970's several research groups became interested in developing ways to mimic this pathway in the laboratory. It was demonstrated that poly-β-carbonyl chains could be synthesised and would undergo many cyclisation reactions analogous to those carried out in nature, without enzyme catalysis.[38-44] This led the way for an extensive study of biomimetic synthesis of polyketides and, in 1979, Harris and Harris published a review of the synthesis and cyclisation products of poly-β-carbonyl compounds from dicarbonyls to nonacarbonyls.[37, 44]

One of the simplest aromatisations demonstrated by Harris *et al.* was that of methyl 3,5,7-trioxooctanoate (**27**), the self-condensation product of methyl acetoacetate (**26**). Treatment of ester **27** over a pH range from 4 to 12 resulted in rapid aldol condensation-dehydration to give methyl orsellinate (**28**), a resorcylate. This procedure was later optimised by Barrett *et al.* to give resorcylate **28** in 78% yield, utilising pH 9.2 buffer (Scheme 4).[45]

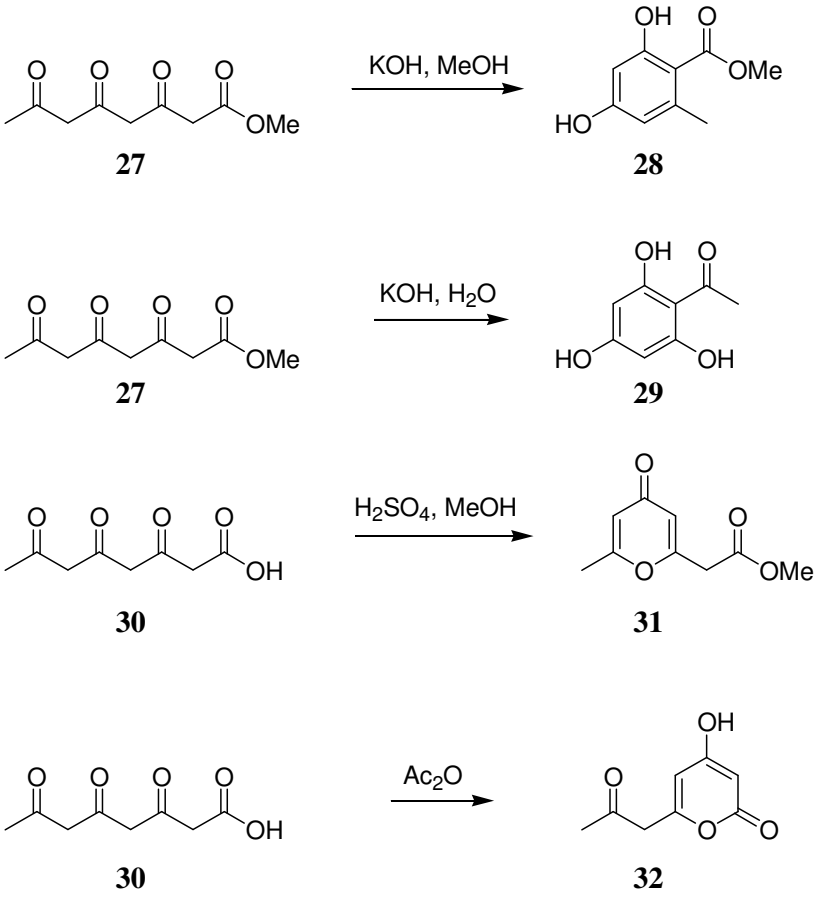


26 **27** **28**

Scheme 4. *Self-condensation and Aromatisation of Methyl Acetoacetate* (**26**)

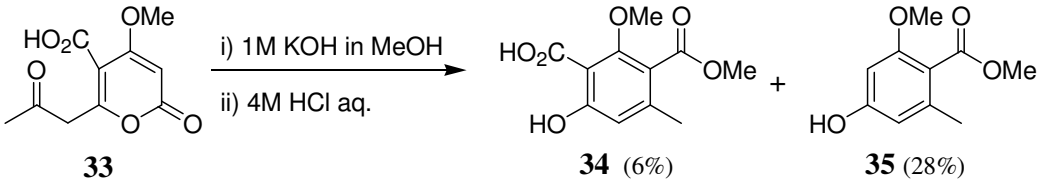
Evidence from the work of Harris *et al.* suggests that of the four possible cyclisations which can occur from β-triketo acid derivatives **17** (Scheme 2), the aldol condensation-dehydration pathway is predominant under the majority of laboratory reaction conditions. It is, however, possible to control which cyclisation product is obtained by careful selection of solvent and pH.

From methyl 3,5,7-trioxooctanoate (**27**), the Claisen product **29** could also be obtained simply by switching to an aqueous reaction medium. The corresponding carboxylic acid, 3,5,7-trioxooctanoic acid (**30**), will undergo *O*-cyclisation to give 4-pyrone **31** in strongly acidic conditions. In the presence of acetic anhydride however, 4-hydroxy-2-pyrone **32** is the product (Scheme 5).[37]



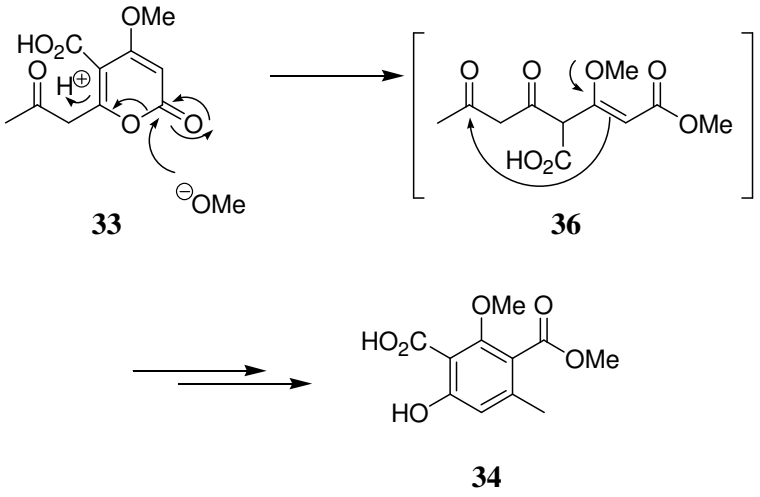
Scheme 5. *Condensations of β-Triketo acid Derivatives*

At the same time as Harris' work, several research groups were carrying out investigations into complex 2-pyrone derivatives and their lactone-opening reactions. It was recognised that the use of a base could initiate lactone cleavage to give acyclic intermediates, which would undergo rearrangement into aromatic polyketide compounds.[38, 44, 46-49] Scott *et al.* developed this approach whilst attempting to introduce control into the base-catalysed intramolecular condensations. It was found that when 2-pyrone **33** was treated with potassium hydroxide in methanol, only aromatic compound **34** and its decarboxylation product, resorcylate **35**, were observed (Scheme 6).[44]



Scheme 6. *Douglas and Money's 2-Pyrone Opening.*

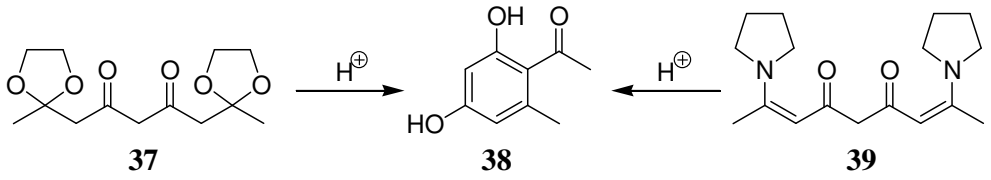
This transformation constituted a rearrangement from one aromatic form to another, presumably occurring *via* open chain polycarbonyl **36** (Scheme 7).



Scheme 7. *Mechanism of Transformation of 2-Pyrone* **33** *to Resorcylate* **34**.

In addition to the use of basic conditions for resorcylate synthesis, several masked β-triketo ester compounds were synthesised in the late 1960's and shown to undergo

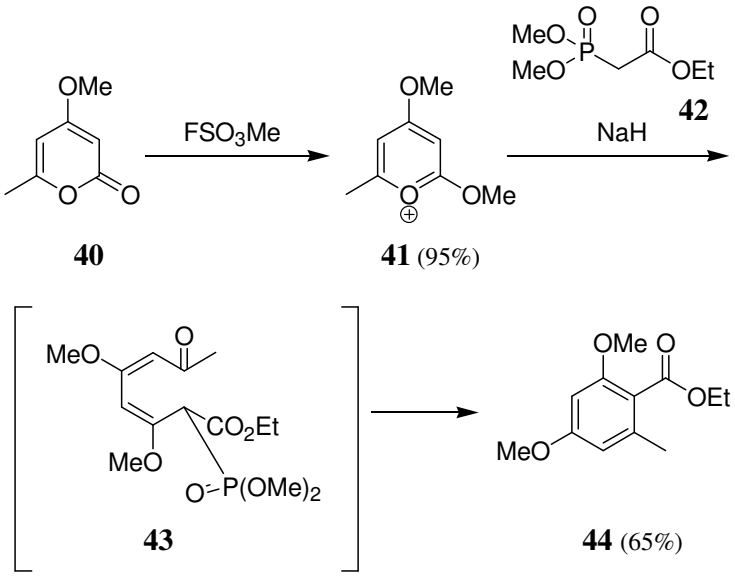
spontaneous aromatisation under acidic deprotection conditions.[50-52] Examples include symmetrical 2,8-bisketal **37**[53] and 2,8-bisenamine **39**,[54] both of which were shown to reveal resorcylate **38** (Scheme 8).



37 **38** **39**

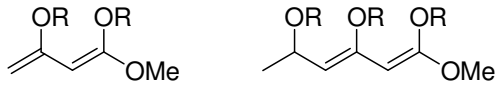
Scheme 8. *Cyclisation of Protected β-Triketo Esters*

Up until this point, the lack of control in the condensation step had usually resulted in poor isolated product yields and complex product mixtures. A key strategy to control selectivity was discovered in 1975 by Griffin and Staunton,[55] who recognised that internal constraints were needed in the poly-β-carbonyl chains in order to control the aromatisation. They successfully achieved the synthesis of resorcylate **44** from 2-pyrone **40**, in 65% isolated yield from the key aromatisation step. They attributed this to the directing effect of the phosphonate group which increases the acidity of the adjacent protons, thus favouring aldol-condensation pathways. The β-triketo ester derivative **43** is generated by opening of intermediate pyrillium ion **41** with phosphonate ester **42** (Scheme 9).



Scheme 9. *Griffin and Staunton's Use of A Directing Phosponate Group*

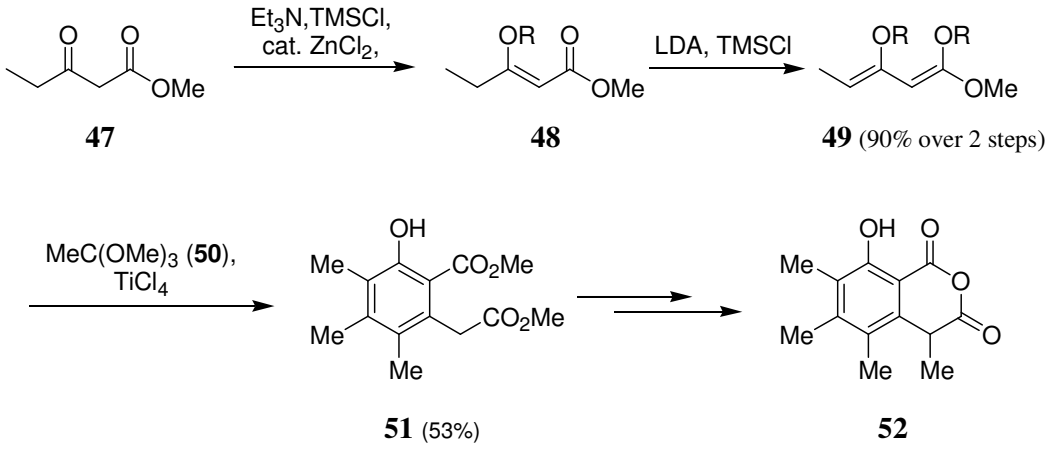
In the 1980's, Chan *et al.* developed intermolecular condensations to form resorcylates from two fragments which represented a second major breakthrough in polyketide synthesis. Chan utilised silyl enol ethers **45** and **46** (Figure 5) as β-keto ester and β-diketo ester equivalents respectively. Condensation of these silyl ethers with activated acid equivalents, under Lewis acid catalysis, generated resorcylates or more complex polyketides.



45 **46**

Figure 5. *Chan et al's Polyketide Synthons (R=TMS).*

This strategy was employed in the synthesis of Sclerin (**52**).[56] Condensation of *bis*(trimethylsilyl)enol ether **49** with methyl orthoacetate (**50**) led to polyketide **51** in 53% yield, which was further elaborated to the natural product by methylation and hydrolysis (Scheme 10).



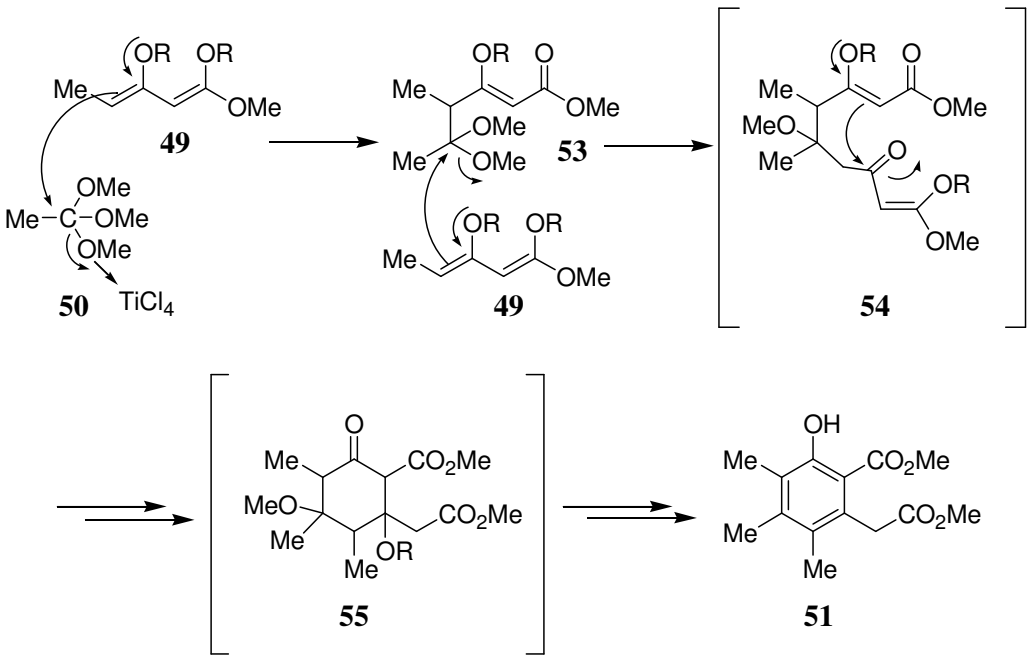
47 **48** **49** (90% over 2 steps)

51 (53%) **52**

Scheme 10. *Chan et al's Synthesis of Sclerin* (**52**) *(R=TMS).*

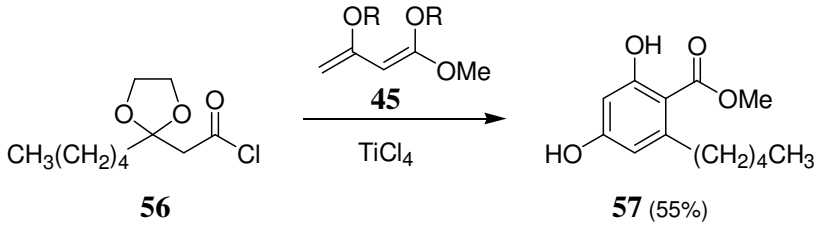
A postulated mechanism for the key step in this sequence is illustrated in Scheme 11. Condensation of *bis*-silyl ether **49** with methyl orthoacetate (**50**) generates intermediate **53**, which undergoes a second condensation with another molecule of

bis-silyl ether **49** to provide the resorcylate **51**, presumably through intermediates **54** and **55**.



Scheme 11. *Mechanism of Key Aromatisation Step in Studies Towards Sclerin (***52***) (R=TMS).*

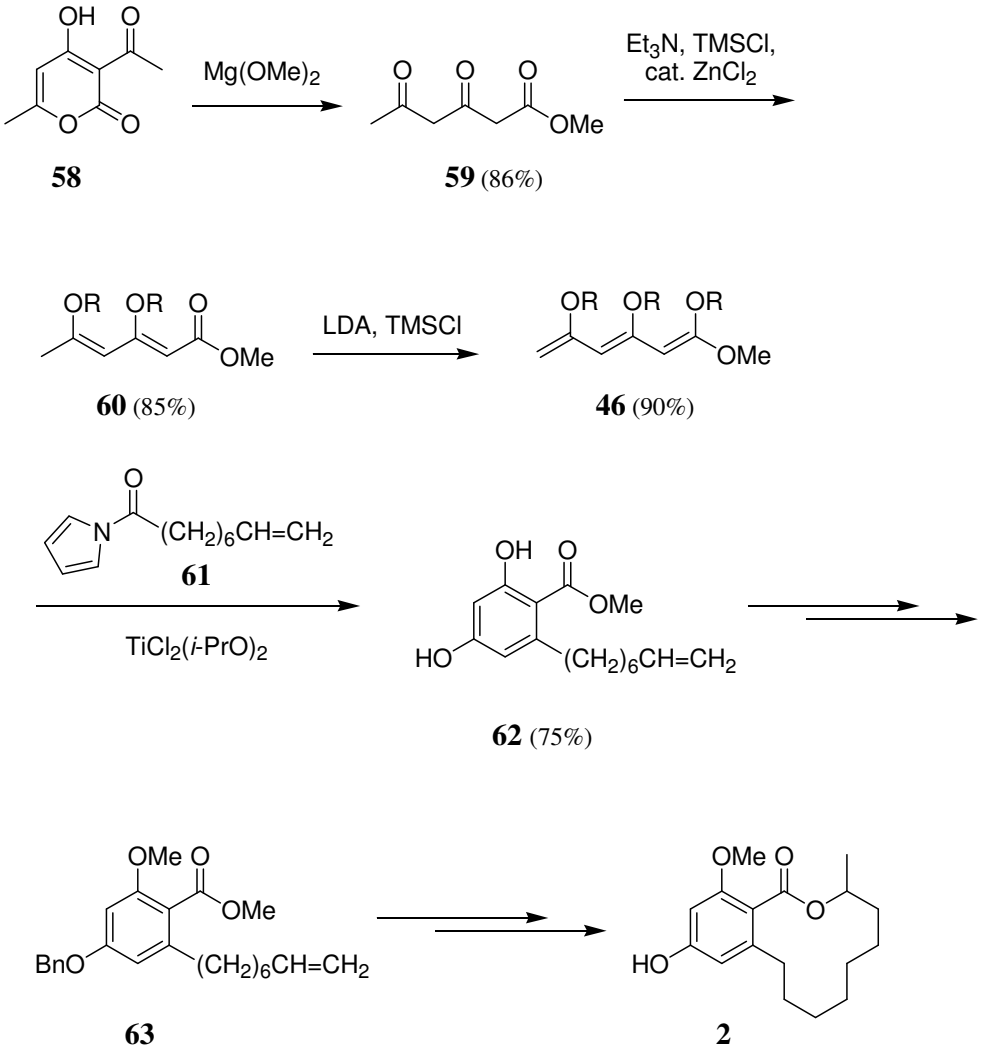
The condensation of a *bis*-silyl ether such as **45** or **49** with more complex β-keto acid derivatives has also led to formation of resorcylates in high yields. For example, β-ketal acid chloride **56** can be employed as the condensation partner, yielding resorcylate **57** in 55% yield after spontaneous ketal deprotection (Scheme 12). Chan notes that the high regioselectivity observed is due to the order of reactivity acid chloride > ketal > ester.[57]



Scheme 12. *Chan et al's Synthesis of Resorcylate* **57** *(R=TMS).*

Chan and co-workers further developed their condensations to allow the use of *tris*(trimethylsilyl)enol ether **46** in resorcylate synthesis. Commercially available

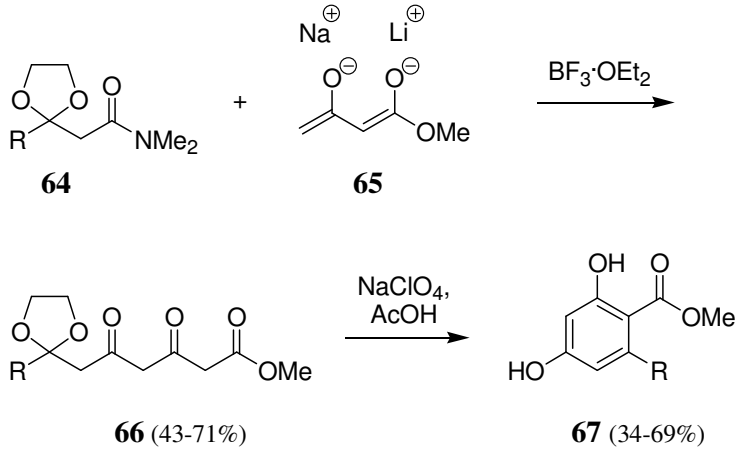
dehydroacetic acid (**58**) was converted to methyl triacetate **59**,[58] which was thus converted to silyl ether **46**, a β-diketo ester trianion equivalent, *via* ester **60**.[59] Reaction with activated acid derivatives, such as acyl imidazole **61**, afforded resorcylates, such as resorcylate **62**. This approach was successfully employed in the formal synthesis of (±)-lasiodiplodin (**2**), the key aromatisation step proceeding in excellent yield (75%) (Scheme 13).[60]



Scheme 13. *Chan et al's Synthesis of (±)-Lasiodiplodin* (**2**) *(R=TMS).*

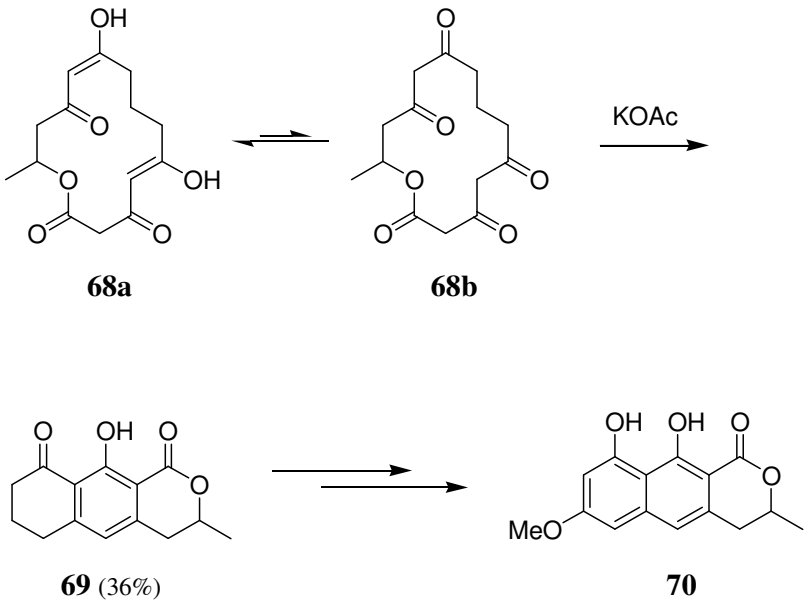
At the end of the 1980's, Yamaguchi *et al.* revisited poly-β-carbonyl condensations. They developed an improved protocol for poly-β-carbonyl synthesis involving the condensation of β-ketal dimethylamides **64** with the dianion of methylacetoacetate **65**

under BF_3-catalysis. The spontaneous aromatisation of the produced ketal protected β-triketo esters **66** in acetic acid with sodium perchlorate formed resorcylates **67** (Scheme 14).[61, 62] Unfortunately however, increasing complexity of side chains 'R' led to a lowering of yields for both of the two steps and functional groups were not well tolerated.

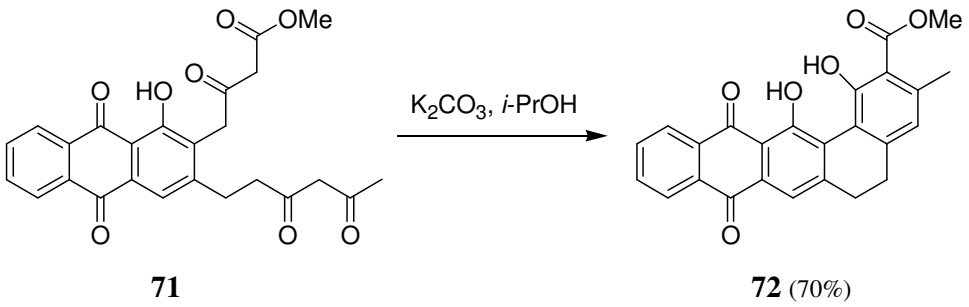


Scheme 14. *Yamaguchi et al.'s Resorcylate Synthesis:*
R = n-C_9H_{19}; $Ph(CH_2)_2$; $C_2H_5(CH_3)CHCH_2$; $CH_2=CH(CH_2)_2$.

In more recent times, several biomimetic syntheses of complex polyketide natural products have been carried out *via* intramolecular poly-β-carbonyl condensations. For example, semivioxanthin (**70**) has been synthesised from ketone **69**, which was generated by the aromatisation of polyketide lactone **68b** (which predominantly exists as the *bis*-enol **68a** in solution) (Scheme 15).[63, 64] Also, a biomimetic aromatisation has been utilised as the key step in the synthesis of benzo[*a*]naphthacenequinone **72**, from poly-β-carbonyl compound **71** (Scheme 16).[65]



Scheme 15. *Biomimetic Synthesis of Semivioxanthin* (**70**)



Scheme 16. *Biomimetic Synthesis of Benzo[a]naphthacenequinone* **72**

In spite of progress in the latter half of the 20th century, biomimetic strategies for the syntheses of simple resorcylate natural products have failed to develop into methods widely used today. Although several potential strategies have been examined, these have either been shown to have limited substrate compatibility, due partly to harsh basic or acidic conditions required for the aromatisation reaction, or to result in side products and moderate yields as a consequence of alternative aromatisation pathways.

In summary, a mild and selective method for the formation and aromatisation of β-triketo acid derivatives remains elusive.

1.4 Initial Project Objectives

Traditionally, syntheses of resorcylate derivatives have begun with aromatic building blocks such as resorcylic acid (**73**), orsellinic acid (**28**) or their derivatives (Figure 6) and the focus is on formation of the macrocycle.

73 Resorcylic acid

28 Orsellinic acid

Figure 6. *Conventional Starting Materials for Resorcylate Synthesis*

Syntheses from such aromatic starting materials have proven fraught with unexpected difficulties, not least of which are manipulations of the necessary protecting groups on the two phenols and in particular their removal as the ultimate step.

Indeed, previous work within the Barrett Group[66] had attempted the total synthesis of polyketide macrolide 15G256-β (**5b**) and failed by conventional means. The resorcylate benzoic ester is hindered and also particularly deactivated to nucleophilic attack by the electron-donating power of the two hydroxy groups, even if these are protected as ethers. This can make macrolactonisation or esterification difficult. In the case of 15G256-β (**5b**), an additional problem was the tendency for elimination under the esterification conditions to form stable lactone **74** (Figure 7).

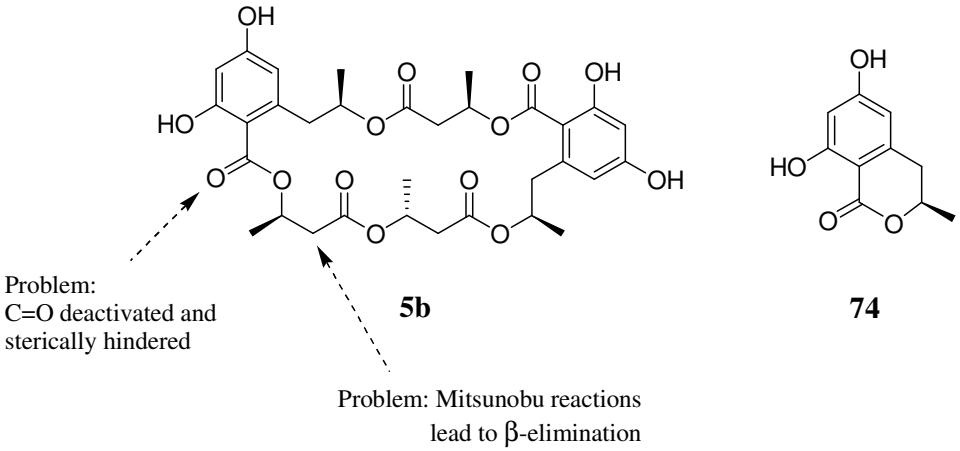
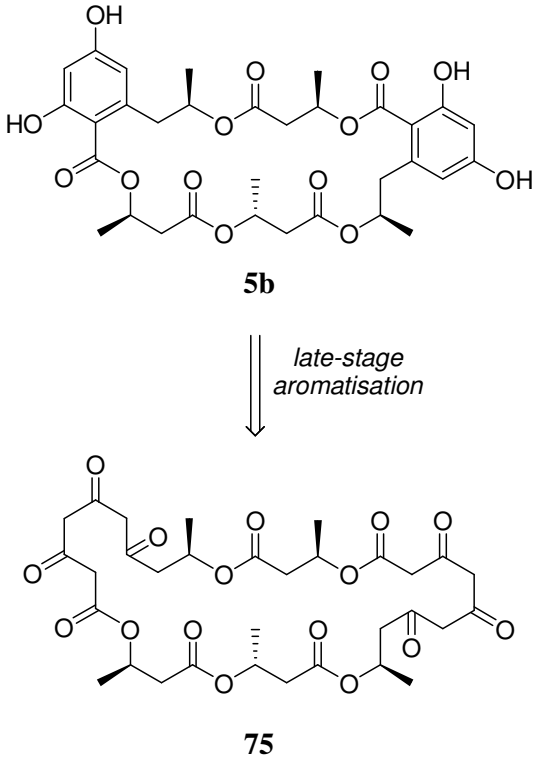


Figure 7. *Encountered Difficulties in 15G256-β* (**5b**) *Synthesis.*

Whilst examining alternative synthetic approaches, the idea of employing a biomimetic strategy to construct the two aromatic units in 15G256-β (**5b**) from poly-β-carbonyl precursor **75** was developed. It was thought that masking the aromatic unit, or late-aromatisation, could potentially avoid some traditionally encountered synthetic problems in resorcylate chemistry (Scheme 17).



Scheme 17. *Proposed New Retrosynthetic Analysis of 15G256-β* (**5b**).

This idea prompted research into general biomimetic resorcylate syntheses, which proved to be an area with the potential for development. It was deemed appropriate to first carry out the total synthesis of a simpler natural product by the same strategy and RAL synthesis was an obvious choice.

Interest in RALs has recently been rekindled by the discovery that some RALs, including radicicol (**4b**) and pochinon D (**7**), are inhibitors of the molecular chaperone Hsp90. Hsp90 is one target currently being investigated for potential new chemotherapy development.[14]

1.4.1 Previous Syntheses of RALs

Conventional retrosynthesis of RALs such as (*S*)-zearalenone (**3**) divide the molecules into two portions: an aromatic moiety and a functionalised aliphatic chain, both of which must be prepared and then joined accordingly. (*S*)-Zearalenone in particular has been utilised to demonstrate several new macrocyclisation methods and to date many total syntheses of both racemic and naturally occurring (*S*)-zearalenone have been completed. Three main strategies have been utilised: macrolactonisation,[67-72] intramolecular alkylation of stabilised carbanions[4, 73-76] and most recently transition metal-catalysed C=C bond formation or metathesis (Figure 8).[77, 78]

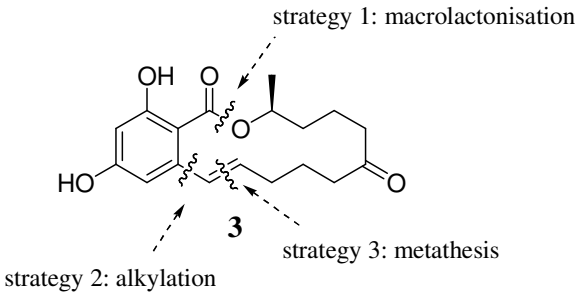
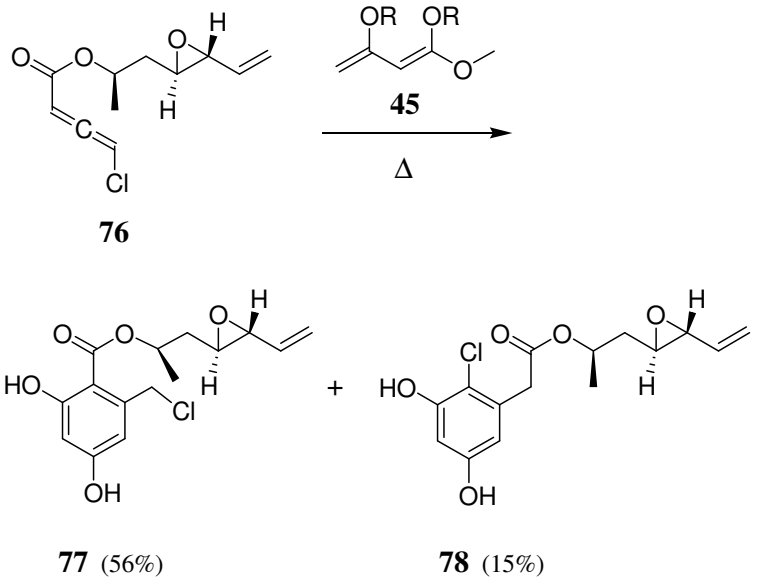


Figure 8. *Previous Strategies in the Synthesis of (S)-Zearalenone* (**3**).

Interestingly, the most problematic steps of the syntheses appeared to be removal of the phenolic protecting groups. Typically, methoxy ethers have been employed which require two steps with a maximum yield of 50-55% to deprotect, generating the

natural product.[79] More recently silyl ethers[80] or MOM-ethers[81] have been utilised, allowing deprotection yields of 60% and 74% respectively.

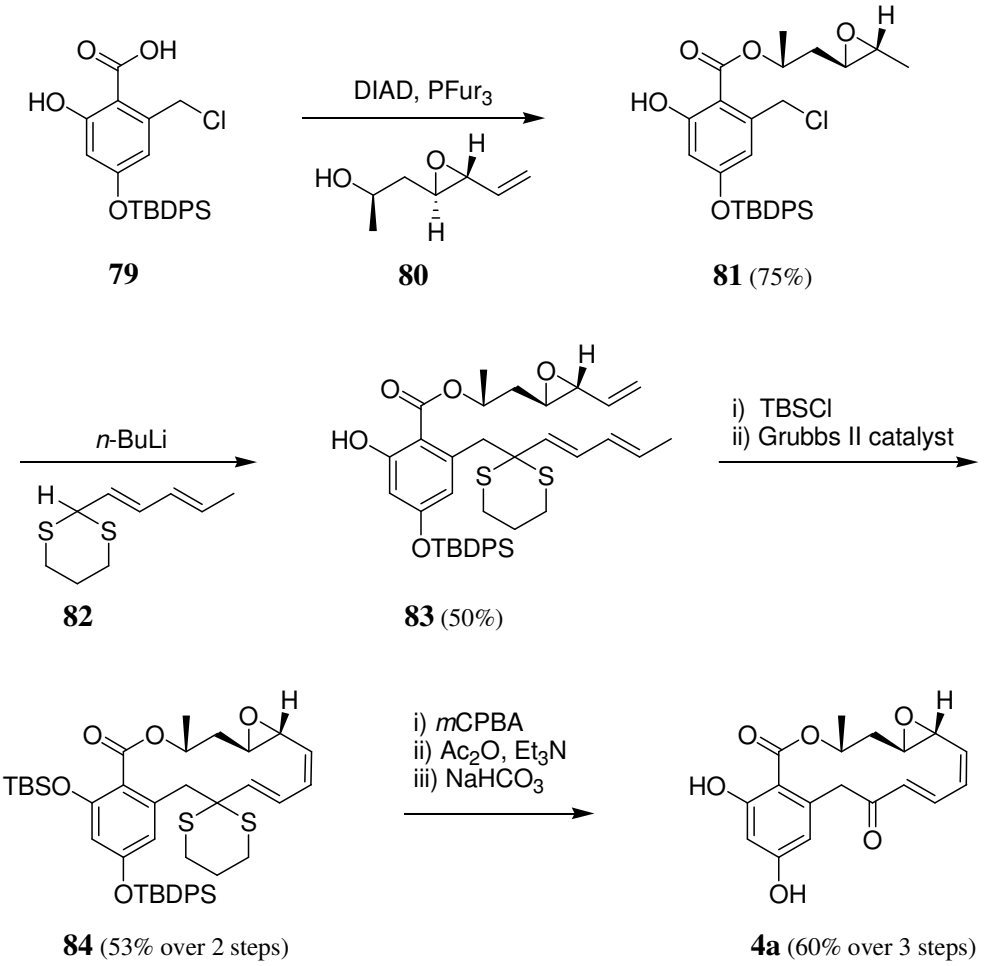
Only one attempt at RAL synthesis from non-aromatic building blocks has so far been attempted. In 2001, Danishefsky *et al.* undertook synthesis of monocillin I (**4a**) and radicicol (**4b**), employing a key Diels-Alder reaction between 1,3-disubstituted allene **76** and Chan's *bis*(trimethylsilyl)enol ether **45**. This resulted in 50% yield of the desired resorcylate **77** and 15% of the unwanted regioisomer **78** (Scheme 18).[80]



Scheme 18. *Key Step of Danishefsky et al.'s Attempted Monocillin I* (**4a**) *Synthesis (R = TMS).*

Due to the disappointing yield and regioselectivity of this step, Danishefsky *et al.* returned to aromatic starting materials. They found that the notoriously difficult esterification of the hindered and electronically deactivated resorcylate benzoic acid (also noted in our own synthetic studies towards 15G265-β, see Figure 7) was easier if the *ortho*-phenol was unprotected. Hence substrate **79** could be esterified with alcohol **80** to afford ester **81**. Subsequent alkylation of the anion generated from dithiane **82** provided ester **83**.

The *meta*-phenol was protected as a TBDPS-ether and the selected retrosynthetic analysis required ring-closing metathesis (RCM). Unfortunately however, the metathesis reaction would not work in the presence of the unprotected second phenol group in ester **83**. Instead, it was necessary carry out further protecting group manipulations, protecting the phenol as a silyl ether before carrying out the RCM to afford macrocycle **84**. Finally, deprotection yielded the natural product **4a** (Scheme 19).[80]



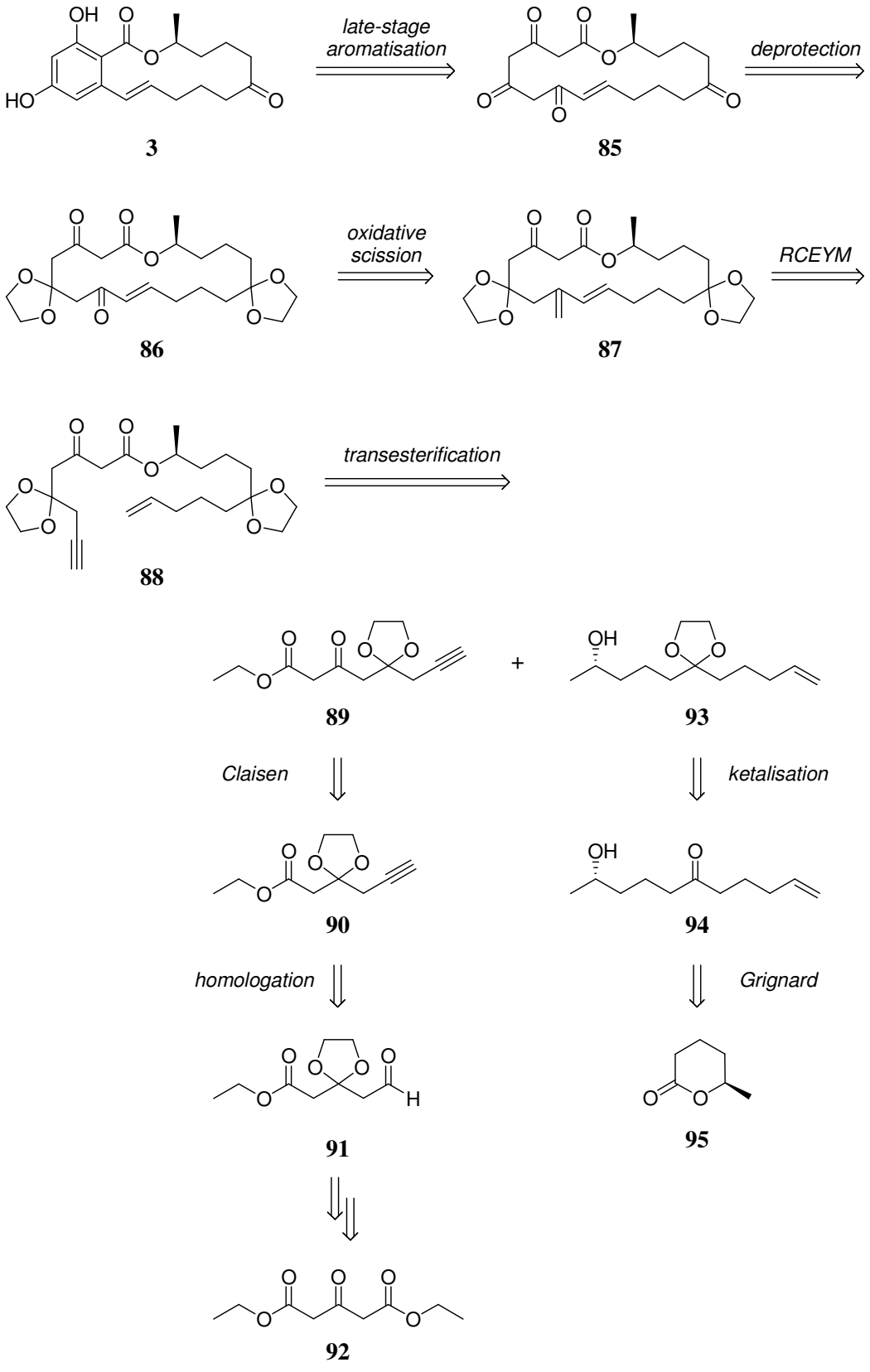
Scheme 19. *Danishefsky et al.'s Synthesis of Monocillin I* (**4a**).

This example illustrates some of the traditionally encountered difficulties with RAL and resorcylate synthesis, which we hoped to avoid if the aromatic unit were to be constructed at a later stage in the synthesis.

A recent review of the synthesis and biology of RALs has been published by Winssinger and Barluenga[14] and the reader is directed towards this if more information is required.

1.4.2 Our Retrosynthetic Analysis of (*S*)-Zearalenone (**3**).

We selected (*S*)-zearalenone (**3**) as the primary target to demonstrate our late-stage aromatisation strategy, due to the relative simplicity of the macrocyclic portion in comparison with other RALs. Our initial retrosynthetic analysis is shown in Scheme 20.



Scheme 20. *Retrosynthetic Analysis of (S)-Zearalenone* (**3**) *Utilising a Late-Stage Aromatisation Strategy.*

Our retrosynthetic analysis of (*S*)-zearalenone (**3**) utilises a final stage aromatisation reaction of β-triketo ester **85** which in turn gives macrocyclic diketal **86** as an intermediate. Diketal **86** could be produced from the selective oxidative cleavage of diene **87**. Disconnection of the macrocycle *via* RCEYM generates enyne **88**, which could be formed from the transesterification of alkyne ester **89** and (*S*)-alcohol **93**.

Alkyne ester **89** could be produced from the Claisen condensation of alkyne **90** and ethyl acetate. Alkyne **90** can be derived from aldehyde **91**, which in turn could be formed from readily available diethyl 1,3-acetonedicarboxylate (**92**). (*S*)-Alcohol **93** may be synthesised in two steps from commercial lactone **95**, *via* firstly a Grignard reaction with 5-bromo-1-pentene and secondly ketal protection of product ketone **94**.

1.5 Summary of Objectives

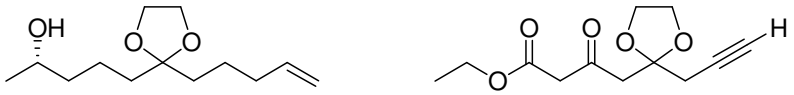
In order to validate our late-stage aromatisation strategy, we first planned to undertake the total synthesis of (*S*)-zearalenone (**3**). It was hoped that this would allow us to develop a high-yielding and selective method for the synthesis of resorcylates and in particular RALs. We would then endeavour to apply this method to the synthesis of other resorcylate natural products and RALs, towards the ultimate goal of 15G256-β (**5b**).

We hope that a biomimetic strategy for the construction of the resorcylate aromatic unit could compete with traditional resorcylate synthesis from aromatic precursors. Forming the aromatic unit after macrocyclisation would aim to eliminate problems associated with the resorcylate phenols, namely protecting group manipulations and macrolactonisation or esterification of the hindered and deactivated resorcylate benzoic acid.

Chapter Two: Results and Discussion – RCEYM Approach to (S)-Zearalenone

2.1 Introduction

Our retrosynthetic analysis of (*S*)-zearalenone (**3**), the initial target for our studies, was discussed in section 1.4.2 (Scheme 20). The envisaged synthetic pathway can be split into four distinct goals: firstly the syntheses of (*S*)-alcohol **93** and alkyne ester **89** (Figure 9); secondly their coupling *via* transesterification and ring-closing enyne metathesis (RCEYM). The third goal is the selective oxidative scission of the *exo*cyclic double bond to give diketal **86** and finally, ketal deprotection and aromatisation to yield the natural product. In this chapter, efforts towards these goals will be discussed in turn.

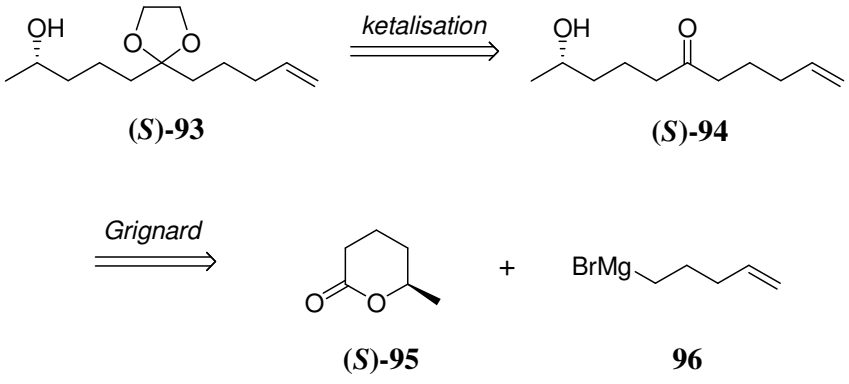


(*S*)-93 **89**

Figure 9. *Primary Targets for Synthesis of (S)-Zearalenone* (**3**)

2.2 Synthesis of (*S*)-Alcohol **93**

Further retrosynthetic analysis of (*S*)-alcohol **93** is shown in Scheme 21. Opening of (*S*)-δ-hexanolactone (**95**) with 4-pentenylmagnesium bromide (**96**) would afford keto alcohol **94**, which then would be protected to provide target (*S*)-alcohol **93**.

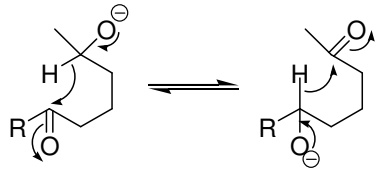


(*S*)-93 **(*S*)-94** **(*S*)-95** **96**

Scheme 21. *Retrosynthetic Analysis of* (*S*)*-Alcohol* **93**.

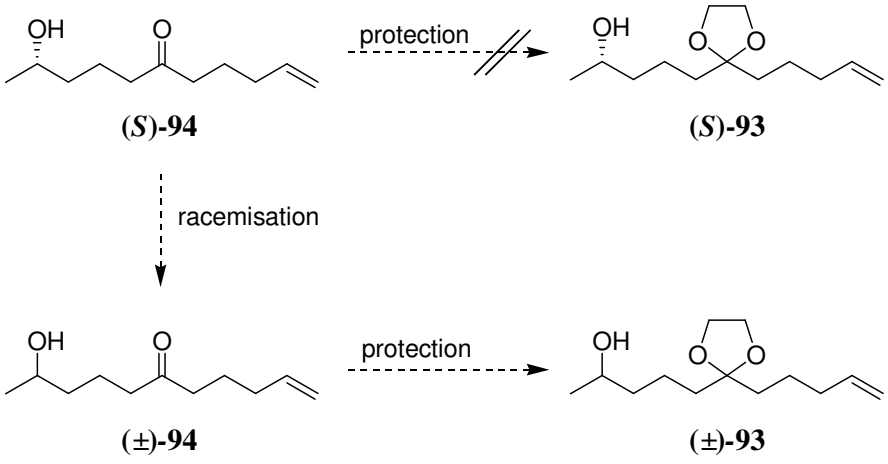
(*S*)-Zearalenone (**3**) contains a single stereocentre which, following our retrosynthesis (Scheme 20), is contained in the alcohol fragment of the molecule. Due to the expense of (*S*)-δ-hexanolactone (**95**), it seemed sensible to first carry out a racemic synthesis.

Another contributing factor to this decision was the knowledge that enantiomerically pure 1,5-keto alcohols can suffer spontaneous loss of optical activity. This phenomenon has been observed during previous studies of (*S*)-zearalenone synthetic intermediates by firstly Urry,[10] then Taub[68] and Fuerstner,[78] being attributed to a rapid and reversible intramolecular 1,5-hydride shift, a type of internal oxidation-reduction (Scheme 22).



Scheme 22. *Mechanism of Intramolecular Hydride Shift.*

This would suggest that (*S*)-1,5-keto alcohol **94**, generated by the opening of (*S*)-δ-hexanolactone (**95**), could racemise by this mechanism. This would mean that (*S*)-δ-hexanolactone (**95**) could not be utilised in the synthesis of the desired (*S*)-alcohol **93** (Scheme 23).

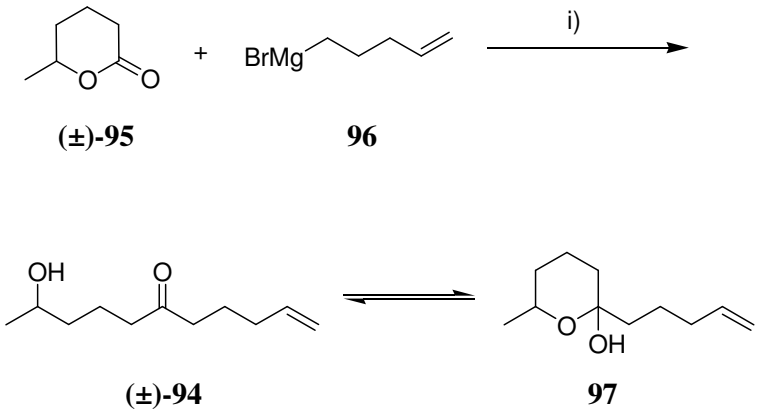


Scheme 23. *Effect of Racemisation of 1,5-Keto alcohol* **94**.

The synthesis of (±)-alcohol **93** from (±)-δ-hexanolactone (**95**) *via* the envisaged two step procedure was therefore a primary goal, to enable us to continue with the synthesis of (±)-zearalenone (**3**) and establish a viable synthetic route. Simultaneously, an alternative route to the (*S*)-alcohol **93**, necessary to introduce chirality, would be investigated.

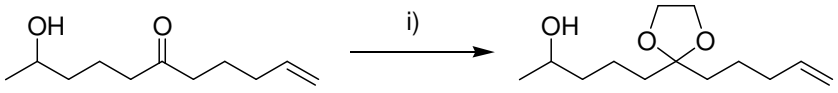
2.2.1 Synthesis of (±)-Alcohol **93**

Synthesis of (±)-alcohol **93** began with reaction of 4-pentenylmagnesium bromide (**96**) with (±)-δ-hexanolactone (**95**). ^{1}H NMR analysis showed crude (±)-keto alcohol **94** to exist approximately 40% as cyclised hemi-ketal **97**, exhibiting an additional equilibria 1,5-keto alcohols are prone to (Scheme 24).



Scheme 24. *Reagents and conditions*: i) THF, –78 °C, 2 h.

(±)-Keto alcohol **94** proved to be unstable to chromatography, so ketal protection was attempted on the crude product. Treatment with ethylene glycol in toluene using PPTS catalysis was unsuccessful, therefore milder reaction conditions were investigated. Use of 1,2-*bis*(trimethylsilyl)oxyethane with TMSOTf catalysis[82] gave (±)-alcohol **93** in moderate yield (47%) over two steps following chromatography (Scheme 25).

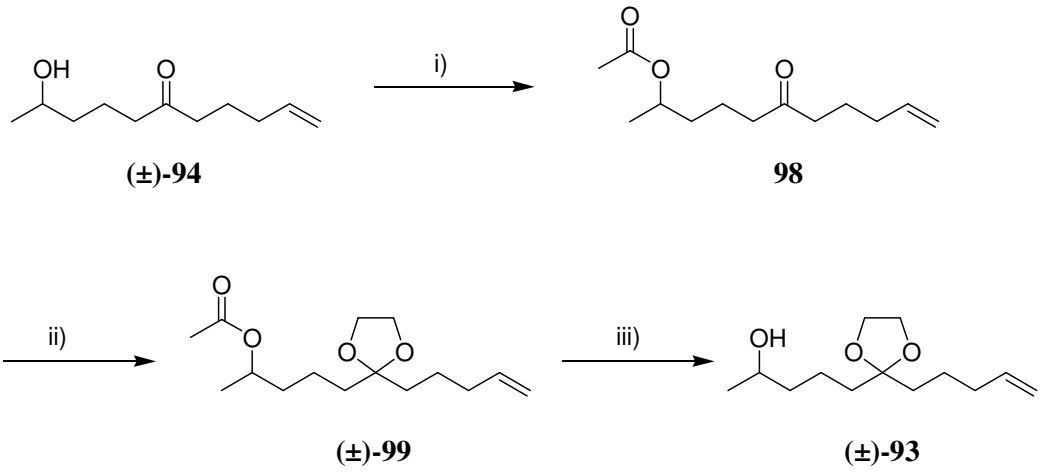


(±)-94 **(±)-93**

Scheme 25. *Reagents and conditions*: i) $TMSOCH_2CH_2OTMS$, TMSOTf, CH_2Cl_2, –78 °C, 3 h, 47% over two steps.

It was possible that the difficulties encountered during the protection of (±)-keto alcohol **94** were caused by acidic conditions and elevated temperatures, which encouraged competing side reactions, such as hemi-ketal formation. We proposed that these could be reduced or eliminated by firstly protecting the alcohol group as an acetate, which would require basic conditions.

Acetylation of (±)-keto alcohol **94** gave acetate **98** in good yield, which was then ketal protected under a number of conditions. It was found that refluxing in toluene led to a complex mixture of compounds of which no desired product was detected, however the use of milder 1,2-*bis*(trimethylsilyl)oxyethane as used previously, this time gave no reaction at all. The solution we found was to use benzene as a solvent to lower the reflux temperature, yielding product (±)-ketal **99** in 88%. Deprotection of the acetate group proceeded smoothly to give (±)-alcohol **93** in an improved overall yield of 61% over four steps (Scheme 26).



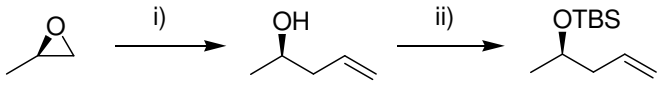
(±)-94 **98** **(±)-99** **(±)-93**

Scheme 26. *Reagents and conditions*: i) Ac_2O, pyr., 60 °C, 24 h, 71% over two steps; ii) $HOCH_2CH_2OH$, PPTS, PhH, 80 °C, 18 h, 88%; iii) KOH (3 M aq.), MeOH, 23 °C, 3 h, 98%.

This route was thus employed on large scale to provide approximately 20 g of (±)-alcohol **93** for initial studies into the synthesis of (±)-zearalenone (**3**). In the remainder of this section, our investigations into the synthesis of enantiopure (*S*)-alcohol **93** will be discussed.

2.2.2 Enantiopure Synthesis of (*S*)-Alcohol **93**

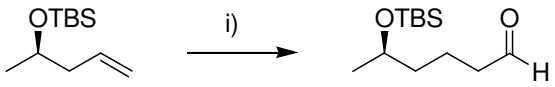
Fuerstner *et al* reported the synthesis of (*R*)-alcohol **93** in a six step procedure, beginning with commercial (*R*)-propylene oxide (**100**).[78] As only (*R*)-propylene oxide and not the (*S*)-enantiomer was readily available to us, it was decided to first test the reliability of this exact reaction sequence and therefore its potential for large scale use. To this effect, opening of (*R*)-epoxide **100** was accomplished with vinylmagnesium bromide, using CuCl(COD) catalysis. Distillation gave (*R*)-alcohol **101** in only 37% yield, with subsequent TBS protection to afford silyl ether **102** occurring in 52% (Scheme 27).



100 **101** **102**

Scheme 27. *Reagents and conditions*: i) vinylmagnesium bromide, CuCl(COD), THF, –78 °C to 23 °C, 18 h, 37%; ii) TBSCl, Imid., DMF, 23 °C, 16 h, 52%.

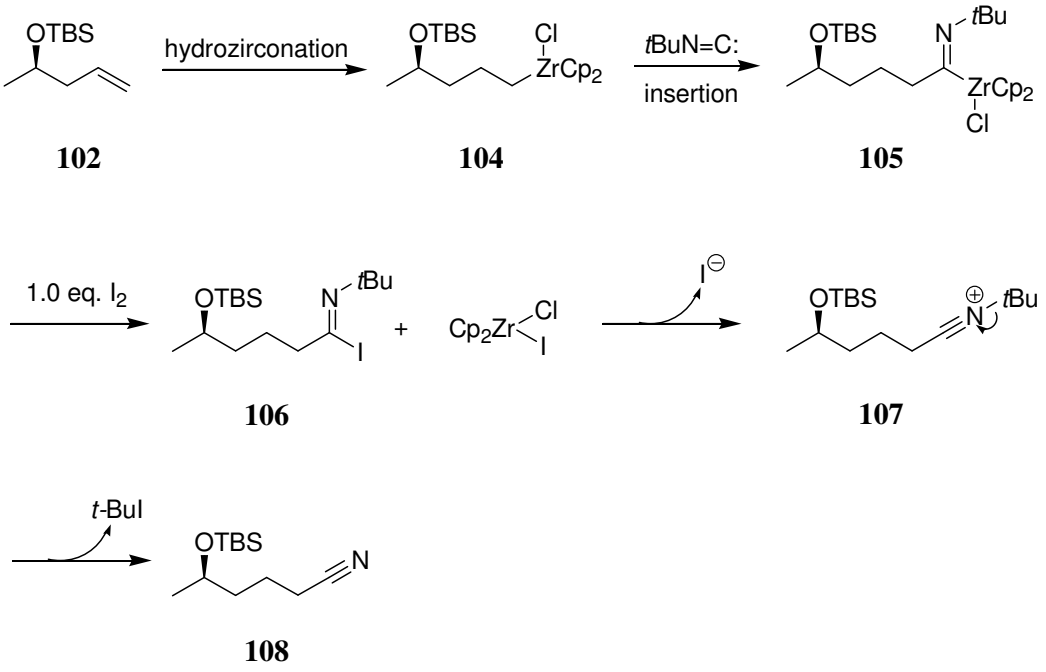
Next, hydrocyanation of silyl ether **102** using Schwartz's reagent was carried out according to Buchwald's procedure,[83] however the only isolated product from the initial attempt was aldehyde **103** (Scheme 28).



102 **103**

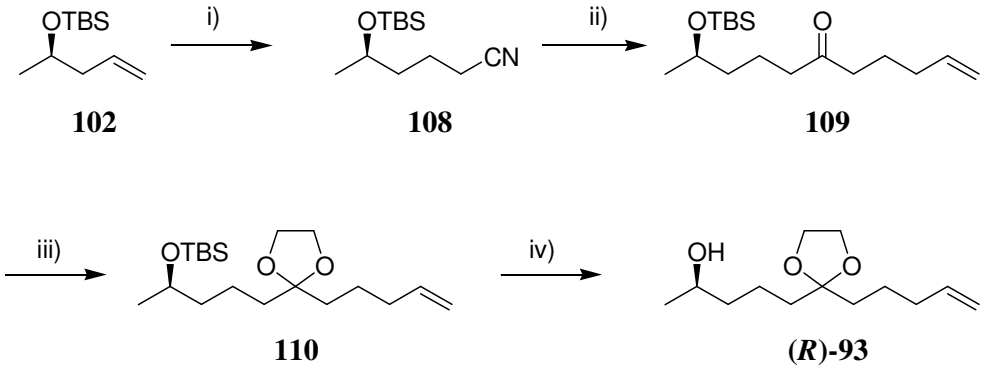
Scheme 28. *Reagents and conditions:* i) a) Cp_2ZrHCl, CH_2Cl_2, 23 °C, 2 h; b) *t*-BuNC, 23 °C, 2 h; c) I_2, PhMe, 0 °C, 0.5 h, 21%.

The proposed mechanism for the hydrocyanation reaction is illustrated in Scheme 29. Initial hydrozirconation of alkene **102** is regioselective towards the least hindered, terminal end and is followed by insertion of the *iso*cyanate. Addition of a stoichiometric amount of iodine results in halogen/metal exchange, forming imidoyl iodide **106**, which is then spontaneously converted to nitrilium ion **107** by loss of iodide. The *tert*-butyl group is then lost, either as a carbonium ion or by assisted attack of iodide, to form the product nitrile **108**. The formation of aldehyde **103** suggests water was present in the reaction before the iodine quench, hydrolysing imino compound **105** (Scheme 29).



Scheme 29. *Mechanism of Nitrile Formation by Buchwald's Procedure.*[83]

Careful repetition with rigorously dried solvents afforded nitrile **108** in moderate yield (60%). Subsequent reaction with 4-pentenylmagnesium bromide (**96**) gave (*R*)-ketone **109**, which was then protected to form (*R*)-ketal **110**. Silyl deprotection afforded 42 mg of (*R*)-alcohol **93**, which had a recorded optical rotation of $[\alpha]_D$ –6.7 (*c* 1.22, CH_2Cl_2). The literature optical rotation for (*R*)-alcohol **93** has previously been recorded as $[\alpha]_D$ –6.8 (*c* 1.02, CH_2Cl_2),[84] a comparable value to ours (Scheme 30).



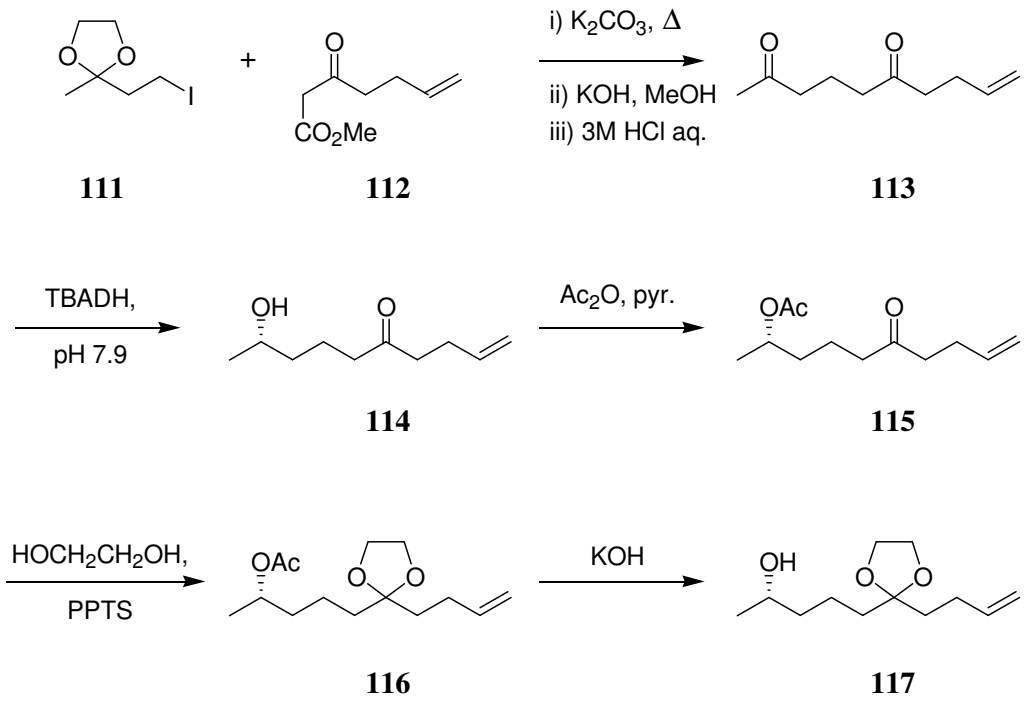
Scheme 30. *Reagents and conditions*: i) a) Cp_2ZrHCl, CH_2Cl_2, 23 °C, 2 h; b) *t*-BuNC, 23 °C, 2 h; c) I_2, PhMe, 0 °C, 0.5 h, 60%; ii) **96**, Et_2O, 80 °C, 4 h, 74%; iii) $HOCH_2CH_2OH$, PTSA, PhMe, 120 °C, 12 h, 28%; iv) *n*-Bu_4NF, THF, 23 °C, 24 h, 68%.

The synthesis of (*R*)-alcohol **93** was thus completed in an unsatisfactory 2.7% yield over six steps from commercial (*R*)-propylene oxide **100**. This prompted the search for an alternative synthetic route to (*S*)-alcohol **93**.

2.2.3 Alternative Strategy from Chiral Starting Materials

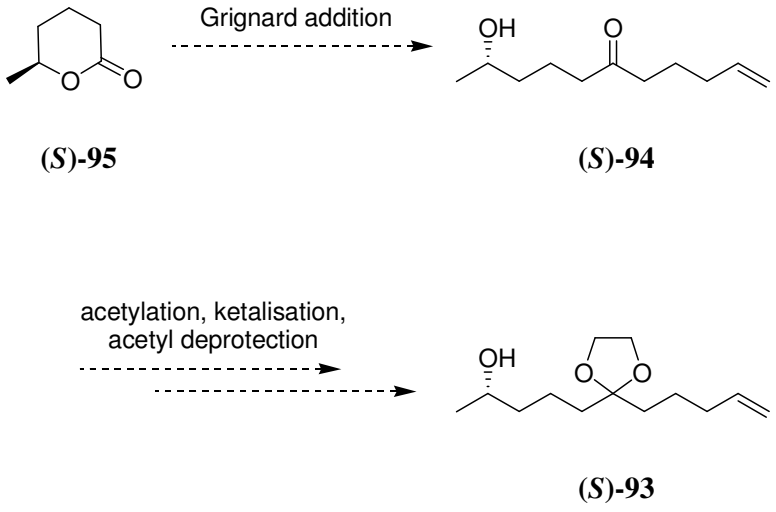
As mentioned in section 2.2, 1,5-keto alcohols, such as alcohol **94**, are reported to undergo spontaneous racemisation and also exist in equilibrium with a six-membered hemi-ketal form. However contrary to this observation, Keinan *et al.* published a synthesis of (*S*)-zearalenone (**3**) which in fact employs enantiopure (*S*)-1,5-keto alcohol **114** with no reported loss of optical activity. The key step in the synthesis is the stereoselective reduction of (±)-diketone **113** with *Thermoanaerobium brokii* alcohol dehydrogenase (TBADH).[85] This enzyme is selective for the least hindered ketone.

Keinan notes that (*S*)-keto alcohol **114** can be isolated and characterised, but it will undergo spontaneous cyclisation to its hemi-ketal, which concurs with our own observations. Instead of carrying out the direct ketal protection of (*S*)-keto alcohol **114**, the crude product was firstly acetylated and purified as the (*S*)-acetate **115**. This was then utilised in the total synthesis of (*S*)-zearalenone (**3**) resulting in an optical purity exceeding 99.5% (Scheme 31).



Scheme 31. *Keinan et al.'s Synthesis of (S)-alcohol* **117**.

Thus, it may be envisaged that our previous method for the synthesis of (±)-alcohol **93** (Scheme 26) actually would be applicable to the synthesis of (*S*)-alcohol **93**, *via* the opening of (*S*)-δ-hexanolactone (**95**) (Scheme 32).



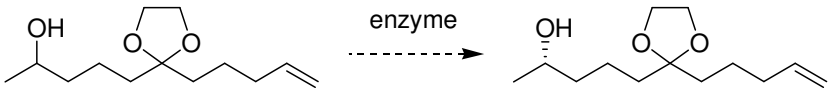
Scheme 32. *Proposed Route to (S)-Alcohol* **93**

However, due to expense of lactone (*S*)-**95**, we first became interested in introducing chirality to the (±)-alcohol **93** already in hand, for example by kinetic resolution. This strategy will be discussed in the following section.

2.2.4 Kinetic Resolution of (±)-Alcohol **93** with CAL-B

In the last decade, the tools available for the synthesis of enantiomerically pure compounds have been vastly expanded by the use of enzymes as chiral catalysts. Biocatalysis employing lipases or esterases is no longer regarded as exotic, due to the ease of use and commercial availability of many enzymes. Mild reaction conditions, the lack of sensitivity to air or water and the high chemo-, regio- and stereoselectivities demonstrated by lipases has led biocatalysis to become a popular way to introduce chirality by resolution. Screening sets of enzymes and tools to predict which enantiomer will react faster[86] allow chemists to select the best enzyme for their desired transformation.

Our desired transformation was to carry out a kinetic resolution of secondary (±)-alcohol **93** to provide optically pure (*S*)-alcohol **93** (Scheme 33).

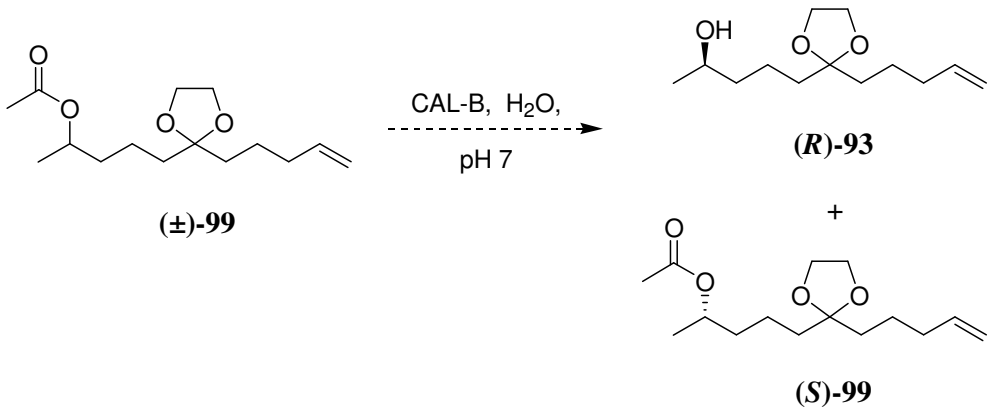


(±)-93 **(*S*)-93**

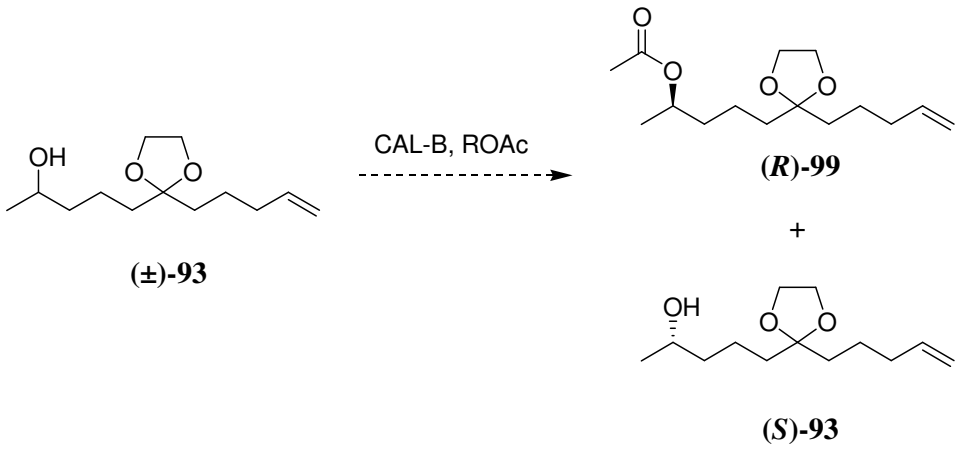
Scheme 33. *Proposed Kinetic Resolution Route to (S)-Alcohol* **93**.

It is known that lipases such as *Candida antarctica lipase B* (CAL-B) can be used to enable the stereoselective transformation of alcohols (amines) or carboxylic acids to esters (amides) by esterification[87] (amidation) or transesterification[88] and also for the stereoselective hydrolysis of esters (amides) to alcohols (amines). CAL-B is commercially available immobilised on a macroporous resin and has previously been used in our group[66] to carry out achiral transesterification reactions.

CAL-B can be applied to the kinetic resolution of (±)-alcohol **93** in two ways: either *via* selective hydrolysis of the (*R*)-enantiomer of (±)-acetate **99** to provide (*R*)-alcohol **93** and (*S*)-acetate **99** (Scheme 34), or *via* the selective acetylation of the (*R*)-enantiomer of (±)-alcohol **93** to generate (*R*)-acetate **99** and (*S*)-alcohol **93** (Scheme 35). These two strategies will be discussed in turn in the following sections.



Scheme 34. *CAL-B Mediated Hydrolysis*



Scheme 35. *CAL-B Mediated Transesterification*

For any kinetic resolution the theoretical maximum yield is 50%, therefore reactions can be monitored to 50% conversion and then halted (work-up) and products separated to give enantiomerically pure products and starting materials. It is also important to be able to measure the *ee* values obtained for products and starting materials, for example by chiral HPLC, chiral GC or by utilising chiral shift reagents in NMR spectroscopy.

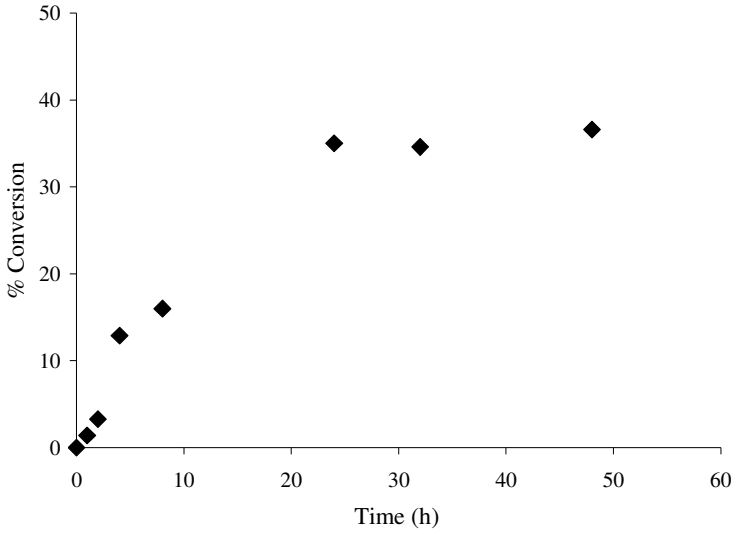
2.2.4.1 CAL-B Mediated Hydrolysis of Acetate **(±)-99**

The hydrolysis of (±)-acetate **99** was carried out utilising 10% w/w CAL-B in pH 7.2 phosphate buffer, at a concentration of 0.1 M at 35 °C under air. The conversion of acetate to alcohol was monitored by GC (Table 1, Graph 1).

Time (h)	*% Acetate* **99**†	*% Alcohol* **93**†
0	100	0
1	98.6	1.4
2	96.7	3.3
4	87.1	12.9
8	84.0	16.0
24	65.0	35.0
32	65.4	34.6
48	63.4	36.6

Table 1

†percentage determined by GC analysis

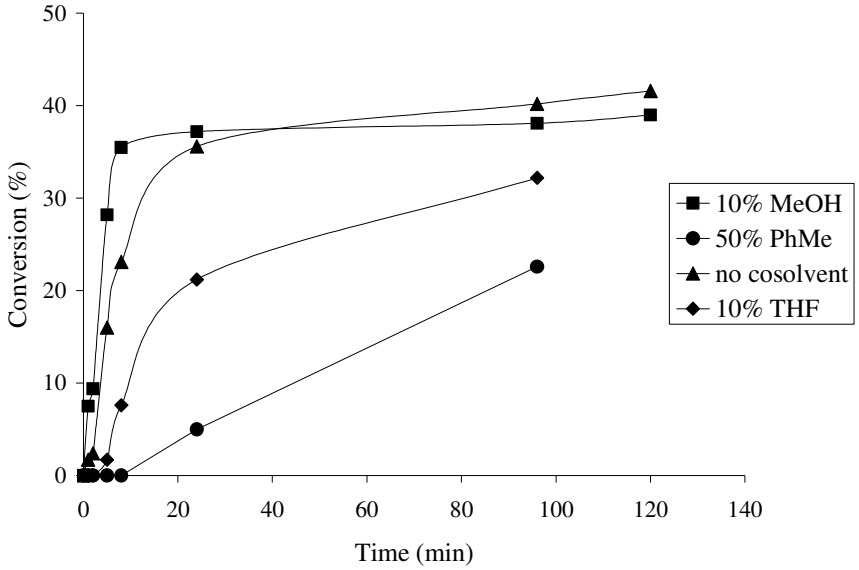


Graph 1. *Graph of CAL-B Mediated Hydrolysis*

As indicated by Graph 1, the hydrolysis reaction failed to reach 50% conversion even after 48 h. With less than 50% conversion, it would be expected that the product alcohol would be enantiomerically pure but the starting material would only be

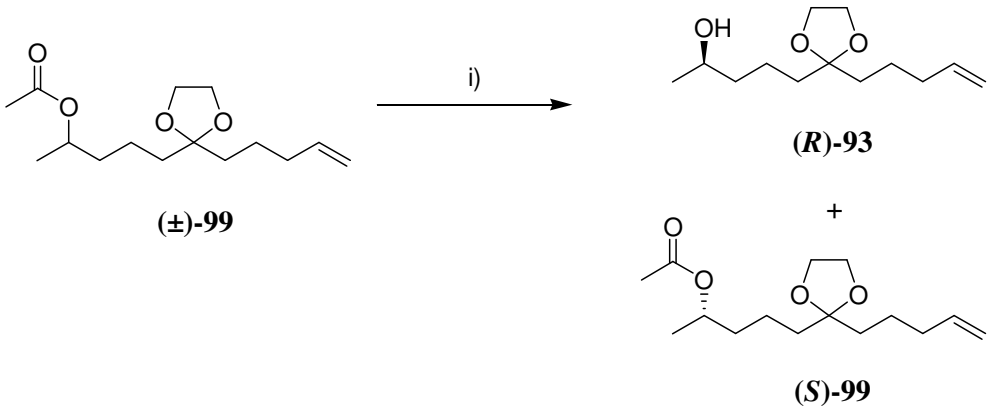
slightly enantiomerically enriched, as it would still contain some of the (*R*)-enantiomer along with the unreactive (*S*)-enantiomer.

A possible reason for the slow rate of hydrolysis is a solubility problem, hence investigations into various co-solvents were carried out. It is known that CAL-B hydrolyses can be performed in a variety of solvents and even with bi-phasic systems, however in all attempted cases the results were either similarly sluggish (10% MeOH) or worse than the buffer-only system (10% THF, 50% PhMe; Graph 2).



Graph 2. *CAL-B Mediated Hydrolysis with Co-Solvents*

A second possible reason for the slow rate of the hydrolysis reactions is the acetic acid produced, which raises the pH of the system and may inhibit the enzyme and thus retard the reaction rate. It is possible to combat this by the controlled addition of concentrated aqueous sodium hydroxide, to maintain a steady pH. A further reaction was carried out and after 24 h the conversion was again only ~35%, but the pH was shown to be pH 5.0. Careful addition of sodium hydroxide to pH 7.0 enabled the reaction to reach 44% conversion after a further 10 h (Scheme 36).



Scheme 36. *Reagents and Conditions:* i) CAL-B, pH 7.2 phosphate buffer, 0.1 M, pH 7-7.2, air, 35 °C, 34 h, (***R***)-**93**: 27%, (***S***)-**99**: 35%.

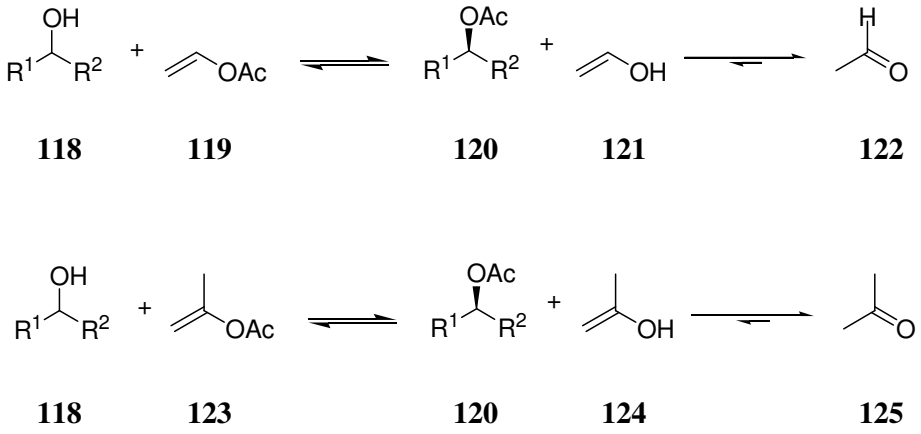
This procedure was repeated on a multi-gram scale and the reaction mixture purified *via* column chromatography to provide (*S*)-acetate **99** (35%, $[\alpha]_D$ +0.9 (*c* 1.64, CH_2Cl_2)) and (*R*)-alcohol **93** (27% , $[\alpha]_D$ –4.3 (*c* 1.22, CH_2Cl_2)). The literature optical rotation for (*R*)-alcohol **93** is $[\alpha]_D$ –6.8 (*c* 1.02, CH_2Cl_2)).[84] The apparent lower optical activity may be due to the extended reaction times being less ideal for a kinetic resolution.

Although these initial kinetic resolution studies were promising, it was expected that the enzyme-mediated transesterification of (±)-alcohol **93** with an acetate group could be more suited to our needs, as the transesterification procedure would directly form our desired (*S*)-alcohol **93** without the need for further steps (see Scheme 35).

2.4.2.2 CAL-B Mediated Transesterification of (±)*-Alcohol* **93**

Biocatalysed transesterifications of alcohols **118** are commonly employed as resolution techniques, with the most common transesterification partners being vinyl acetate (**119**) or isoprenyl acetate (**121**). During the resolutions the acetate is transferred from the vinyl or isoprenyl group to one of the alcohol enantiomer preferentially, forming an enantiopure acetate **120**. The by-products are vinyl alcohol (**121**) or isoprenyl alcohol (**124**), which rapidly tautomerise to the more favoured keto-tautomers acetaldehyde (**122**) and acetone (**125**), which can take no

further part in the reaction. Removal of these 'alcohol' by-products shifts the reaction equilibrium towards the product side (Scheme 37).



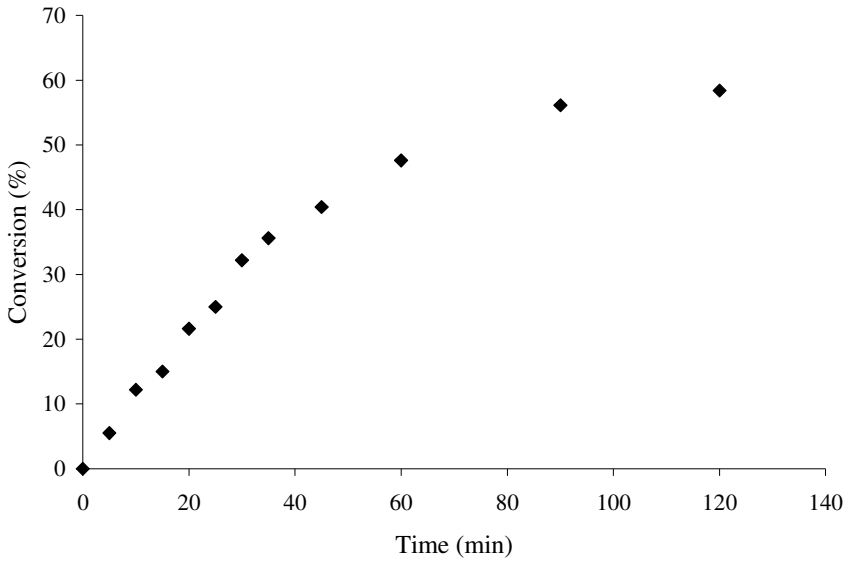
Scheme 37. *Enzyme-mediated Transesterifications with Vinyl- and Isoprenyl-acetate*

The CAL-B mediated transesterification of (±)-alcohol **93** was carried out with ten equivalents of vinyl acetate (**119**) in hexanes, with a concentration of 0.1 M at 35 °C under air. Conversion to the acetate was monitored by GC (Table 2, Graph 3).

Time (min)	*% Acetate*[†]	*Time (min)*	*% Acetate*[†]
0	0	30	32.2
5	5	35	35.6
10	12.2	45	40.4
15	15	60	47.6
20	21.6	90	56.1
25	25	120	58.4

Table 2

[†]percentage determined by GC analysis



Graph 3. *CAL-B Mediated Transesterifications of Alcohol* **(±)-93**

The transesterification reaction proved to be much faster than the CAL-B mediated hydrolysis, approaching 50% conversion at approximately 65 minutes. At longer reaction times however, the conversion approaches 60%. This suggests that although the reaction is highly selective for the (*R*)-enantiomer, the (*S*)-alcohol will also react slowly.

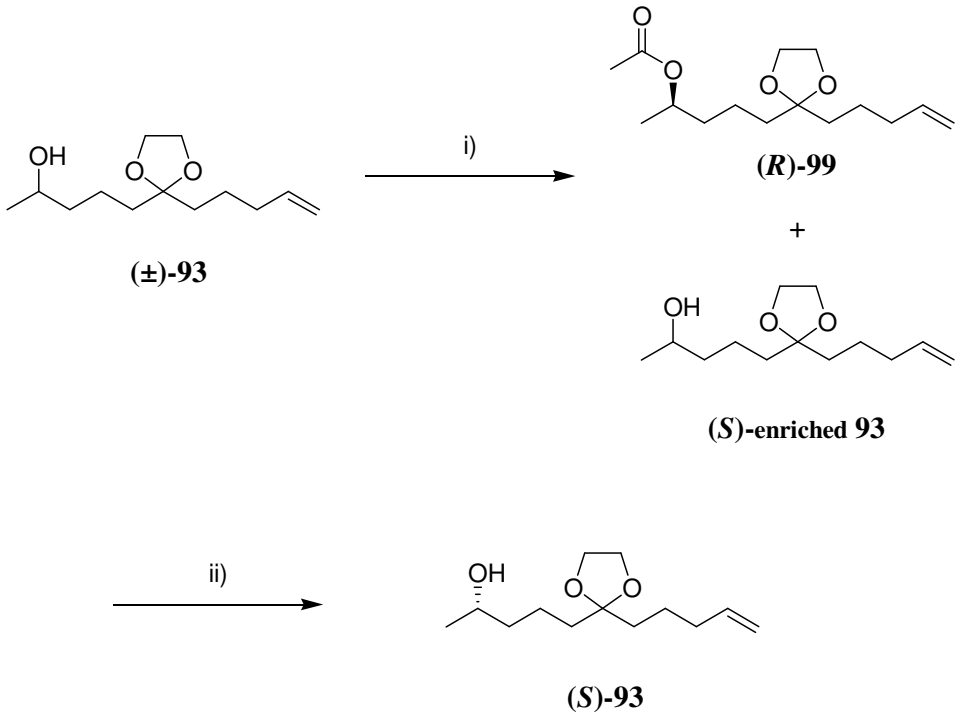
The reaction procedure was repeated on a multi-gram scale, halted after 65 min and the reaction mixture purified *via* column chromatography to provide (*R*)-acetate **99** (51%, $[\alpha]_D$ –1.1 (*c* 1.10 CH_2Cl_2)) and (*S*)-alcohol **93** (48%, $[\alpha]_D$ +5.8 (*c* 1.19 CH_2Cl_2)). These values suggest a slightly higher degree of optical purity than obtained *via* hydrolysis, although not yet comparable to the `literature observations.

To improve the optical purity during the transesterification reaction, it was thought to halt the reaction after 60 min, at ~45% conversion. At this time the products would be separated by chromatography. This would theoretically provide (*R*)-acetate **99** with a high optical purity, along with a lower optical purity (*S*)-alcohol **93**.

This isolated (*S*)-alcohol (contaminated with some remaining (*R*)-alcohol) would then be re-exposed to the same reaction conditions for a longer time. This would ensure that any remaining (*R*)-alcohol will be converted to its acetate, although according to

our initial observations that the reaction proceeded to >50% conversion, some of the (*S*)-alcohol would also be converted to its acetate. After a second chromatography step, this would result in an enhanced optical purity of the isolated (*S*)-alcohol, albeit with lower isolated yield. The time for the second 'resolution' would be chosen to counterbalance the increase in optical purity with the drop in yield.

Following this procedure, with a second 'resolution' time of 3 h, (*R*)-acetate **99** (46%, $[\alpha]_D$ –1.1 (*c* 1.05 CH_2Cl_2)) and (*S*)-alcohol **93** (41%, $[\alpha]_D$ +6.9 (*c* 1.19 CH_2Cl_2)) were isolated (Scheme 38).



Scheme 38. *Reagents and Conditions:* i) CAL-B (10% w/w), vinyl acetate (**119**) (10 eq.), hexanes, air, 35 °C, 1 h, **(*R*)-99**: 46%; ii) CAL-B (10% w/w), vinyl acetate (10 eq.), hexanes, air, 35 °C, 3 h, **(*S*)-93**: 41%.

The (*S*)-alcohol **93** obtained *via* the resolution method had thus proven to have a level of optical purity equal to that obtained previously from chirally pure starting materials (see Section 2.2.2). However, to determine the precise degree of optical purity it was necessary to measure the *ee* value. This will be discussed in the next section.

2.2.5 Determining Enantiomeric Excess of the Resolution Products

2.2.5.1 Chiral HPLC Method

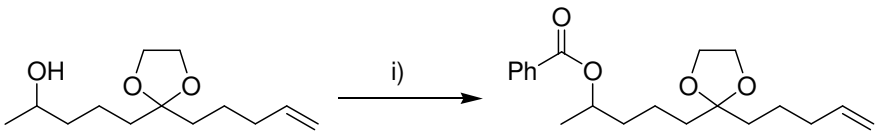
To determine the enantiomeric excess of the products obtained from the biocatalysed resolution studies, we first sought to use chiral HPLC. The *ee*'s can be determined by integrating the peaks obtained from each enantiomer, as given by Equation 1:

$$ee\ (\%) = \frac{I_R - I_S}{I_R + I_S} \times 100$$

Equation 1.

Where $\mathbf{I_R}$ (or $\mathbf{I_S}$) is the intensity or integral of the respective (*R*)- or (*S*)- peak in the HPLC output.

The samples were run using a CHIRALPAK AD amylase carbamate column with a HP 1100 chiral-HPLC with a UV detection method at a range of 200-280 nm (reference 525 nm), eluting with 1%-10% *i*-PrOH / hexanes. Unfortunately, neither alcohol **93** or acetate **99** have chromophores and so do not absorb UV-radiation strongly, hence spectra with messy baselines were obtained and the results were ambiguous. It was thought that forming the benzoyl esters **126** would increase the UV absorption, thus acylation of (±)-alcohol **93** with benzoyl chloride was carried out (Scheme 39). However (±)-benzoyl ester **126** still did not enhance the chiral-HPLC spectra sufficiently to resolve the two enantiomeric peaks.

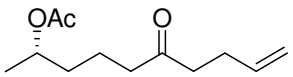


(±)-93 **126**

Scheme 39. *Reagents and conditions:* i) BzCl, pyr., 23 °C, 4 h, 92%.

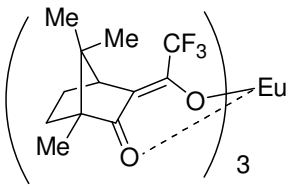
2.2.5.2 Chiral Shift Reagent Method.

In Keinan's[85] synthesis of (*S*)-zearalenone (**3**) outlined in Scheme 31, section 2.2.3, the *ee* of (*S*)-acetate **115** (Figure 10) is determined using a europium chiral shift reagent, Eu(tfc)$_3$ (**127**, Figure 11).



115

Figure 10. *Acetate* **115**

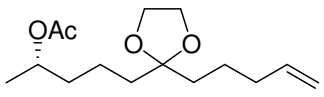


127

Figure 11. *Eu(tfc)$_3$* (**127**)

Eu^{3+} is a Lewis acid and thus can coordinate to both the carbonyl oxygen and one of the acetyl oxygens, causing a spreading of chemical shifts over a wider range of the spectrum. As Eu(tfc)$_3$ (**127**) is chiral, a diastereomeric complex is formed which will display visibly different chemical shifts in its ^{1}H NMR spectrum. In the case of Keinan *et al.*'s acetate **115**, the methyl doublet at 1.2-1.5 ppm is examined and different chemical shifts are observed for each of the two diastereomeric complexes formed, which can be integrated to provide the *ee* using the same equation as for the chiral HPLC.

In light of the structural similarity between (*S*)-acetate **115** and our (*S*)-acetate **99** (Figure 12), the ^{1}H NMR spectra of (±)-acetate **99**, (*S*)-acetate **99** and (*R*)-acetate **99** with chiral shift reagent Eu(tfc)$_3$ (**127**) were examined at 400 MHz. Unfortunately, the method proved extremely sensitive to the quantity of europium in the samples.



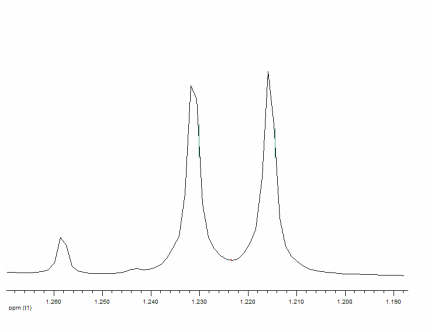
(*S*)-99

Figure 12. *(S)-Acetate* **99**

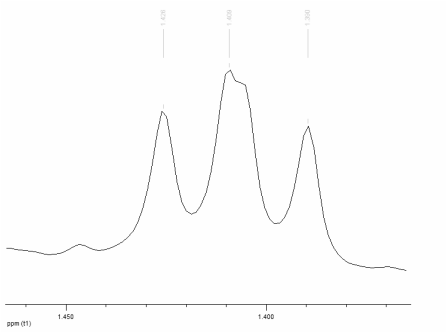
Portions of the spectra of (±)-acetate **99** corresponding to the methyl group, recorded with 0.7, 1.0 and 1.2 equivalents of $Eu(tfc)_3$, are shown in Figure 13. Without the shift reagent this is usually visible as a doublet at 1.2 ppm (J = 6.0 Hz) (Figure 13a), however even with 0.7 eq. of $Eu(tfc)_3$ this shifted downfield to 1.4 ppm (Figure 13b). Increasing the amount of europium increased this shift further.

Although splitting of the methyl peak into two doublets was observed, the close proximity of other peaks in the spectra made it impossible to integrate the doublets to a satisfactory degree to obtain an *ee* value. No alternative proton signals were observed which could be integrated satisfactorily.

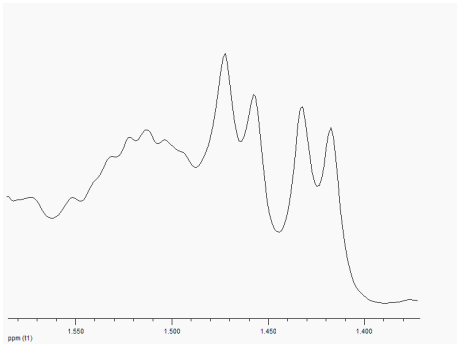
a)



b)



c)



d)

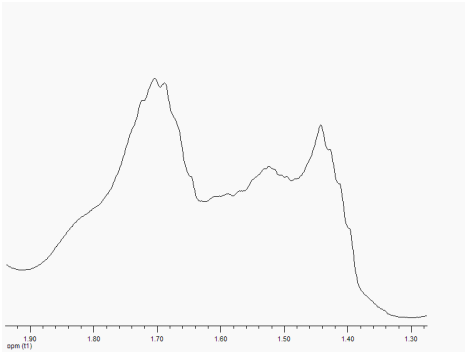
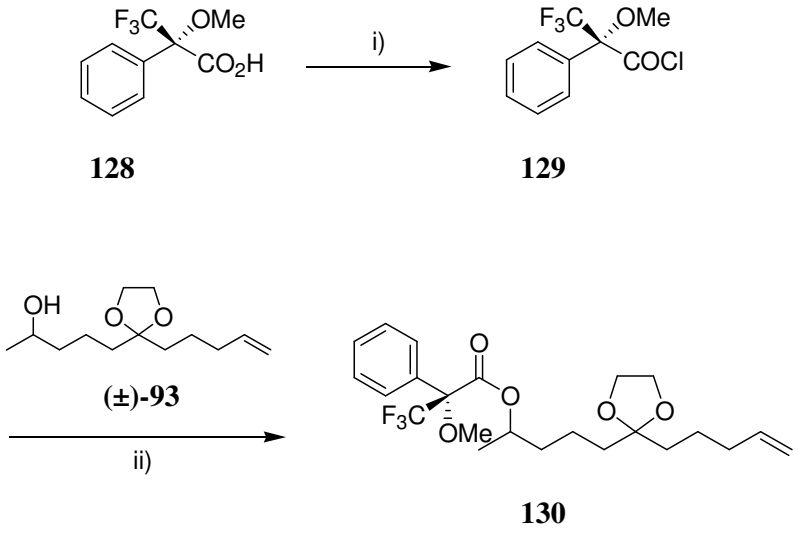


Figure 13. *Portions of the 1H NMR Spectra of* (±)*-acetate* **99** *with a) 0 eq.; b) 0.7 eq.; c) 1.0 eq.; d) 1.2 eq. of* $Eu(tfc)_3$ (**127**)

2.2.5.3 Mosher's Esters Method

A further way to determine an *ee* is to synthesise diastereoisomers. Whilst enantiomers cannot be distinguished by their NMR spectra, diastereoisomers can be. Thus by using an enantiomerically pure acid, esterification of (±)-alcohol **93** would lead to a mixture of diastereoisomers. Integration of the ^{1}H NMR spectra would prove the ratio of diastereoisomers, hence the enantiomers, of the alcohol substrate by Equation 1. A popular acid employed in this technique is Mosher's acid **128**,[89] as the presence of the trifluoromethyl group allows the use of ^{19}F NMR spectroscopy, which would only show one peak for a single diastereoisomer.

Mosher's esters of (±)-alcohol **93**, (*S*)-alcohol **93** and (*R*)-alcohol **93** were synthesised from the corresponding Mosher's acid chloride **129**[89] (Scheme 40).



Scheme 40. *Reagents and conditions:* i) $SOCl_2$, 80 °C, 46 h; ii) pyr., 23 °C, 24 h.

To avoid ambiguity, the esterifications carried out until complete starting material consumption was observed by GC. As isolated yields were poor, the Mosher's esters **130** were examined by crude ^{19}F NMR and ^{13}C NMR. Unfortunately extra peaks were visible, attributed to the presence of excess acid chloride **129** and acid **128**

and therefore it was impossible to determine an *ee* value. The non-quantitative yield of the reactions also hinted that any result obtained would be unreliable.

2.2.5.4 Chiral GC Method

Finally, samples of (±)-alcohol **93**, (*S*)-alcohol **93** and (*R*)-alcohol **93** were sent to AstraZeneca in Bristol,[90] where utilising an 80 °C isotherm, the enantiomers were visualised as two peaks and successfully quantified.

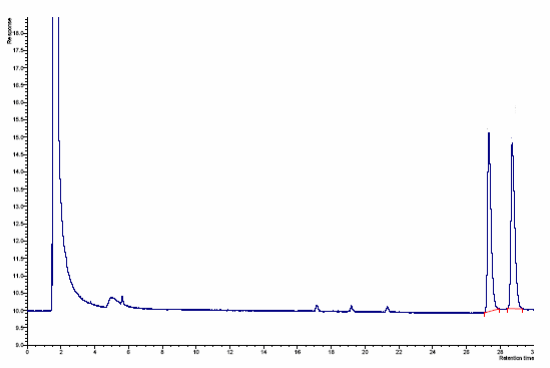
Gratifyingly, both the (*S*)-alcohol **93** and the (*R*)-alcohol **93** (obtained through hydrolysis of (*R*)-acetate **99**) were shown to have *ee*'s of >99% (Table 3, Figure 14).

Entry	R_t *27.5 min*	R_t *29.0 min*	*Assignment*	*ee*[†]
1	50.0% area	50.0% area	racemic	-
2	99.6% area	0.4% area	(*R*)-enantiomer	>99%
3	0.2% area	99.8% area	(*S*)-enantiomer	>99%

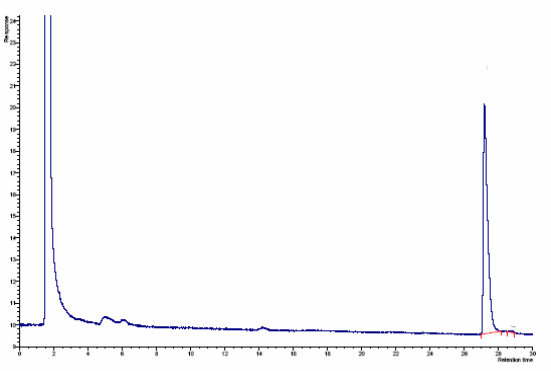
Table 3

[†]*enantiomeric excess* determined by Equation 1

a)



b)



c)

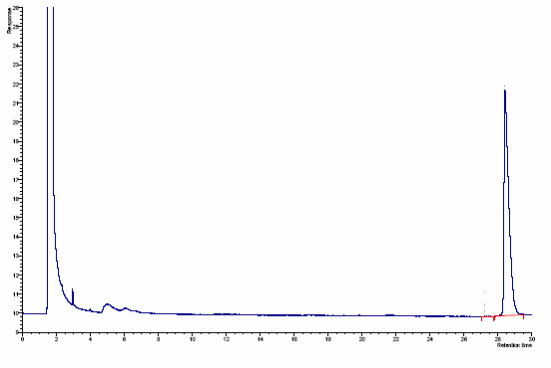
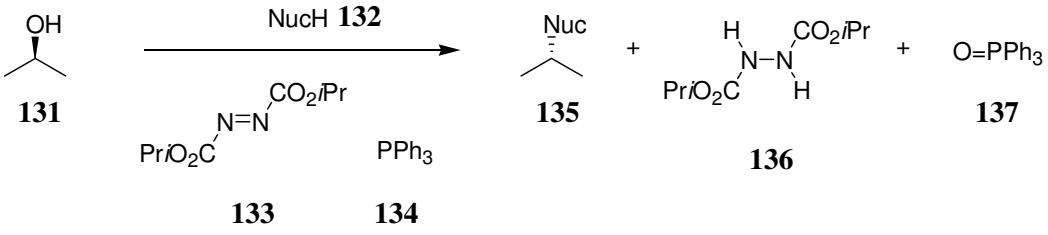


Figure 14: *Chiral GC Traces of a) (±)-, b) (R)- and c) (S)-alcohols* **93**.

With these results in hand, a series of further CAL-B transesterification reactions were carried out in a similar fashion on large scale. The products were either acylated or hydrolysed to give the corresponding alcohols/acetates and the subsequent [α_D]'s for all four compounds recorded and compared to the known >99% *ee* samples. The only drawback of the transesterification procedure was that the overall yield of the conversion from the racemic alcohol (±)-**93** to (*S*)-alcohol **93** was just 41%. If it was possible to somehow recycle the unwanted (*R*)-alcohol **93**, this would be an advantage.

2.2.6 Recovery of the (*R*)-Enantiomer

One general method for inverting a hydroxy chiral centre **131** is by utilising the well known Mitsunobu reaction.[91] This proceeds *via* the S_N2 attack of a nucleophile **132** on an activated alcohol substrate to generate inverted product **135**. The activation is achieved by treatment with triphenylphosphine (**134**) and an azo-compound, DIAD (**133**), which together remove one molecule of water forming by-product **136** and triphenylphosphine oxide (**137**) (Scheme 41).



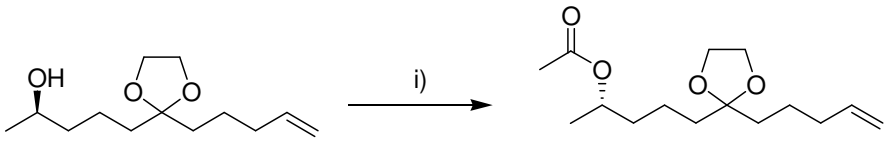
131 **135** **136** **137**

133 **134**

Scheme 41. *Mitsunobu Reaction.*

By employing acetic acid as the nucleophile and hydrolysing the resultant acetate, it is possible to directly invert the configuration of the alcohol.

Pleasingly, the Mitsunobu reaction of (*R*)-alcohol **93** with acetic acid provided (*S*)-acetate **99** in 91% ($[\alpha]_D$ +1.1 (*c* 1.12 CH_2Cl_2)) which enabled the unwanted alcohol from the transesterification to be 'recycled'(Scheme 42).

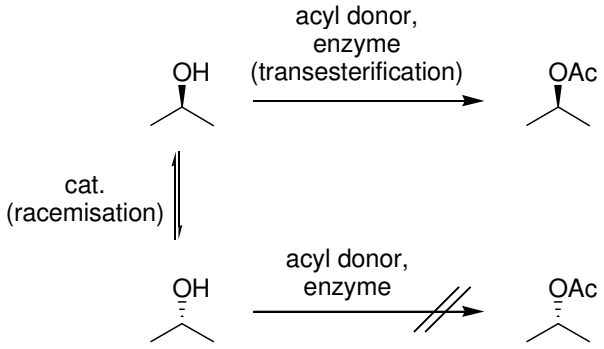


(*R*)-93 **(*S*)-99**

Scheme 42. *Reagents and Conditions:* i) AcOH, PPh_3 (**134**), DIAD (**133**), PhMe, –15 to 23°C, 91%.

2.2.6.1 Potential for Dynamic Kinetic Resolution.

Dynamic kinetic resolution (DKR) is an active area of research in organic synthesis and can be used as a powerful tool to overcome the 50% yield limitation of traditional kinetic resolutions. The principle of DKR is based on combining a kinetic resolution procedure with a simultaneous *in situ* racemisation process, which only affects the substrate and not the reaction product (Scheme 43). Standard conditions for racemisation involve the use of a ruthenium-based hydrogen transfer catalyst (such as $(C_5Ph_5)Ru(CO)_2Cl$) at elevated temperatures. More recently, biocatalysed DKR reactions have been investigated and proven facile.[92-94]



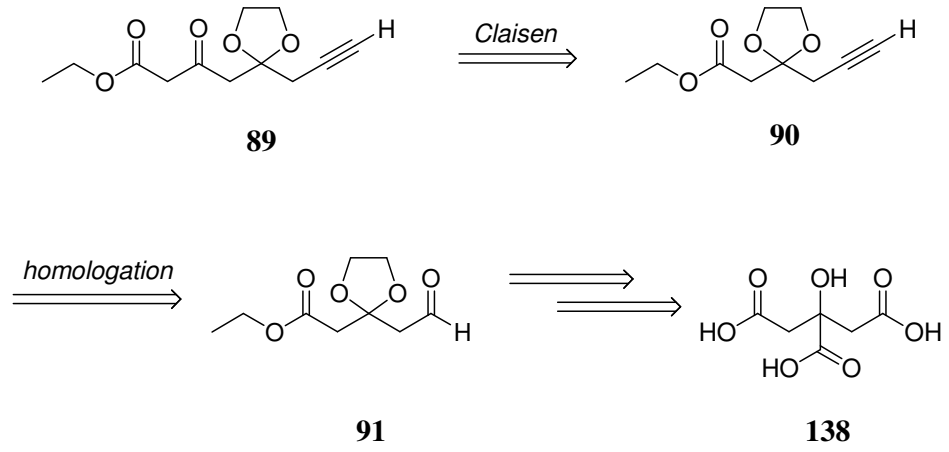
Scheme 43. *DKR Principles.*

Were it not for the fact that using DKR in combination with our CAL-B transesterification procedure would yield the wrong enantiomer, (*R*)-acetate **99**, this would be an ideal strategy. There is still potential to employ this procedure in the future, converting the (*R*)-acetate **99** to (*S*)-alcohol **93** in three steps by hydrolysis, Mitsunobu and a second hydrolysis - all proven reliable reactions.

With (*S*)-alcohol **93** in hand in excellent optical purity, the next section will discuss the synthesis of the coupling partner, alkyne ester **89**.

2.3 Synthesis of Alkyne Ester **89**

The second coupling partner from our retrosynthetic analysis (Scheme 20) is alkyne ester **89**. Further analysis of this target reveals a carbonylmethyl homologation (Claisen condensation) and disconnection of alkyne function to aldehyde (Scheme 44). Aldehyde **91** is a literature known compound, which can be made from citric acid (**138**).

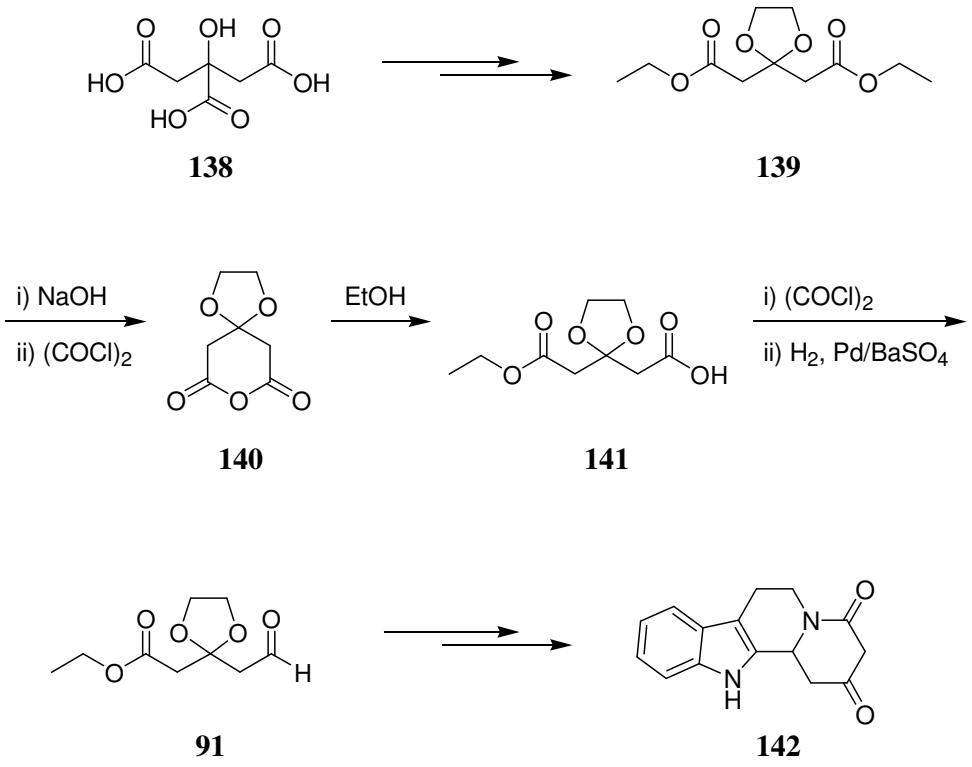


89 **90** **91** **138**

Scheme 44. *Retrosynthetic Analysis of Alkyne ester* **89**

2.3.1 Synthesis of Aldehyde **91** *via* Literature Procedure

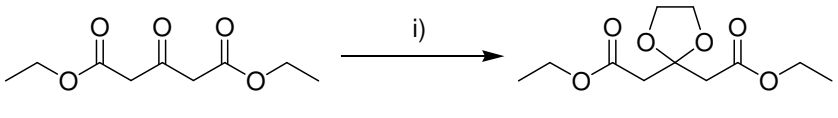
Aldehyde **91** was first synthesised in 1972 by Bruchter *et al.*[95] in an eight step procedure from citric acid (**138**) and thence utilised in the synthesis of keto lactam **142**, which is a precursor for indole alkaloids (Scheme 45).



138 **139** **140** **141** **91** **142**

Scheme 45. *Bruchter et al.'s Synthesis of Aldehyde* **91**.

Today, diethyl 1,3-acetone dicarboxylate (**92**) is a cheap, readily available starting material, thus work was begun by carrying out the ketal protection of ketone **92** using boron trifluoride catalysis.[96] This gave diester **139**, which was sufficiently pure to use crude in the next step (Scheme 46).

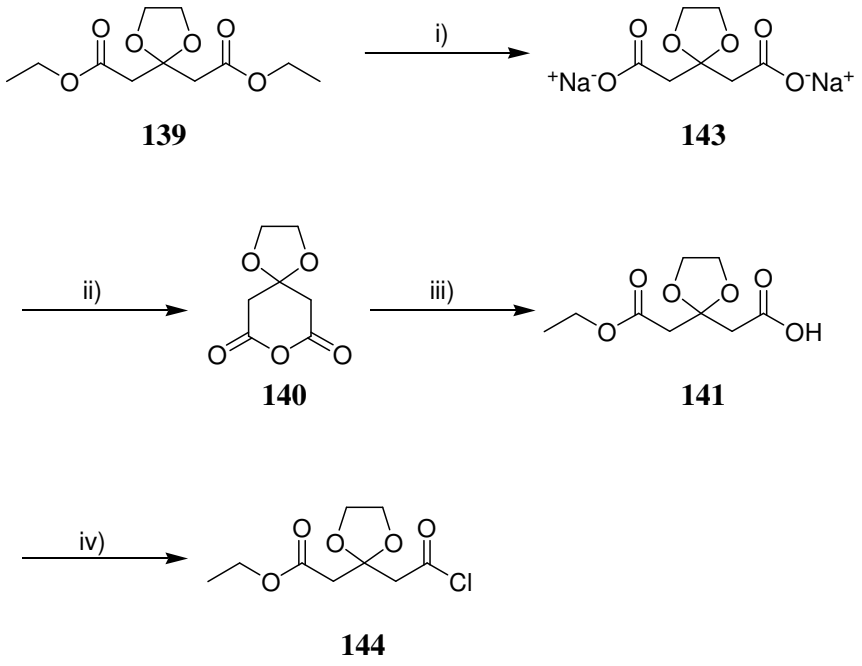


92 **139**

Scheme 46. *Reagents and conditions*: i) $HOCH_2CH_2OH$, $BF_3 \cdot OEt_2$, PhMe, 120 °C, 18 h.

Saponification of diester **139** with sodium hydroxide gave disodium salt **143** in 62% yield over two steps, after recrystalisation. Upon treatment with oxalyl chloride, disodium salt **143** cyclised to afford anhydride **140** in 68% yield. The latter reaction was found to be sensitive to the method of stirring utilised, with overhead stirring proving the most efficient to enable satisfactory mixing of the insoluble starting material with the reagents. Treatment of anhydride **140** with excess absolute ethanol

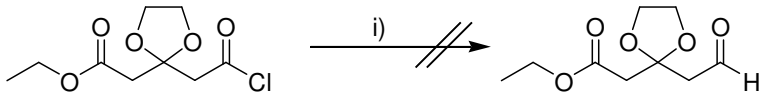
followed by heating to reflux yielded 99% of carboxylic acid **141**, which was subsequently transformed to the acid chloride **144** by oxalyl chloride (Scheme 47).



139 **143** **140** **141** **144**

Scheme 47. *Reagents and conditions*: i) NaOH, EtOH, 80 °C, 1 h, 62% over two steps; ii) $(COCl)_2$, CH_2Cl_2, 45 °C, 2h, 68%; iii) EtOH, 80 °C, 18 h, 99%; iv) $(COCl)_2$, PhMe, 23 °C, 3 h.

Acid chloride **144** proved unstable to chromatography or distillation, therefore a method to convert the crude product to aldehyde **91** was sought. Bruchter's synthesis had employed a Rosenmund reduction for this step, using a 'poisoned' palladium on barium sulphate catalyst and hydrogen gas.[97] Unfortunately our attempts to apply these conditions gave only starting material or decomposition (Scheme 48).



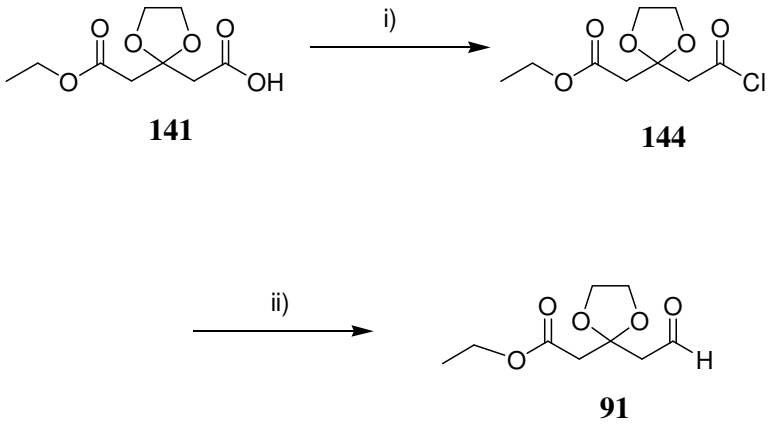
144 **91**

Scheme 48. *Reagents and conditions:* i) $H_{2\ (g)}$, 5% $Pd/BaSO_4$, xylene, 130 °C, 1 h.

We therefore sought to modify the literature procedure, as will be discussed in section 2.3.2.

2.3.2 Synthesis of Aldehyde **91** *via* Modifications to the Literature Procedure

Our attention was drawn to Fleet *et al.*'s alternative method for reduction of acid chlorides to aldehydes, utilising *bis*(triphenylphosphine)copper(I) borohydride, synthesised from copper (I) chloride, sodium borohydride and triphenylphosphine.[49] Promisingly, the initial trial of this method allowed isolation of aldehyde **91** in 48%. This was later optimised to 88% over two steps from carboxylic acid **141**, by both reducing the reaction time from 30 to 15 minutes and an improved workup procedure. This involved dissolving the crude product in the minimum amount of Et_2O and chilling, which facilitated the precipitation of the triphenylphosphine oxide by-product which could thus be removed by filtration (Scheme 49).



141 **144** **91**

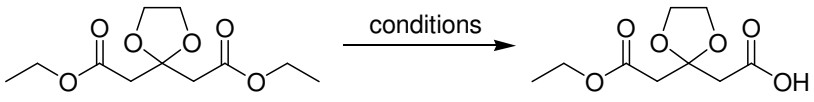
Scheme 49. *Reagents and conditions:* i) $(COCl)_2$, PhMe, 120 °C, 2 h; ii) $Cu(PPh_3)_2BH_4$, PPh_3 (**134**), acetone, 23 °C, 15 min, 88% over two steps**.**

Further optimisation of the route revealed that it was possible to synthesise aldehyde **91** in good yield from diethyl 1,3-acetone dicarboxylate (**92**) in six steps, using each intermediate crude and with only one purification step at the final stage.

Unfortunately however, on more than one occasion the reaction of disodium salt **143** with oxalyl chloride failed to provide anhydride **140** and results of this reaction proved unreliable. Therefore a more efficient route was investigated.

2.3.2.1 Mono-hydrolysis of Diester **139**

It was envisaged that the six-step procedure could be shortened by carrying out the mono-hydrolysis of diester **139** to directly provide carboxylic acid **141**. Control of this reaction proved difficult, with a mixture of product and starting material being isolated in low yield along with, it was assumed, the very polar diacid. A variety of different conditions for the reaction were screened (Scheme 50, Table 4).



139 **141**

Scheme 50. *Mono-hydrolysis of Diester* **139**.

Entry	*Reagent*[†]	*Solvent*	*Yield* (**141**)[*]	*S.M. Recovery* (**139**)[*]
1	0.25 M NaOH in H_2O	EtOH	24%	39%
2	0.25 M NaOH in H_2O	PhMe	15%	33%
3	solid NaOH	PhMe	0%	100%
4	0.25 M KOH in H_2O	EtOH	56%	35%
5	0.25 M KOH in EtOH	EtOH	0%	100%
6	0.25 M CsOH in EtOH	PhMe	28%	58%
7	0.25 M CsOH in H_2O	EtOH	52%	22%
8	0.5 M CsOH in H_2O	EtOH	48%	33%

Table 4

[†] reactions carried out with 1.0 eq. base at 23 °C for 18 h; [*] isolated product yields

Initial conditions, with the use of dilute aqueous sodium hydroxide in ethanol gave a low yield of desired acid **141**, along with recovery of starting diester **139** (Table 4, Entry 1). The use of toluene to encourage precipitation of the mono-sodium salt failed to improve the procedure (Entry 2). Increasing the concentration of sodium hydroxide resulted in quantitative starting material recovery, presumably due to insolubility of the sodium hydroxide in the reaction medium (Entry 3). Changing to potassium

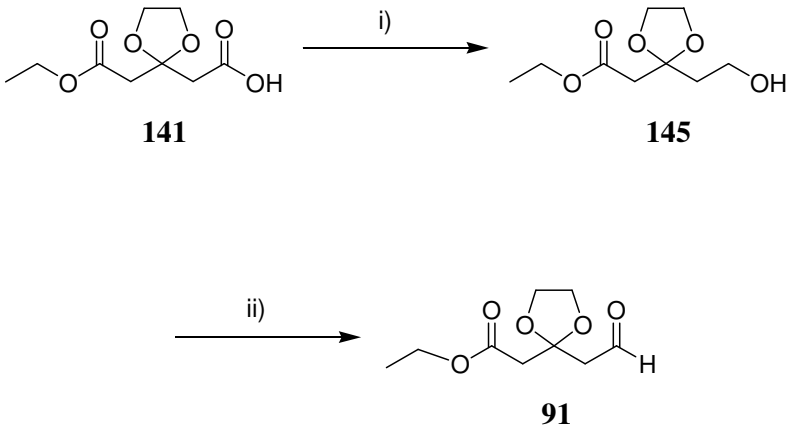
hydroxide resulted in a slight improvement (Entry 5), however the use of caesium hydroxide gave no significant change (Entries 7-10).

The best conditions found were the use of aqueous potassium hydroxide with ethanol as a solvent, which afforded the acid **141** in a moderate 56% yield. Employing the mono-hydrolysis route saves two steps in the synthesis of aldehyde **91**, thus also saving time and costs. Although the yield is moderate, significant starting material is also recovered, resulting in a yield of 91% based on recovery of starting material, hence this route was deemed to have a greater overall efficiency.

2.3.2.2 Reduction-Oxidation Strategy

Although excellent results were obtained from the *bis*(triphenylphosphine)copper(I) borohydride reduction of acid chloride **144** on small scales, it was found that scaling up this procedure resulted in less satisfactory yields. This was due to the stoichiometric quantities of solid reagents required, which were difficult to separate from the product during chromatography. Often the isolated product aldehyde **91** still contained triphenylphosphine (**134**) as an impurity.

An alternative conversion of acid **141** to aldehyde **91**, *via* borane reduction to alcohol **145** and then Swern oxidation, was trialled. The yields proved similar overall, however this second route proved more reproducible, the purification was simpler and the procedure was more readily adapted to large scale (Scheme 51).



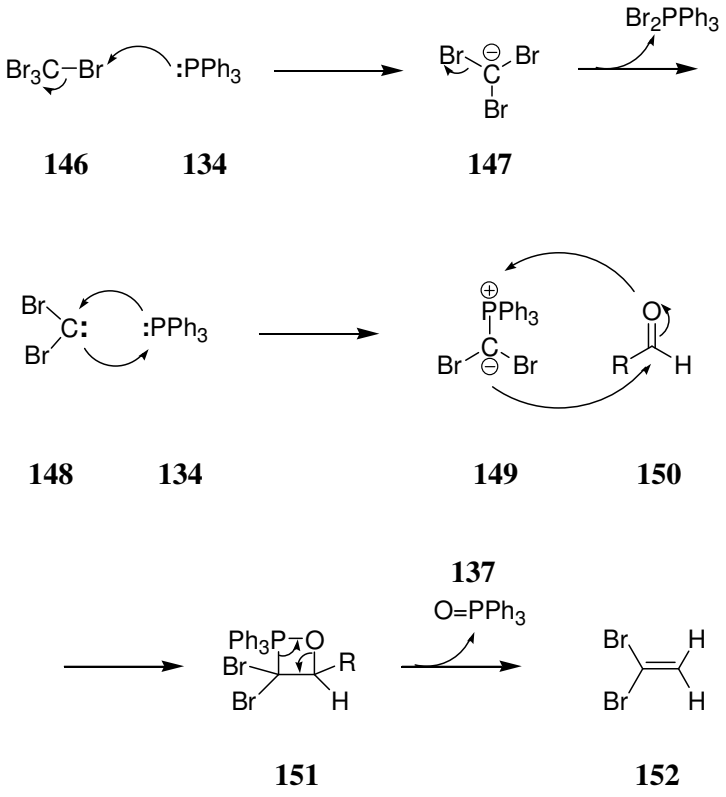
141 **145** **91**

Scheme 51. *Reagents and conditions:* i) $BH_3 \cdot THF$, THF, 0 °C, 3 h then MeOH, 23 °C, 2 h; ii) $(COCl)_2$, DMSO, –78 °C, 30 min then Et_3N, –78 °C to 23 °C, 1 h, 84% over two steps.

2.3.3 Conversion of Aldehyde **91** to Alkyne **90**

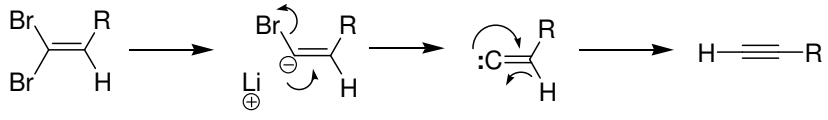
2.3.3.1 Corey-Fuchs Strategy

Initial attempts to convert aldehyde **91** to alkyne **90** focused on the well known two-step Corey-Fuchs homologation procedure.[98] The intermediate product in the Corey-Fuchs procedure is a dibromoalkene **152**. The first step involves a Wittig-like reaction between the aldehyde **150** and reactive dibromo ylide **149**, which is generated from carbon tetrabromide (**146**) and triphenylphosphine (**134**) through intermediates **147** and **148**. The resultant oxaphosphetane **151** eliminates triphenylphosphine oxide (**137**) to generate the dibromoalkane **152** (Scheme 52).



Scheme 52. *Mechanism of the Corey-Fuchs Procedure, Step One.*

A base, such as *n*-BuLi, is then utilised to transform the dibromide **152** to the product alkyne **155**. The mechanism of the elimination proceeds *via* lithium-halogen exchange forming intermediate **153**, followed by α-elimination to generate an olefinic carbene **154**. A Fritsch-Buttenberg-Wiechell[99] type rearrangement *via* a 1,2-hydride migration provides the alkyne **155** (Scheme 53).

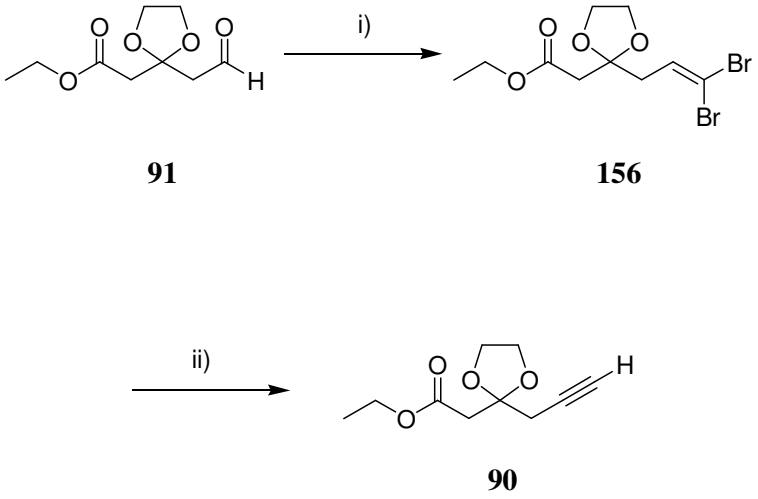


152 **153** **154** **155**

Scheme 53. *Mechanism of the Corey-Fuchs Procedure, Step Two.*

Following this procedure, the treatment of aldehyde **91** with carbon tetrabromide (**146**) and triphenylphosphine (**134**) enabled dibromide **156** to be isolated in good yield. The subsequent bromide elimination to afford the alkyne **90**, however, was not straightforward. Treatment with *n*-BuLi gave an isolated product yield of just 10%. This was attributed to the presence of the ester group, along with other acidic protons in the molecule which led to significant side reactions.

Fortuitously, it was found that magnesium could be used to carry out the elimination and this procedure improved the yield of alkyne **90** to 65% (Scheme 54).



91 **156**

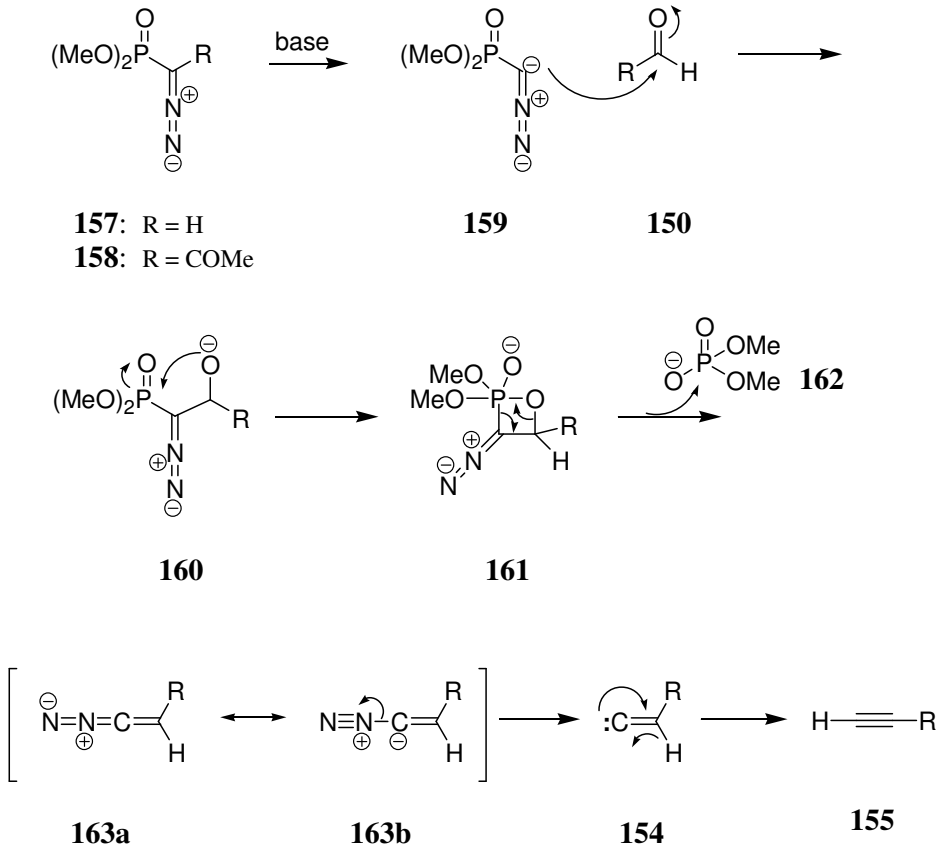
90

Scheme 54. *Reagents and conditions*: i) CBr_4 (**146**), PPh_3 (**134**), CH_2Cl_2, 23 °C, 48 h, 77%; ii) Mg, THF, 70 °C, 1 h, 65%.

The initial complications encountered during the Corey-Fuchs procedure prompted us to search for an alternative, single step procedure and our findings will now be discussed.

2.3.3.2 One-Pot Procedures

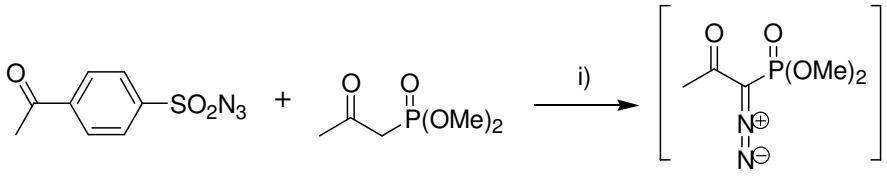
Our first idea was to employ a phosphonate azide ester, for example the Ohira-Bestmann reagent (**158**), as a one-carbon homologating agent.[100] The Ohira-Bestmann reagent (**158**) is a modification of the Gilbert-Seyforth reagent (**157**)[101] and the key reacting species in both cases is the same: deprotonated azide **159**. This reacts with the aldehyde **150** following a similar pathway to both the first step of the Corey-Fuchs reaction and the Wittig reaction, with alkenation of the carbonyl and oxaphosphetane **161** formation. The difference in this case is that the elimination of dimethyl phosphate (**162**) leads to an unstable diazo alkene **163**, which spontaneously loses nitrogen to generate an olefinic carbene **154**. A Fritsch-Buttenberg-Wiechell type rearrangement *via* a 1,2-hydride migration provides the alkyne **155**, analogous to the Corey-Fuchs elimination step (Scheme 55).



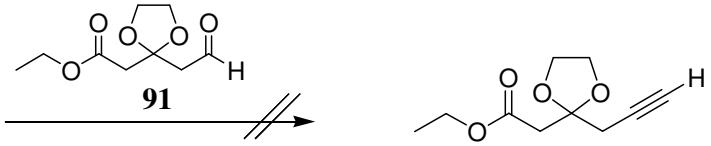
Scheme 55. *Mechanism of Alkyne formation from Phosphonate Azide Esters.*

The Ohira-Bestmann modification allows the use of potassium carbonate as a milder base instead of *t*-BuOK which is traditionally utilised with the Gilbert-Seyforth reagent and hence this reagent is compatible with a wider range of functional groups. It has been reported that the Ohira-Bestmann reagent (**158**) can be generated by *in situ* azo transfer from tosyl azide to commercial phosphonate ester **165**. Thus, the alkyne can be formed in a one-pot process upon addition of the aldehyde and base.[102]

The one-pot procedure was initially attempted with 4-carboxybenzene sulfonazide (**164**) instead of tosyl azide, as this material was available within our group (Scheme 56).[100]



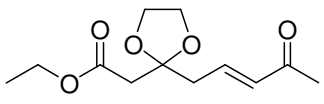
164 **165** **158**



90

Scheme 56. *Reagents and conditions*: i) a) K_2CO_3, CH_3CN, 23 °C, 2 h; b) **91**, 23 °C, 8h.

Disappointingly, desired alkyne **90** could not be detected and instead the only isolated product was the Horner-Wadsworth-Emmons reaction product **166** (MS (CI) *m/z* 243 $[M+H]^+$), from the reaction of phosphonate ester **165** with aldehyde **91** (Figure 15). This suggested a problem with the diazotisation process and therefore investigations were made into isolation of the Ohira-Bestmann reagent.

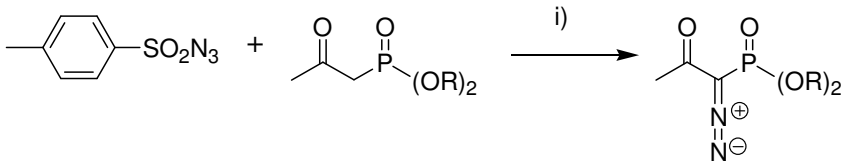


166

Figure 15

Due to concern for the ethyl ester present in our aldehyde **91**, both the Ohira-Bestmann reagent (**158**) and the analogous phosphonate azide ethyl ester **179** were isolated. It was hoped that the latter could be utilised with ethanol as a solvent thus preventing transesterification, a side-reaction possible under the basic reaction conditions. The azo transfer[103] from 4-carboxybenzene sulfonazide (**164**) to either phosphonate ester resulted in the recovery of starting material. Therefore, it was assumed that the reactivity of azide **164** was lower than that of tosyl azide (**177**), or our starting azide had decomposed.

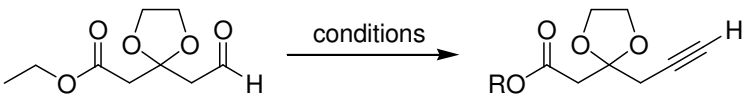
Thus tosyl azide (**177**) was synthesised from tosyl chloride and sodium azide according to the literature procedure[104] in 99% yield. The diazotisations were then repeated to afford 96% of the Ohira-Bestmann reagent (**158**) and 90% of the analogous ethyl ester product **179** after chromatography (Scheme 57).



177 **165**: R = Me, **178**: R = Et **158**: R = Me, **179**: R = Et

Scheme 57. *Reagents and conditions:* i) K_2CO_3, CH_3CN, 23 °C, 2 h, **158**: 96%, **179**: 90%.

With both phosphonate azide esters **158** and **179** in hand, the conversion of aldehyde **91** to alkyne ester **90** was attempted under several different sets of conditions (Scheme 58, Table 5).



91

90 R = Et
180 R = Me

Scheme 58. *Homologation of Aldehyde* **91**

Entry	*Azide*	*Reagents and conditions*	*Yield of Alkyne*[†]
1	**158**	NaOMe (4.0 eq.), THF, –78 °C, 2 h	25%
2	**179**	NaOMe (2.5 eq.), THF, –78 °C, 2 h[105]	33%
3	**158**	K_2CO_3 (2.0 eq.), MeOH, 23 °C, 18 h[100]	57%[*]
4	**179**	K_2CO_3 (2.0 eq.), EtOH, 23 °C, 18 h	[$]

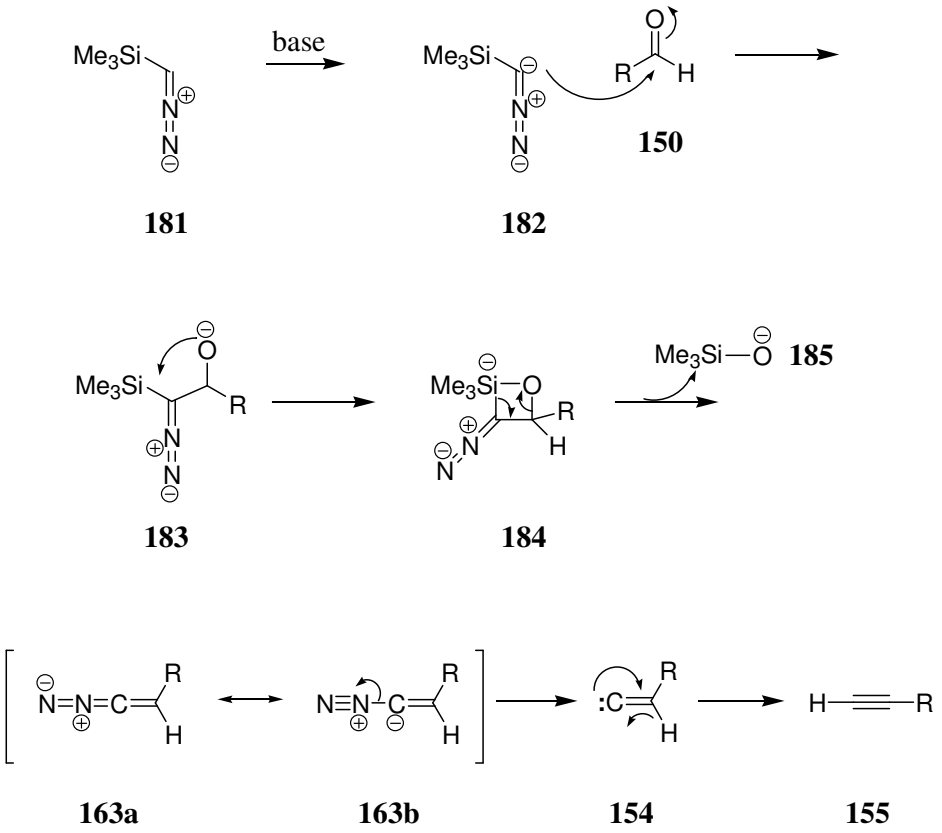
Table 5

[†] isolated product yields; [*] product from transesterification, **180**; [$] S.M recovery

The use of sodium methoxide as a base led to low yields of product **90** (Table 5, Entries 1 and 2) but proved that the reaction was working. Switching to potassium carbonate in methanol gave 57% of alkyne product, however with concomitant transesterification to afford methyl ester **180** (Entry 3). The use of ethyl phosphonate ester **179** in ethanol resulted in starting material recovery (Entry 4).

Disappointingly, when these same reaction conditions were applied on a larger scale, the yields dropped to 9-16%. The unreliability of this method prompted investigation into a third method using trimethylsilyldiazomethane (**181**). In the same way that the Ohira-Bestmann homologation mechanism is analogous to the Wittig reaction mechanism, so trimethylsilyldiazomethane (**181**) reacts with aldehydes to provide alkynes by a mechanism similar to that of the Peterson olefination reaction.[106] The key steps follow a similar mechanism to that outlined previously (see Scheme 55), the main differences being that in this case the attacking species is anion **182** and

secondly, trimethylsiloxane (**185**) is the stable elimination product instead of triphenylphosphine oxide (**137**) (Scheme 59).

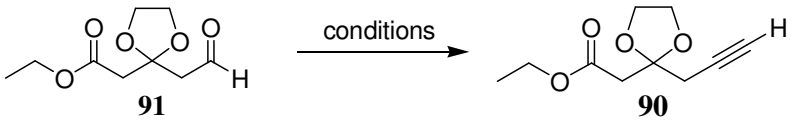


Scheme 59. *Mechanism of Homologation with TMS-Diazomethane* (**181**).

The advantages of this procedure over the Ohira-Bestmann protocol are firstly that only one equivalent of base is necessary to generate the attacking species and secondly, that this is formed before the addition of the aldehyde, which would hopefully prevent side reactions.

Following the literature procedure,[107] TMS-diazomethane (**181**) was treated with *n*-BuLi at –78 °C, followed by the addition of aldehyde **91**. After 1 h, TLC analysis showed product formation and starting material consumption, thus the reaction was quenched at –78 °C with pH 7.0 buffer and extracted with diethyl ether several times. Subsequent column chromatography, however, provided alkyne **90** in just 16% yield (Scheme 60).

The poor isolated yield was attributed to the work-up procedure and indeed, when the reaction was repeated but this time simply evaporated *in vacuo* upon completion, column chromatography provided alkyne **90** in an improved 39% yield. Further modifications of the work-up procedure were carried out, however the results proved to be similarly irreproducible as with the Ohira-Bestmann reagent (Scheme 60, Table 6).



Scheme 60. *Homologation of Aldehyde* **91**.

Entry	*Quench/ Workup*[†]	*Yield* **90**[*]
1	Quench pH 7.0 buffer Extract Et_2O	16%
2	Evaporate	39%
3	Evaporate to 1/3 volume Quench pH 7.0 phosphate buffer Extract CH_2Cl_2	24-42%
4	Quench AcOH (2.0 eq.) at –78 °C Dilute with pH 7.0 phosphate buffer Extract CH_2Cl_2	11-31%

Table 6

[†] *Reagents and conditions:* a) **181**, *n*-BuLi, THF, –78 °C, 30 min;
b) **91**, THF, –78 °C, 1 h; [*] isolated product yield

The lack of reproducible yields observed for both this procedure and the Ohira-Bestmann method prompted us to conclude that the two-step Corey-Fuchs protocol was most suitable for repetition on large scale during our synthesis.

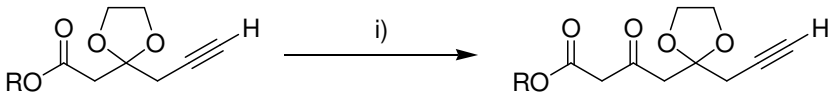
2.3.4 Claisen Condensation of Alkynes **90** and **180**

With the alkyne-moiety in place, the next step to be investigated was the Claisen condensation to generate the β-keto ester functionality. As both ethyl- and methyl-esters **90** and **180** were in hand, studies commenced by looking at their condensations with ethyl acetate and methyl acetate respectively.

Initial trials into the Claisen condensations were performed by addition of the acetate to lithium di*iso*propylamine in order to preform the enolate under kinetic control. Three equivalents of both base and acetate were used in order to reduce the degree of self-condensation.

The alkyne was added to the enolate, resulting in the disappointing yields of 29% and 30% of methyl ester **186** and ethyl ester **89** respectively (Scheme 61). *tert*-Butyl acetate was also reacted with ethyl ester **90**, giving an improved yield of 69% of the corresponding *tert*-butyl ester **187**. This suggested that the nature of the alkyl group on the acetate had an effect on the yield, with bulkier acetates favouring product formation.

.



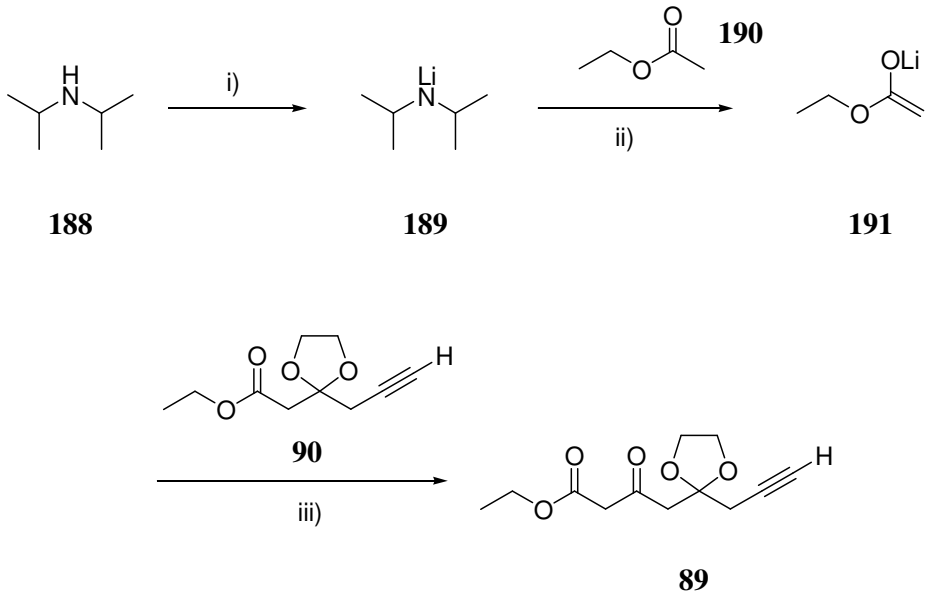
180: R = Me
90: R = Et

186: R = Me
89: R = Et
187: R = *t*-Bu

Scheme 61. *Reagents and conditions*: i) CH_3CO_2R (3.0 eq.), LDA (3.0 eq.), THF, –78 °C to 0 °C, 3 h, **186**: 29%; **89**: 30%; **187**: 69%.

We postulated that the extra bulk of the ester group in the Claisen product might pose a problem in the subsequent transesterification step, thus it was decided to optimise the ethyl acetate procedure.

Encouragingly, when LDA (**189**) was formed *in situ* from *n*-BuLi and DIPA (**188**) at –78 °C before the addition of ethyl acetate (**190**), with the additional use of six equivalents of enolate **191**, homologous ethyl alkyne ester **89** could be isolated in a greatly improved 86% yield (Scheme 62).

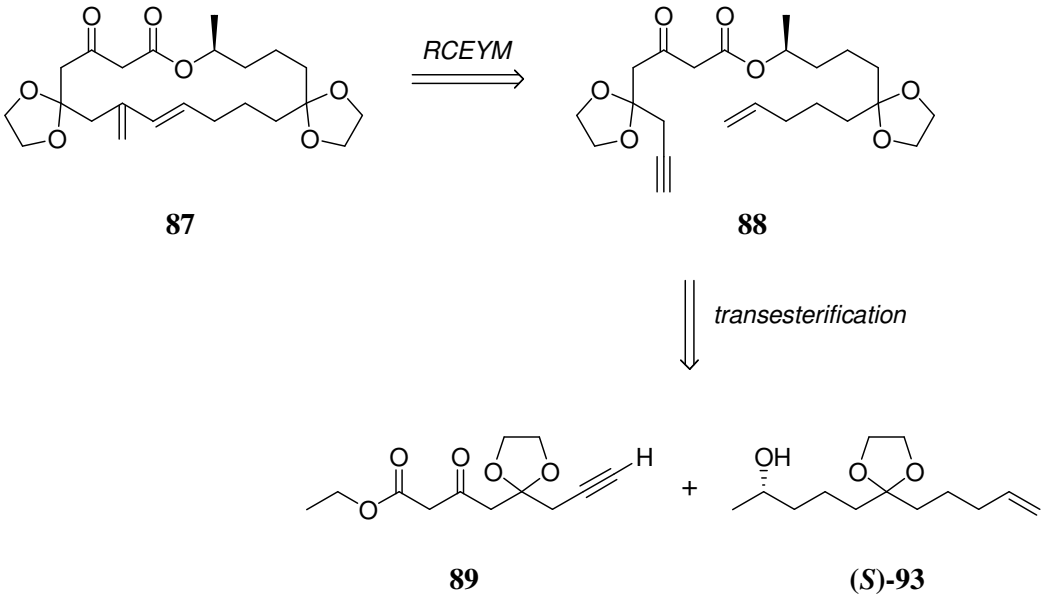


Scheme 62. *Reagents and conditions*: i) *n*-BuLi, THF, 0 °C, 15 min; ii) **190** , –78 °C, 30 min; iii) **90**, –78 °C to 23 °C, 4 h, 86%.

Therefore, we now had access to both alkyne ester **89** and (*S*)-alcohol **93** in gram scale quantities. In the next section, their coupling *via* transesterification and ring-closing enyne metathesis will be examined.

2.4 Coupling of (*S*)-Alcohol **93** and Alkyne Ester **89**

Our retrosynthetic analysis of (*S*)-zearalenone (**3**) (Scheme 20) involves disconnection of macrocyclic diene **87** *via* RCEYM, giving enyne **88** as a target which can be generated from the transesterification of (*S*)-alcohol **93** and alkyne ester **89** (Scheme 63).



Scheme 63. *Retrosynthesis of Macrocyclic Diene* **87.**

Efforts towards these two steps will be discussed in turn in this section.

2.4.1 Transesterification

As detailed in section 2.2.1, (±)-alcohol **93** had been synthesised before the introduction of chirality *via* the kinetic resolution. In fact, it had then taken some time to find a viable route to control the stereochemistry and subsequently to measure the *ee* of resulting (*S*)-alcohol **93**, to be confident of our results. While this work was in progress, the transesterification of (±)-alcohol **93** with alkyne ester **89** was also examined, to enable us to test further steps in the route to (*S*)-zearalenone (**3**).

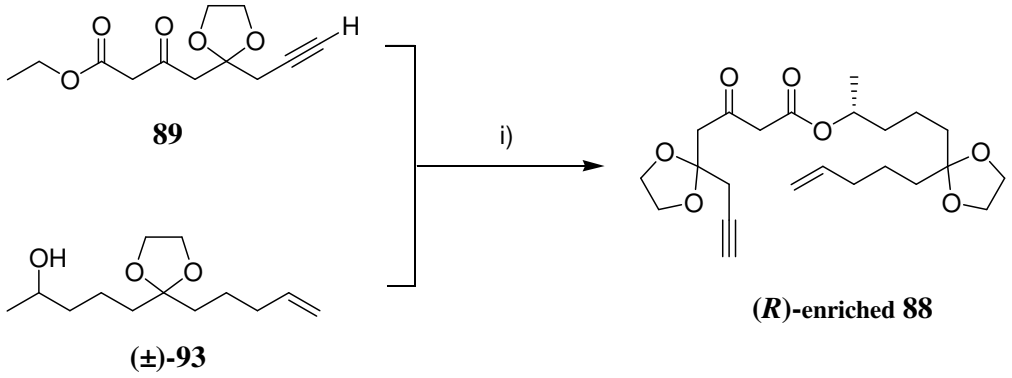
2.4.1.1 CAL-B Mediated Transesterifications

Before we had realised the potential of CAL-B for the kinetic resolution of (*S*)-alcohol **93** (section 2.2.4), we had intended to see if CAL-B could be employed in the transesterification of (±)-alcohol **93** and alkyne ester **89**. CAL-B had been used previously within our group[66] and in the literature[108, 109] to enable transesterifications under mild conditions and with good yields, regardless of stereochemistry.

Janda[108] reports that the use of CAL-B is effective for transesterifications of β-keto esters with a wide range of alcohols. The procedure involves treating equimolar amounts of the neat alcohol and β-keto ester with CAL-B (10% w/w of alcohol) and swirling in a flask connected to a Büchi rotavapor at 40 °C and 10 Torr for 8 h. The reduced pressure allows easy removal of the alcohol by-product. More recently Nanda and Scott[109] reported the use of CAL-B for transesterifications at atmospheric pressure and 50 °C.

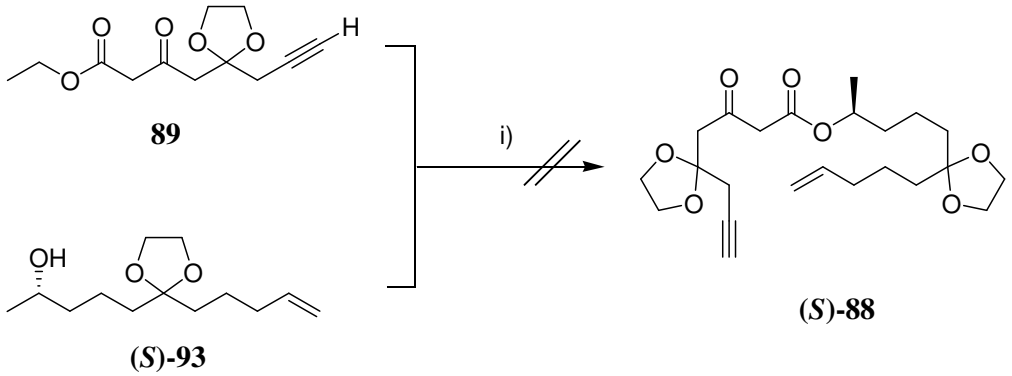
To this end, the transesterification was carried out employing three equivalents of (±)-alcohol **93**, at 40 °C under an air condenser, without additional solvent. The reaction was monitored until alkyne ester **89** was consumed, which took about 5 days. Product enyne **88** was isolated *via* chromatography in 54%.

At this time, the moderate yield of this transesterification method prompted us to look at other possible reactions. However, as we became aware of the stereoselectivity of CAL-B, we returned to the reaction product and measured its optical rotation. Interestingly, the product enyne was found to have some optical activity, with $[\alpha]_D$ –1.7 (*c* = 1.25, CH_2Cl_2). Examination of the literature however,[86] revealed that CAL-B would have preference for the transesterification of the (*R*)-enantiomer of the alcohol **93** and that therefore it was likely that the product was in fact (*R*)-enriched enyne **88** (Scheme 64).



Scheme 64. *Reagents and conditions:* i) CAL-B (10% *w/w*), 40 °C, 5 d, 54%

Inversion of the product enyne stereochemistry with a Mitsunobu reaction, which had been successful for (*R*)-alcohol **93** (see Section 2.2.6), would not be possible in this case and therefore this CAL-B transesterification would be of no use in our synthesis of (*S*)-zearalenone (**3**). This was confirmed by the reaction of *S*-alcohol **93** with alkyne ester **89** under identical conditions, which yielded only starting materials (Scheme 65). An alternative transesterification procedure was definitely necessary.

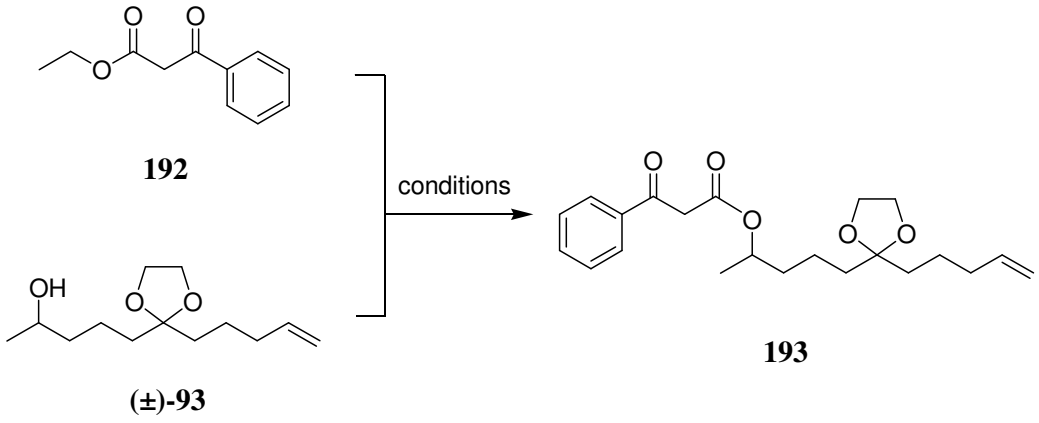


Scheme 65. *Reagents and conditions:* i) CALB (10% *w/w*), 40 °C, 5 d.

These results however, led to the successful kinetic resolution of (±)-alcohol **93** described in section 2.2.4.

2.4.1.2 Transition Metal Mediated Transesterifications

Transition metal catalysed transesterifications are well described in the literature.[110, 111] Two known protocols were screened and compared, employing (±)-alcohol **93** and a substitute β-keto ester, ethyl benzoylacetate (**192**), to give product ester **193** (Scheme 66, Table 7).



Scheme 66. *Transesterification Model Study.*

Entry	*Reagent*	*Conditions*	*Yield* **193**[†]
1	$Ti(OiPr)_4$ (10 mol%)	140 Torr, PhMe, 80 °C, 18 h	0%
2	Zn dust (10 mol%)	PhMe, 110 °C, 1.5 h[*]	15%[*]
3	Zn dust (20 mol%)	PhMe, 110 °C, 18 h[*]	64%

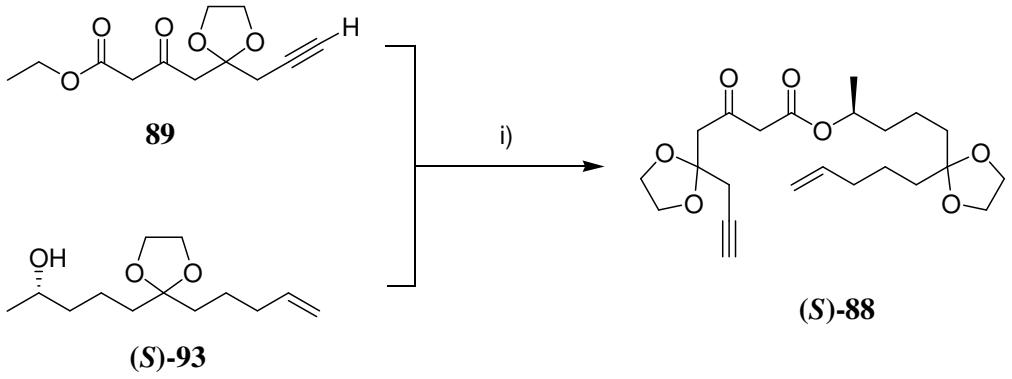
Table 7

[†] isolated product yields; [*] reaction carried out under a distillation condenser.

Firstly, according to Krasik's procedure,[110] (±)-alcohol **93** and β-keto ester **192** were treated neat with catalytic titanium *iso*propoxide at 80 °C and 140 Torr. However, after 18 h only starting material remained and no product could be detected (Table 7, Entry 1).

Secondly, according to the procedure of Bandgar and Uppalla,[111] (±)-alcohol **93** and β-keto ester **192** were treated with catalytic zinc dust in toluene at 110 °C at atmospheric pressure, under a distillation condenser to remove the alcohol by-product. This time a new product was isolated (Entry 2). Extending the reaction time and increasing the amount of catalyst (Entry 3) enabled the desired product **193** to be isolated by chromatography in 64% yield.

With this result, the zinc-mediated transesterification was attempted on our real system, employing (*S*)-alcohol **93** and alkyne ester **89**. Gratifyingly, despite initial difficulties in separating product (*S*)-enyne **88** from starting alkyne ester **89**, it was possible to optimise the conditions and obtain (*S*)-enyne **88** in 68% yield using 2.5 equivalents of (*S*)-alcohol **93**. The product optical activity was measured as $[\alpha]_D^{25}$ +2.9 (*c* = 1.10 CH_2Cl_2). Furthermore, we were able to recover the excess equivalents of (*S*)-alcohol **93** with undiminished optical purity (Scheme 67).

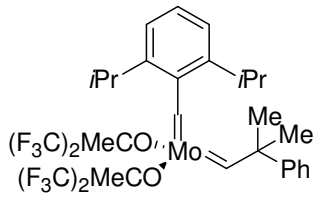


Scheme 67. *Reagents and conditions:* i) Zn dust (20 mol%), PhMe, 110 °C, 18 h, 68%.

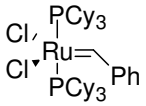
With (*S*)-enyne **88** in hand, the next step was to investigate the ring-closing enyne metathesis (RCEYM).

2.4.2 Ring-closing Enyne Metathesis (RCEYM)

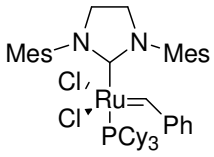
Ring-closing metathesis (RCM) is an extremely powerful carbon-carbon bond forming synthetic tool. Molybdenum or ruthenium carbene catalysts for olefin metathesis have been pioneered by Schrock *et al.*[112] and Grubbs *et al.*[113] respectively, with further developments leading to increasingly robust and reactive catalysts, as exemplified in Figure 16. RCM has found increasing use as a key step for the total synthesis of many polyfunctional natural products.[114-117]



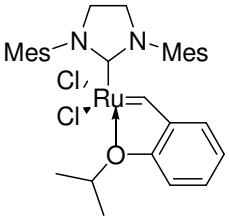
194



195



196



197

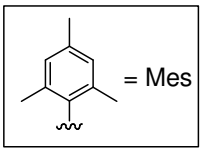
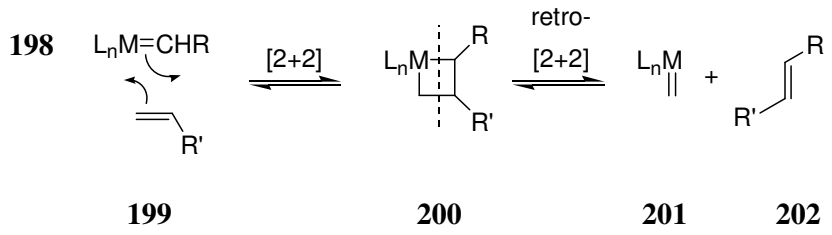


Figure 16. *Metathesis Catalysts: Schrock's Catalyst* **194**, *Grubbs' First Generation Catalyst* **195**, *Grubbs' Second Generation Catalyst* **196**, *Hoveyda-Grubbs' Second Generation Catalyst* **197**.

The Chauvin[118] mechanism of olefin metathesis proceeds *via* the cycloaddition of the active metallocarbene catalyst **198** with the olefin **199** to produce a metallocyclobutane intermediate, such as **200**. This then cycloreverts into a new olefin **202** and a new metallocarbene **201**, which can continue the catalytic cycle (Scheme 68). All steps of the reaction are reversible.[119-121]



Scheme 68. *Mechanism of Olefin Metathesis.*[118, 120]

RCEYM, utilising Grubbs' second generation catalyst (**196**) (Figure 16) under mild reaction conditions, was demonstrated by Kinoshita and Mori to generate conjugated dienes.[122] RCEYM involves cleavage of both double and triple bonds, with the formation of two new double bonds. In the case of macrocyclic RCEYM there are two potential products from an enyne **203**, the *exo*-mode product **202** or the *endo*-mode product **204**. The mode of selectivity also dictates the ring size that is formed, with *endo*-mode products having one additional carbon in the ring compared with products derived from *exo*-mode closure (Figure 17).

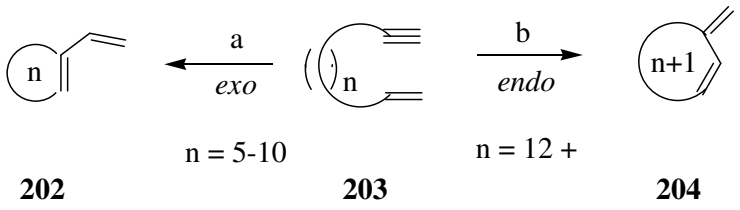
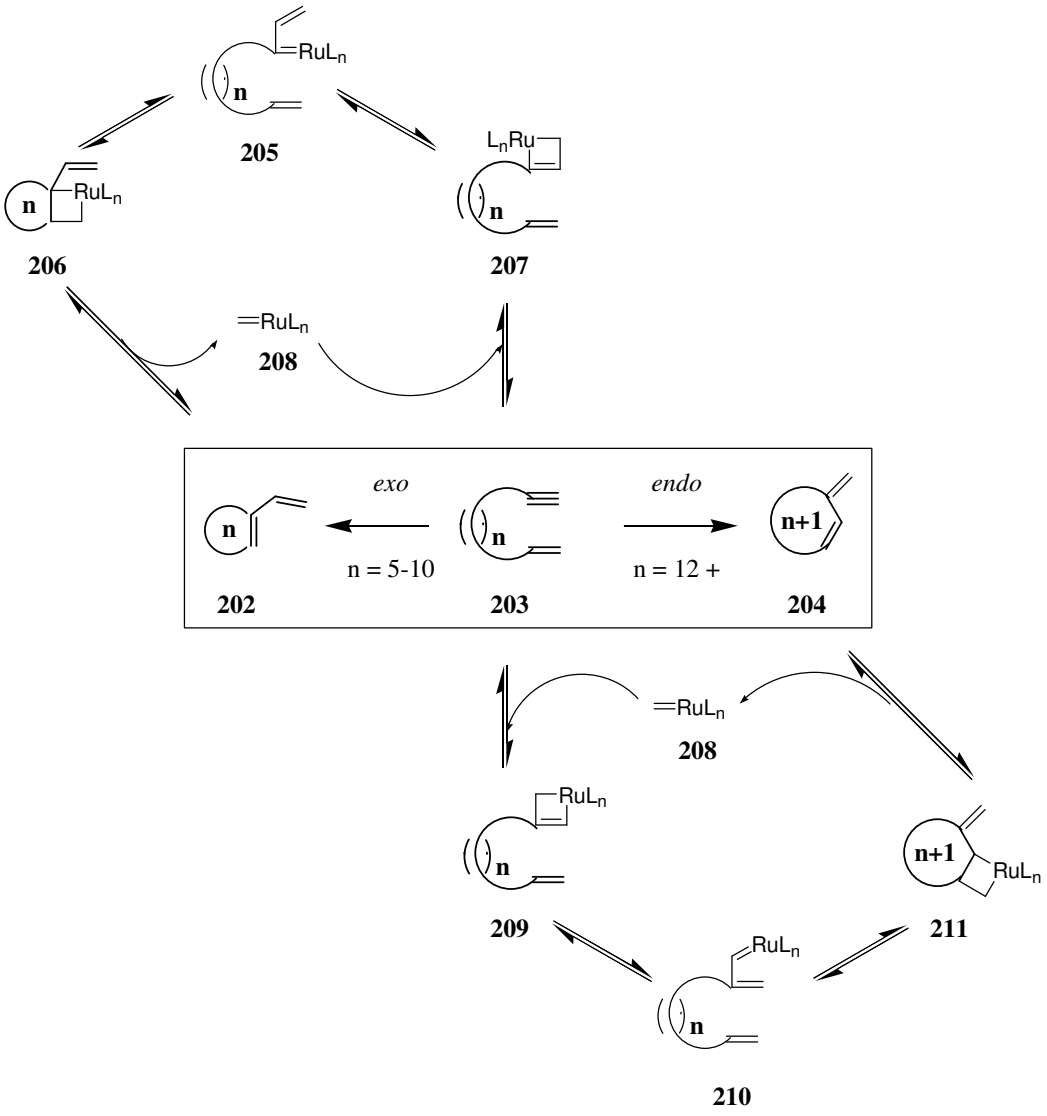


Figure 17. *Exo/endo-mode Selectivity in RCEYM*

RCEYM has been examined extensively by Hansen and Lee[123] for 10- to 15-membered macrocycles. Their findings imply that 12-membered rings or larger have a preference for forming *endo*-mode products, whereas adversely 10-membered rings or smaller prefer to form *exo*-mode products. Hansen and Lee went on to examine in detail the mechanism of RCEYM, in an attempt to explain the observed selectivity switch.

The fundamental mechanistic consideration of RCEYM is whether it is the alkyne or the alkene moiety of the enyne substrate which first reacts with the catalyst. The catalytic cycles of both of these possible mechanisms will now be discussed.

Mechanism A, the –yne before –ene mechanism, shows initial formation of metallocyclobutenes **207** or **209** by reaction of the active catalyst **208** with the alkyne moiety of enyne **203**. Metallocyclobutenes **207** or **209** then decompose to give intermediates **205** or **210**, which then react with the alkene moiety to generate *exo*- or *endo*-mode products **202** or **204**, *via* metallocyclobutanes **206** or **211** respectively (Scheme 69).

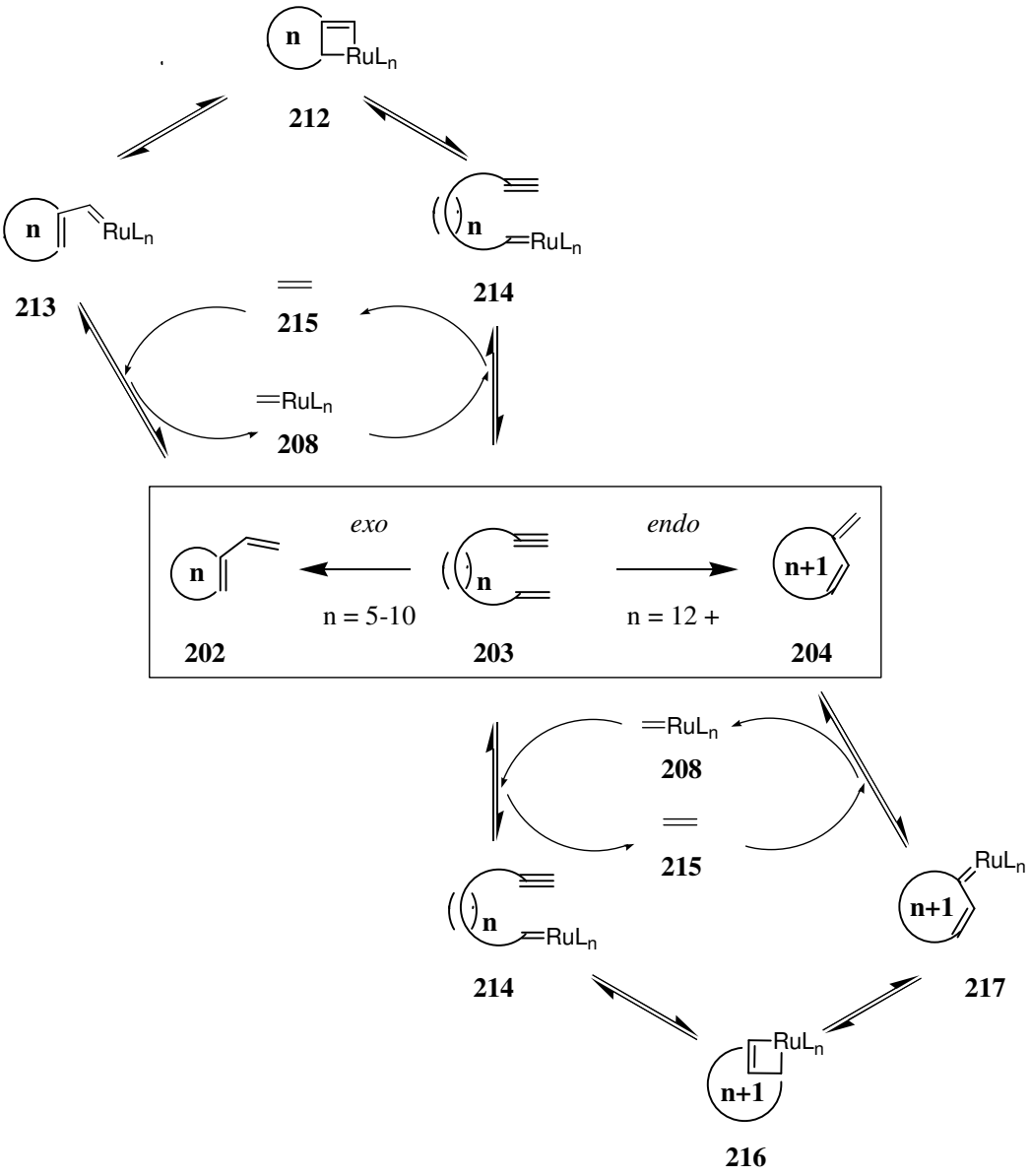


Scheme 69. *Proposed Mechanism A for RCEYM: -yne Before -ene.*

The difference in product selectivity following this mechanism would therefore be governed by the alignment of the alkyne moiety with the active catalyst **208** for the initial [2+2] cycloaddition, forming metallocyclobutenes **207** or **209**. As this process is reversible, there is no obvious reason how the size of the ring could cause a sudden

reversal in mode of selectivity and a statistical mixture of products would be expected.

Mechanism B, the –ene before –yne mechanism, shows the initial reaction occurring with the alkene moiety forming metallocarbene **214**. This then reacts with the alkyne moiety to generate one of the metallacyclobutene intermediates, **212** or **216**. Opening to metallocarbenes **213 or 217** and recombination with ethylene (**215**) generates the *exo*- or *endo*-mode products **202** or **204** (Scheme 70).

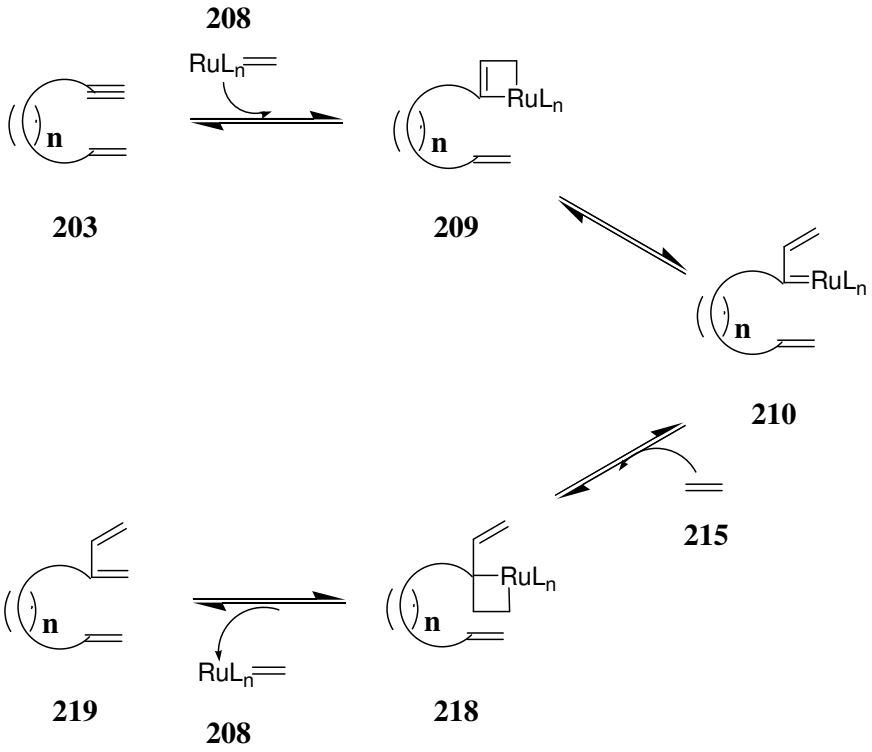


Scheme 70. *Proposed Mechanism B for RCEYM: -ene before -yne.*

The *exo/endo*-mode selectivity, following this mechanism, would arise from the intramolecular alignment of the alkyne moiety with the metallocarbene moiety of intermediate **214**, for the [2+2] cycloaddition to provide either metallocyclobutene **212** or **216**. This could be explained as a consequence of ring strain associated with intermediates, **212** or **216**, which would be influenced by the tether length.[124]

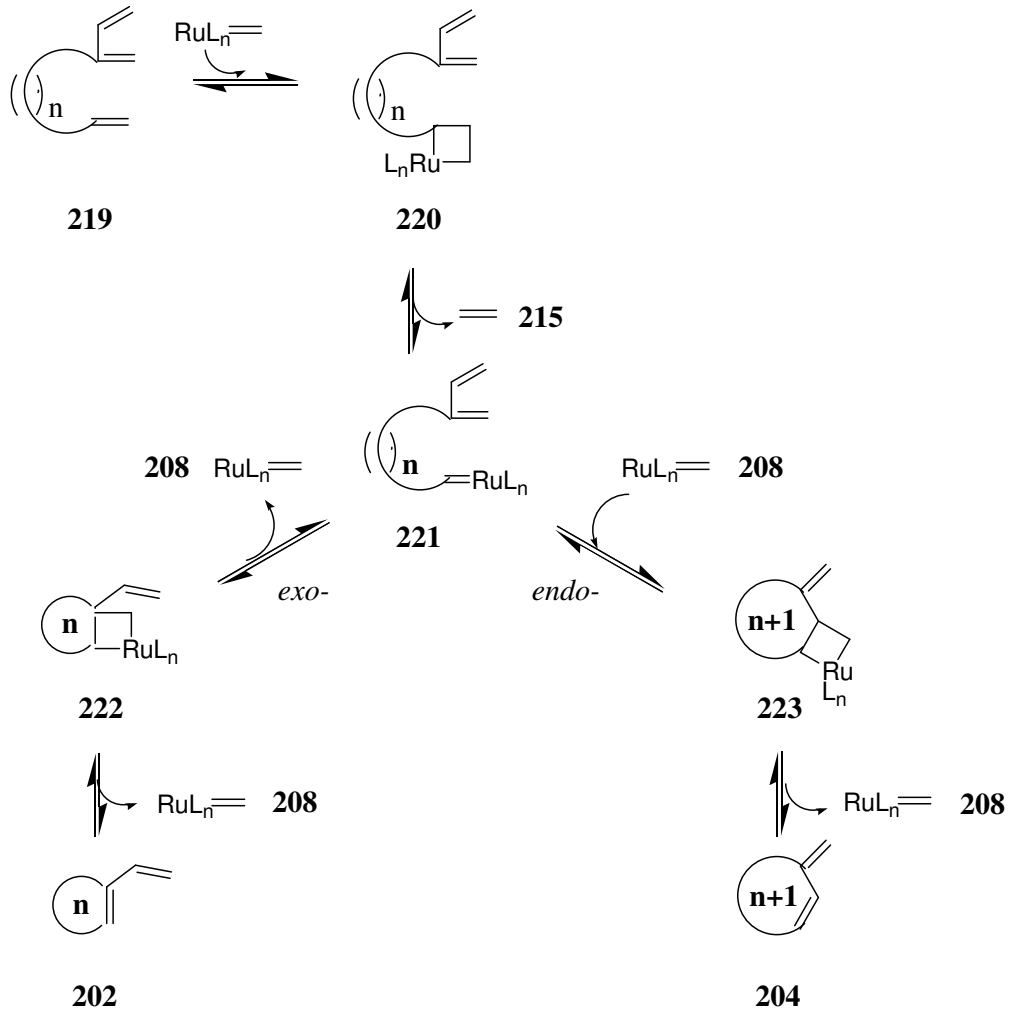
An improved reaction protocol for RCEYM was published by Mori and co-workers in the late 1990s and involved performing the reaction under an atmosphere of ethylene gas.[125] The excess ethylene present forces a different mechanism (Scheme 71 and Scheme 72).[124, 126, 127]

As a result of the relatively slow macrocyclic ring-closure rate, RCEYM in the presence of ethylene gas is dominated by the cross-metathesis (CM) of the alkyne moiety and ethylene (**215**). Initial reaction of the alkyne with the active catalyst **208** occurs similarly to that discussed in Mechanism A, forming intermediate metallocarbene **210**. However, in the presence of ethylene (**215**), metallocarbene **210** then undergoes a cycloaddition-retrocycloaddition to form triene **219** (Scheme 71).



Scheme 71. *Possible Mechanism of Ethylene Catalysed RCEYM Step One: CM*

Triene **219** is a substrate for RCM, hence removal of ethylene by flushing with an inert atmosphere and addition of further catalyst **196** allows RCM to occur to form the product diene **202** or **204** (Scheme 72).



Scheme 72. *Possible Mechanism of Ethylene Catalysed RCEYM Step Two: RCM*

Reaction of active catalyst **208** with the alkene portion of triene **219** would form metallocarbene **221**, through metallocyclobutane **220**. There would now be a choice of two alkenes for the metallocarbene moiety to react intramolecularly with. Thus, depending on whether the proximal or distal double bond of the 1,3-diene moiety underwent RCM, the *exo*- or *endo*-mode products **202** or **204** would be produced, through intermediates **222** or **223**.

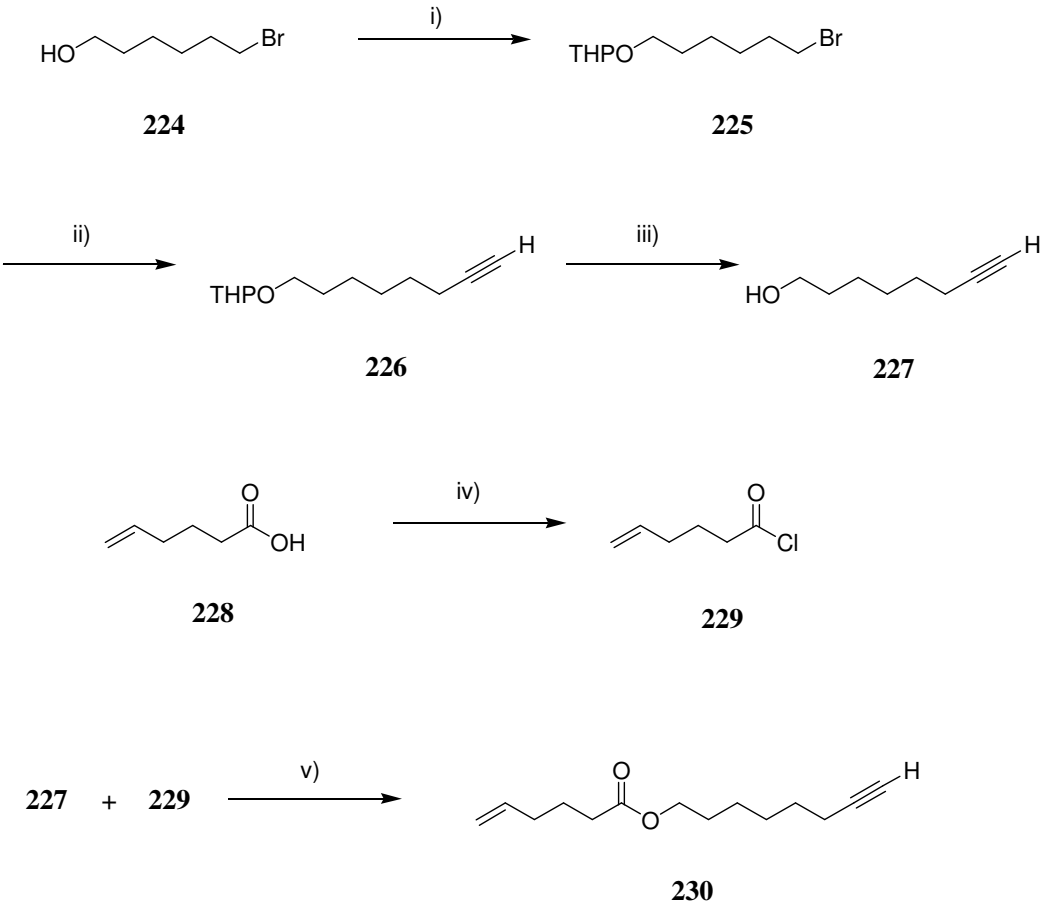
Although all steps in a metathesis mechanism are reversible, catalyst **196** is reported to be sensitive towards steric and stereoelectronic factors. Therefore, the almost exclusive selectivity for *endo*-mode products for the RCEYM of large ring macrocycles in the presence of ethylene can be explained by the least sterically demanding, isolated double bond reacting first.

As the first step in this procedure consumes one molecule of ethylene per cycle and the second step releases one molecule of ethylene per cycle, the overall net consumption is 0. Today, the majority of RCEYMs are carried out utilising ethylene, as a result of both the increased selectivity for the *endo*-mode product and also the greatly increased reaction rate.[124]

In our (*S*)-zearalenone (**3**) system, our target diene **87** has an *endo*-substitution pattern and a 14-membered ring, which suggests that the correct product selectivity should be favoured.

2.4.2.1 Model Study of RCEYM

Before attempting the RCEYM of our authentic substrate, we decided to carry out a simple model study on a similar sized 14-membered macrocycle in order to trial the reaction conditions. To this end, simple enyne **230** was prepared from commercial 6-bromo-1-hexanol (**224**) and 5-hexenoic acid (**228**) as shown in Scheme 73.

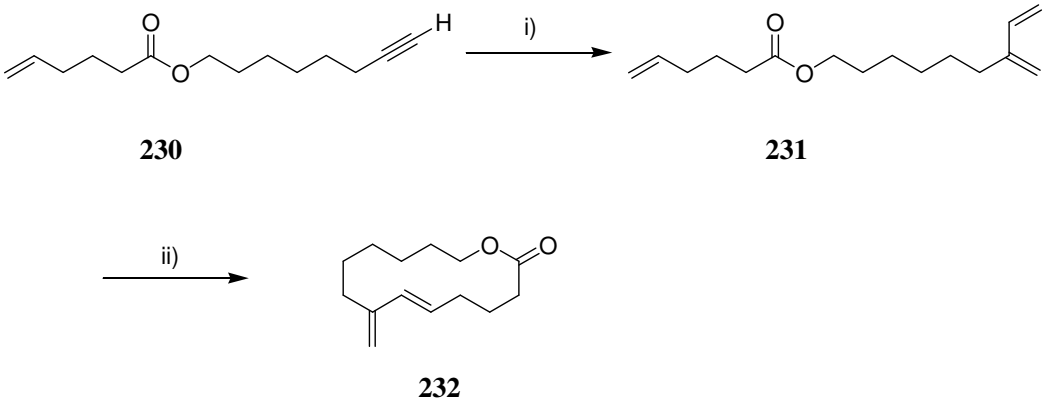


Scheme 73. *Reagents and Conditions:* i) DHP, PPTS, CH_2Cl_2, 23 °C, 18 h, 99%; ii) $LiC{\equiv}CH{\cdot}H_2N(CH_2)_2NH_2$, NaI, DMSO, 23 °C, 4 h, 80%; iii) *p*TSA, EtOH, 23 °C, 45 min, 99%; iv) $(COCl)_2$, DMF, CH_2Cl_2, 23 °C, 2 h; v) DIPEA (2.0 eq.), CH_2Cl_2, 23 °C, 18 h, 92%.

6-Bromo-1-hexanol (**224**) was protected as the THP-ether **225** and then coupled with lithium acetylide ethylene diamine complex following the procedure of Morimoto *et al.*[128] to form alkyne **226** in 80% yield. Deprotection proceeded quantitatively to give alcohol **227**. 5-Hexenoic acid (**228**) was converted to the acid chloride **229**[129] in quantitative yield following careful concentration. Esterification of acid chloride **229** with alcohol **227** in the presence of excess base gave 92% of enyne **230** after purification.

The RCEYM of enyne **230** was performed by bubbling ethylene gas through the CH_2Cl_2 solvent for 10 minutes prior to addition of Grubbs' second generation catalyst (**196**), then stirring the reaction under an atmosphere of ethylene (balloon) for 72 h.

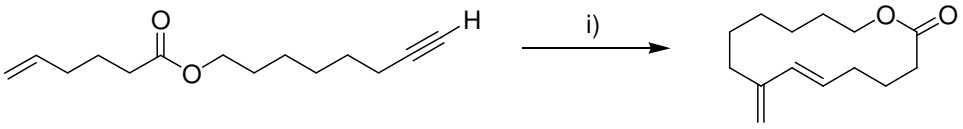
Promisingly, spot to spot conversion was observed by TLC and the product triene **231** was isolated *via* column chromatography in 77% yield. Refluxing triene **231** in CH_2Cl_2 with further catalyst under a nitrogen atmosphere for 48 h gave product macrocycle **232** in an excellent 98% yield (Scheme 74).



230 **231** **232**

Scheme 74. *Reagents and conditions:* i) 1 atm $CH_2{=}CH_{2\ (g)}$, Grubbs' II (**196**) (10 mol%), CH_2Cl_2, 23 °C, 72 h, 77%; ii) Grubbs' II (**196**) (10 mol%), CH_2Cl_2, 45 °C, 48 h, 98%.

A one-pot procedure was also successful. The conversion of enyne **230** to intermediate triene **231** was monitored by TLC. Once complete, the reaction was flushed with nitrogen and further Grubbs' second generation catalyst added. Heating to reflux allowed cyclised product **232** to be isolated in 62% yield (Scheme 75).

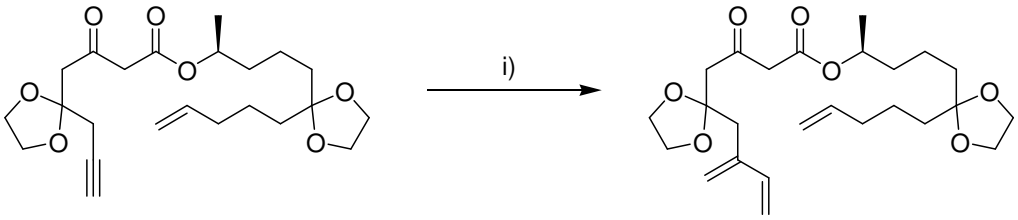


230 **232**

Scheme 75. *Reagents and conditions:* i) a) 1 atm $CH_2{=}CH_{2\ (g)}$, Grubbs' II (**196**) (10 mol%), CH_2Cl_2, 23 °C, 72 h; b) Grubbs' II (**196**) (10 mol%), $N_{2\ (g)}$, CH_2Cl_2, 45 °C, 18 h, 62%.

2.4.2.2 . RCEYM of Enyne **88**

Following this achievement, RCEYM of the genuine substrate was examined. Thus treatment of (*S*)-enyne **88** with Grubbs' second generation catalyst (**196**) in CH_2Cl_2 under an ethylene atmosphere yielded the predicted triene intermediate **233** in 72% yield, after 72 h (Scheme 76).

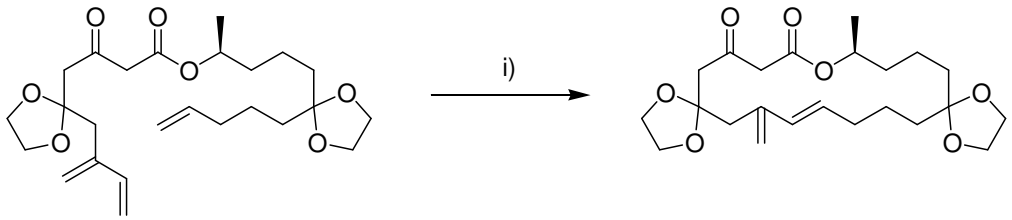


(*S*)-88 **233**

Scheme 76. *Reagents and conditions:* i) 1 atm $CH_2{=}CH_{2\ (g)}$, Grubbs' II (**196**) (10 mol%), CH_2Cl_2, 23 °C, 72 h, 72%.

As RCEYM is an intramolecular process, typically concentrations of ~1 mM are necessary. This means large quantities of solvents are necessary upon scale up. It was found that an efficient method to combat this was to use two syringe pumps, one adding a solution of catalyst and the other a solution of substrate, to the degassed solvent. The additions were carried out slowly over an 8-hour period. This allowed up to a hundred-fold increase in concentration without any observed cross-metathesis or intermolecular reactions.

To close the macrocycle, triene **233** was treated with Grubbs' second generation catalyst (**196**) in refluxing CH_2Cl_2 under a nitrogen atmosphere, however after 18 h a quantitative amount of starting material was recovered. Gratifyingly, changing solvent to toluene with its higher refluxing temperature and switching from a nitrogen to an argon atmosphere, enabled macrocyclic diene **87** to be isolated in an excellent 85% yield after 3 h at 120 °C (Scheme 77). A similar double-syringe pump set up as used previously was also employed, however this time with the additions to pre-heated toluene.



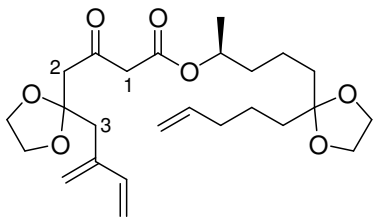
233 **87**

Scheme 77. *Reagents and conditions:* i) Grubbs' II (**196**) (10 mol%), PhMe, 120 °C, 3 h, 85%.

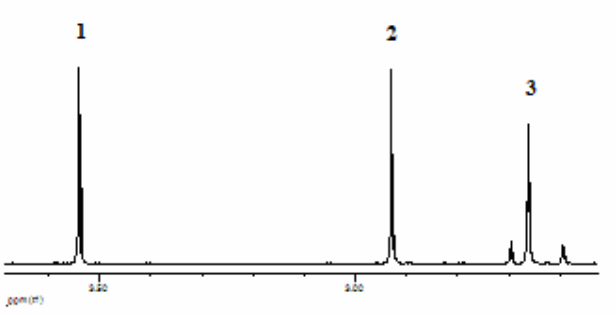
The alkene protons in the ring show a coupling constant of J = 15.4 Hz, which is consistent with *E*-geometry as hoped. There is no evidence of the *Z*-isomer and indeed it may be that the high refluxing temperature of toluene has allowed interconversion of these forms, so that the more thermodynamically stable *E*-isomer is the only product formed.

Another observation from ring-closure was the increased complexity of the ^{1}H NMR spectrum. For example, where previously the spectrum of triene **233** contained three singlet CH_2 peaks in the 2.5-3.5 region, there are now 12 peaks in this region of the spectrum for macrocyclic diene **87**. This can be attributed to the formation of one specific conformation of the product, in which the environments of the methylene protons is no longer equivalent. This allows the methylene protons to couple with each other and therefore what is observed is actually three AB quartets. The observed coupling constants of the methylene geminal protons are between 13 and 17 Hz (Figure 18).

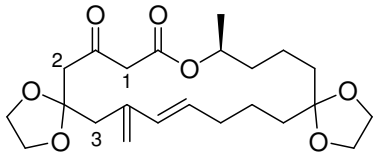
a)



233



b)



87

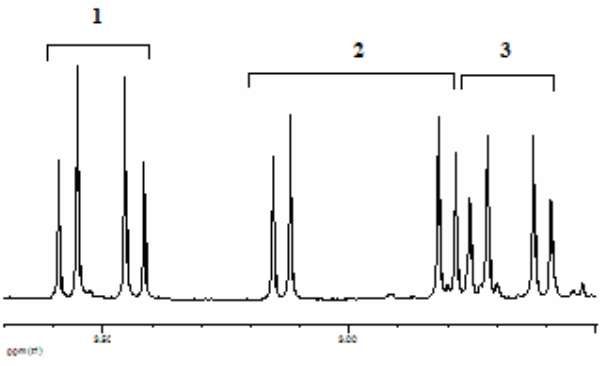


Figure 18. *a) Region of triene* **233** *^{1}H NMR spectrum showing methylene singlets; b) Same region of RCEYM product diene* **87** *spectrum showing the same methylenes splitting into AB quartets.*

A crude sketch of diene **87**, produced using a ChemDraw 3D* MM energy minimisation, can be used to show that the protons on each methylene are orientated either inside or outside the ring, which will cause a different chemical environment for each proton and hence inequivalence (Figure 19).

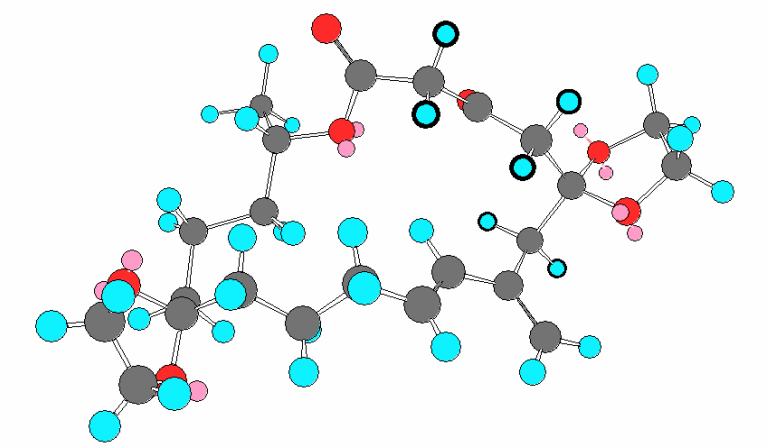
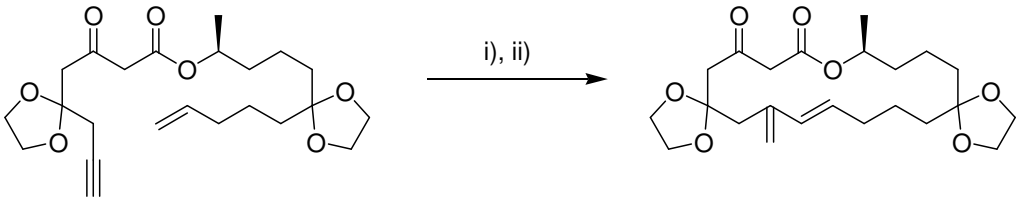


Figure 19. *ChemDraw 3D plot of Macrocycle* **87** *with 3 CH_2s highlighted.*

Building on the success of the two-step RCEYM method, investigations into a one-step procedure were begun. Firstly, enyne **88** was treated with Grubbs' second generation catalyst (**196**) in toluene under an atmosphere of ethylene for 72 h. Unfortunately, only starting material was isolated and no evidence of any new product could be detected. It was postulated that lack of reaction in this case was due to the lack of solubility of ethylene gas in toluene.

Changing to dichloroethane as a solvent consequently allowed spot to spot conversion to desired triene intermediate **233** to be observed after 18 h. Flushing the system with argon and heating to reflux (80 °C) promoted complete ring closure after a further 18 h, with an overall isolated yield of 86%. It was also possible to reduce the amount of catalyst to just 5 mol% (Scheme 78).

* Energy minimisation on basis of steric effects only, electronic effects not taken into consideration.



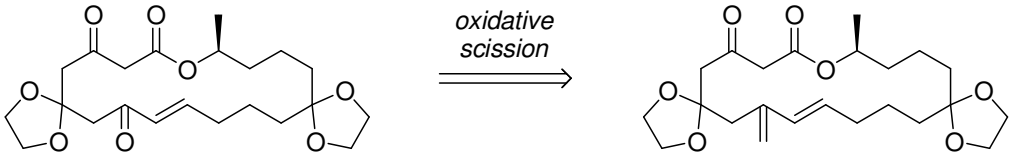
88 **87**

Scheme 78. *Reagents and conditions:* i) 1 atm $CH_2{=}CH_{2\ (g)}$, Grubbs' II (**196**) (5 mol%), $(CH_2Cl)_2$, 23 °C, 72 h; ii) Grubbs' II (**196**) (5 mol%), $(CH_2Cl)_2$, 80 °C, 18 h, 86% over two steps.

Thus the coupling of (*S*)-alcohol **93** and alkyne ester **89** had been achieved and the macrocycle of (*S*)-zearalenone (**3**) was in place. The next goal was the elaboration of the terminal alkene to a carbonyl, *via* selective oxidative scission. This topic will be discussed in the next section.

2.5 Investigations into Selective Oxidative Cleavage of Diene **87**

Disconnection of (*S*)-zearalenone (**3**) (see Scheme 20) gave diketone **86** as a precursor to the natural product. Disconnection to diene **87** is possible *via* selective oxidative cleavage of the *exo*-cyclic double bond (Scheme 79). Strategies towards this transformation will be explored in this section.



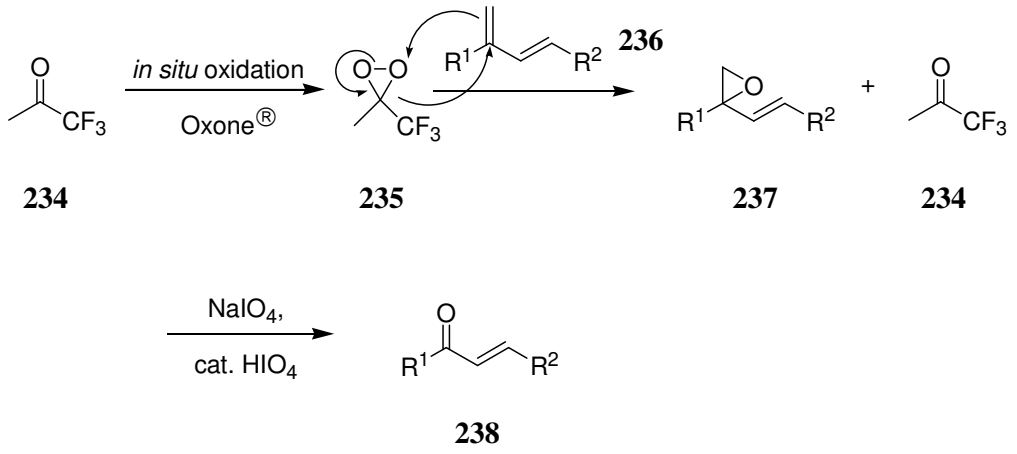
86 **87**

Scheme 79. *Retrosynthetic Analysis of Diketone* **86**.

2.5.1 Oxidative Cleavage by Epoxidation

Literature examples of selective oxidative scissions of conjugated dienes remain scarce. Our initial proposed method involved the use of a DMDO-like dioxirane oxidant to perform a mono-epoxidation, followed by cleavage of the crude product with sodium periodate, catalysed by periodic acid.

Dioxiranes react with both electron-poor and electron-rich alkenes under mild, neutral conditions. Methyl(trifluoromethyl)dioxirane (**235**) has one of the highest reactivities of dioxiranes known, hence was chosen for our first studies.[130] Dioxirane **235** is usually generated *in situ* from ketone **234**, and Oxone® with the use of $NaHCO_3$ to maintain constant pH. During the reaction, an oxygen atom is transferred from dioxirane **235** to the substrate **236**, regenerating the ketone **234** at the same time as producing the epoxide **237**. This allows catalytic amounts of the dioxirane to be sufficient for the transformation. Cleavage of epoxide **237** with sodium periodate generates α,β-unsaturated ketone **238** (Scheme 80).



Scheme 80. *Proposed use of Methyl(trifluoromethyl)dioxirane* **235** *for Selective Oxidative Cleavage.*

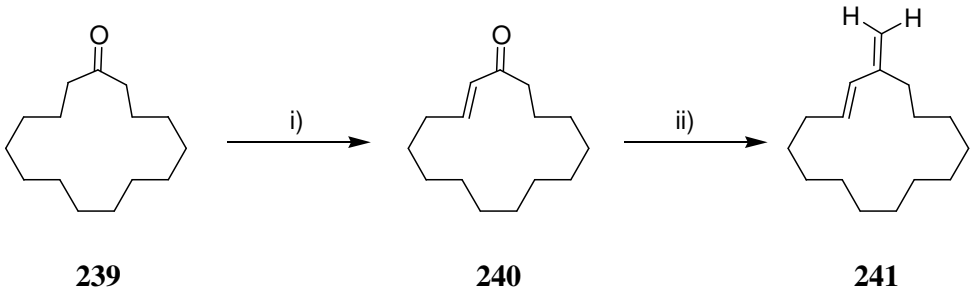
Epoxidations of alkenes are usually governed by electronic factors, with electrophilic reagents used to carry out the transformations. This means that more electron rich alkenes, such as those with more alkyl-substituents, are usually epoxidised preferentially. In the case of macrocyclic diene **87**, both alkene groups have two substituents, the only difference being the substitution pattern (Figure 20). This suggests that the electronics will be similar and that selectivity may be a problem.

Figure 20. *a) disubstituted terminal alkene; b) E-alkene*

With this concern in mind, it was decided to perform a simple model study on a macrocyclic conjugated diene to test the reaction scope.

2.5.1.1 Model Study for the Selective Oxidative Cleavage

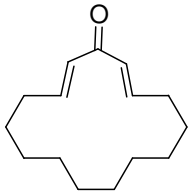
A model study employing commercial 15-membered ring cyclopentadecanone (**239**) was devised. Dehydrogenation adjacent to the carbonyl would provide cyclopentadec-2-enone (**240**), which would undergo olefination by the Petasis reagent to form diene **241**. This would form our model substrate for cleavage. This reaction sequence was carried out as depicted in Scheme 81.



239 **240** **241**

Scheme 81. *Reagent and conditions:* i) IBX (1.8 eq.), DMSO : fluorobenzene 7 : 1, 65 °C, 18 h, 51%; ii) Cp_2TiMe_2 (0.33 M in PhMe), 75 °C, 4 h, 74%.

The dehydrogenation[131] was performed using IBX (generated from 2-iodobenzoic acid and Oxone® according to the procedure of Frigerio *et al.*[132]) and gave 51% of the desired *trans*-enone **240**, along with 30% starting material and 9% of the over-oxidised diene **242** (Figure 21).

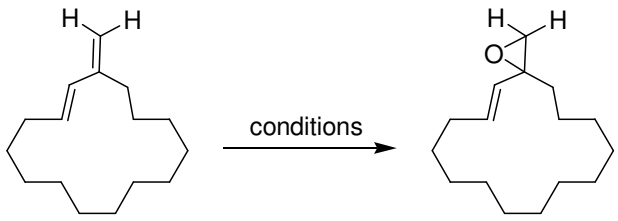


242

Figure 21. *Over-oxidation Product* **242**.

Next the olefination was carried out using the Petasis reagent, Cp_2TiMe_2,[133, 134] formed in 94% yield from treatment of Cp_2TiCl_2 with methyl lithium in toluene at 0 °C.[135] The reagent was not isolated, but stored and utilised as a deep red 0.33 M solution in toluene. The precise molarity was calculated from integration of the ^{1}H NMR spectrum. The olefination proceeded to give diene **241** in 74% yield (Scheme 81).

With model diene **241** in hand, studies commenced into the mono-epoxidation (Scheme 82). Initially, investigations into the required equivalents of 1,1,1-trifluoroacetone (**234**) and Oxone® were carried out and products identified by GC-MS monitoring. Table 8 summarises the GC results for the first set of experiments carried out.



241 **243**

Scheme 82. *Mono-epoxidation of Diene* **241**

Entry	*CF_3COCH_3*[†]	*Oxone®*	*Time*	*S.M.*[*]	*Product*[*]	*other unknown products*[*]
1	0.5 eq.	0.5 eq.	1 h	90%	10%	-
2	0.5 eq.	0.5 eq.	4 h	73%	15%	-
3	1.0 eq.	1.0 eq.	2 h	10%	77%	1 other product.
4	1.0 eq.	1.0 eq.	4 h	<2%	64%	3 other products.
5	1.2 eq.	1.2 eq.	6 h	0%	56%	3 other products.

Table 8

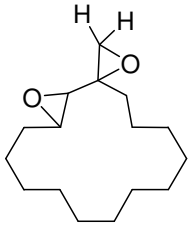
[†]*Reagent and conditions:* i) CF_3COCH_3, Oxone®, $NaHCO_3$, CH_3CN, aq. Na_2·EDTA 10^{-4} M, 0 °C, time;

[*] yields determined by GC analysis.

The GC results indicated that sub-stoichiometric equivalents of 1,1,1-trifluoroacetone and Oxone® allowed clean conversion to one product with the correct mass for a mono epoxide (Table 8, Entry 1). Extended reaction times did not show other products (Entry 2). With stoichiometric quantities of reagents, however, by-products were observed, with increasing reaction times resulting in further by-products (Entries 3 and 4). Excess reagents encouraged complete starting material consumption, however resulted in lower product yield by GC (Entry 5).

These results indicated that the best conditions for mono-epoxidation would be with stoichiometric quantities of 1,1,1-trifluoroacetone and Oxone® and reaction times of ~2 h. At this time however, it was not certain which monoepoxide had formed, or if both were present.

A sample reaction was carried out (Scheme 82), using the optimal conditions, and this time worked-up and the products separated by column chromatography on silica gel. Inspection of the alkene signals in the ^{1}HNMR spectra indicated that the isolated monoepoxide (15% yield) was the desired regioisomer **243**. Diepoxide by-product **244** (Figure 22) was also identified in 4% yield, although no other products or starting material were recovered. The low yields and overall mass recovery suggested instability to silica.

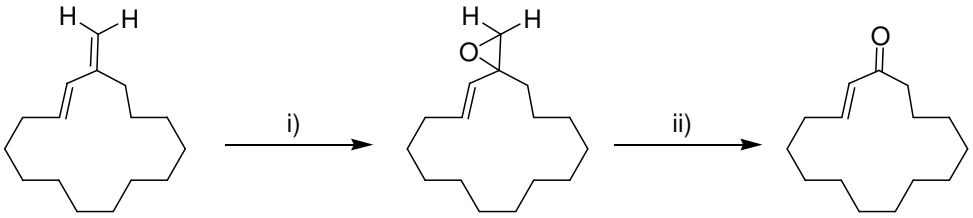


244

Figure 22. *Diepoxide side product.*

It was resolved to try the oxidative cleavage of the crude mixture of monoepoxide **243**, diepoxide **244** and other products, in order to try and isolate product enone **240** and thus obtain a realistic overall yield for the two-step process. The epoxidation was carried out as before but this time the crude reaction mixture was treated with sodium periodate and catalytic periodic acid.[136]

The epoxidation of diene **241** on a 20 mg scale gave 90% of the desired monoepoxide **243** by GC and to our delight, after periodate cleavage desired enone **240** was isolated by silica gel chromatography in an excellent overall 77% yield (Scheme 83). This process was repeated to give 81% and 83% overall yields respectively of the oxidative cleavage on scales of 66 mg and 360 mg.



241 **243** **240**

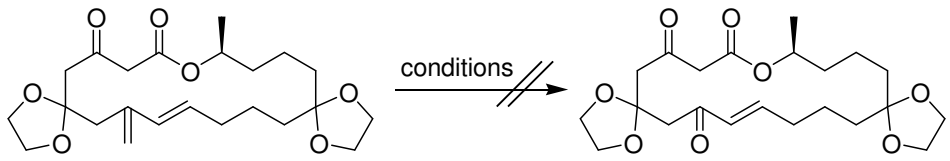
Scheme 83. *Reagent and conditions:* i) CF_3COCH_3, Oxone®, $NaHCO_3$, CH_3CN, aq. Na_2·EDTA 10^{-4} M, 0 °C, 2 h; ii) $NaIO_4$, cat. HIO_4, *t*-BuOH : H_2O : THF, 45: 45 : 10, 23 °C, 4 h, 83% over two steps.

These excellent results gave us confidence to apply our reaction protocol to the real (*S*)-zearalenone (**3**) system.

2.5.1.2 Selective Oxidative Cleavage of the Real (S)-Zearalenone (**3**) *System*

The success of our model study was encouraging, although we remained aware that the real (*S*)-zearalenone (**3**) system was more complicated. Therefore additional factors, such as electronic effects, could play a role in deciding this reaction outcome.

The reaction conditions employed in the model study, along with a variety of modified conditions, were attempted on the authentic substrate **87** (Scheme 84) and the initial results are shown in Table 9.



87 **86**

Scheme 84. *Oxidative Scission Investigations.*

Entry	*Ketone (eq.)*[†]	*Buffer*	*Crude Mass Recovery*	*Product Step i)*[*]	*Product Step ii)*[*]
1	**234** (1.0)	$NaHCO_3$	29%	S.M. monoepoxide diepoxide	Decomposition.
2	**234** (1.0) Stock solution	$NaHCO_3$	90%	S.M. monoepoxide diepoxide	Decomposition.
3	**245** (0.04)	K_2CO_3	53%	S.M.	-
4	**234** (2.0)	K_2CO_3	88%	monoepoxide (major product)	Decomposition.

Table 9

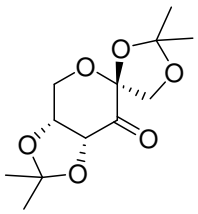
[†]*Reagents and conditions:* i) ketone, Oxone® (1.0 eq.), buffer (5.0 eq.), CH_3CN, aq. Na_2·EDTA 10^{-4} M, 0 °C, 2 h; ii) $NaIO_4$, cat. HIO_4, *t*-BuOH : H_2O : THF, 45: 45 : 10, 23 °C, 4 h;

[*] products determined by MS analysis.

The first attempted mono-epoxidation used the same conditions which had previously been successful in the model study. Whereas promisingly the correct mass for the monoepoxide was found by MS, (along with smaller peaks for starting material and the diepoxide) the crude mass recovery was low. Upon treatment of the crude product with sodium periodate and periodic acid no desired enone **86** was found by MS (Table 9, Entry 1).

To control more precisely the equivalents of dioxirane, the reaction was repeated utilising a stock solution of 1,1,1-trifluoroacetone **234**. Ketone **234** has a low boiling point and even with a precooled syringe it had proven difficult to measure precisely the minimal quantities required on this scale. A 1 M solution of ketone **234** in acetonitrile was used. As a result the crude mass recovery was much better (Entry 2), however once again no product was observed from sodium periodate treatment.

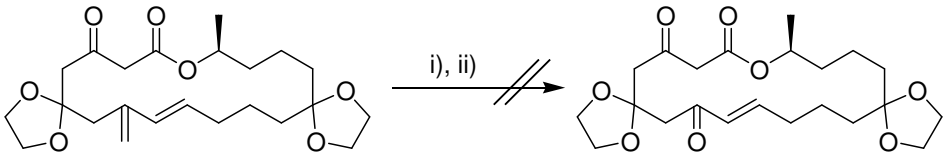
The Shi catalyst (**245**, Figure 23) catalyses selective epoxidations upon slow addition of a stoichiometric amount of Oxone® to generate the active dioxirane.[137] This procedure was attempted on diene **87** with the hope that this bulky epoxidant may be more selective for the least hindered alkene, which could be the terminal alkene. Unfortunately, although the reaction looked much cleaner by TLC, no desired epoxidation product was observed in the MS spectrum and only starting material was recovered (Entry 3).



245

Figure 23. *Shi's catalyst.*[137]

Finally, using the Shi reaction protocol with an excess of ketone **234** gratifyingly gave a good mass recovery and mainly the monoepoxide product by MS. Unfortunately, again sodium periodate cleavage failed to produce product **86** (Entry 4). At this point it appeared that the mono-epoxidation strategy for selective oxidative cleavage of the authentic substrate **87** would not work (Scheme 85).



87 **86**

Scheme 85. *Reagents and conditions:* i) **234**, Oxone®, buffer, CH_3CN, aq. Na_2·EDTA 10^{-4} M, 0 °C, 2h; ii) $NaIO_4$, cat. HIO_4, *t*-BuOH : H_2O : THF, 45: 45 : 10, 23 °C, 4 h.

The conclusions which could be drawn from this work are that either a) the wrong epoxide is forming, which is leading to decomposition under the cleavage conditions; b) the periodate conditions are leading to side reactions and decomposition or c) enone **86** is unstable and decomposing spontaneously.

If the wrong epoxide is forming preferentially, it may be difficult to find any reagent which will epoxidise the desired alkene selectively. This may be due to steric hindrance of the ketal group or the electron-withdrawing effect of the nearby oxygen atom in macrocyclic diene **87** (Figure 24).

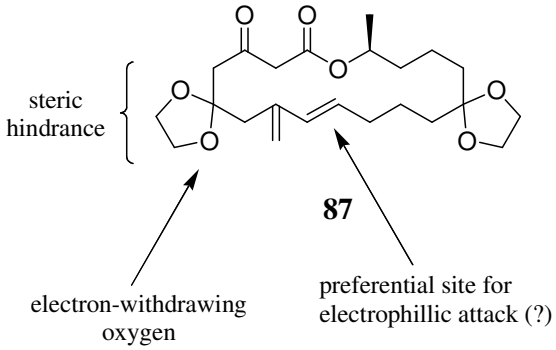
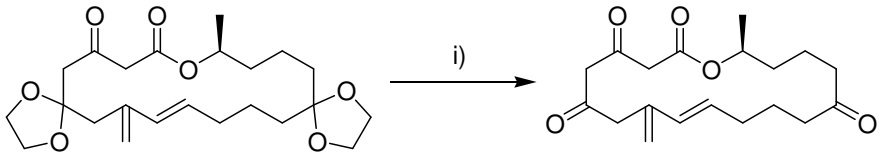


Figure 24. *Potential Selectivity issues of Mono-epoxidation of Macrocyclic Diene* **87**.

It was proposed that the steric bulk could be reduced by deprotecting the ketal group. This was attempted on a 10 mg scale with 90% acetic acid, however TLC and MS indicated a mixture of starting material and mono-deprotection, as well as desired product **246** (MS (CI) *m/z* 334 $[M+H]^+$, 352 $[M+NH_4]^+$) (Scheme 86).



87 **246**

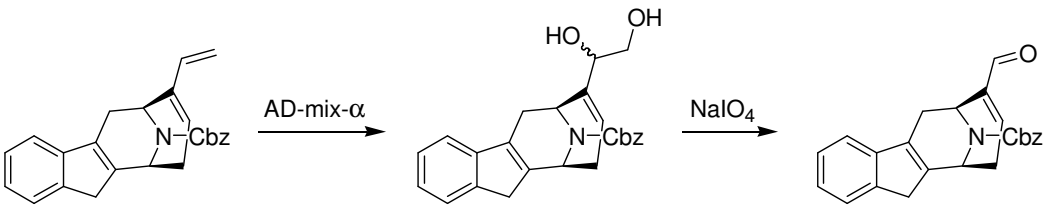
Scheme 86. *Reagents and conditions:* i) 90% AcOH, 40 °C, 72 h, mixture of products.

An alternative method of cleavage to epoxidation was sought.

2.5.2 Oxidative Cleavage by Dihydroxylation

An alternative strategy for the oxidative scission of an alkene is the cleavage of a 1,2-diol, formed from dihydroxylation, which is usually carried out with osmium catalysis. Literature searches revealed a couple of examples of selective dihydroxylations of conjugated dienes, which had been generated by enyne metathesis.[138, 139] In both cases the terminal alkene was selectively dihydroxylated in the presence of the more substituted, electron-rich double bond.

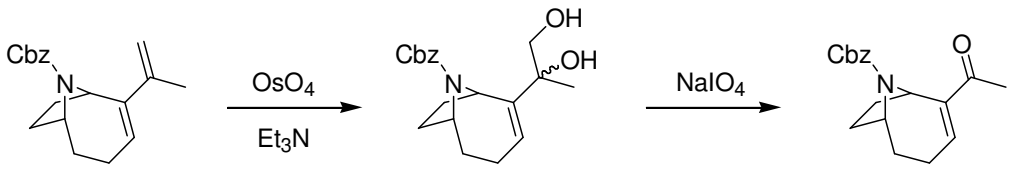
The first example was from a publication by Neipp and Martin,[138] who formed aldehyde **249** in 54% yield from diene **247**, *via* diol **248**. AD-mix-α, which is catalytic in osmium, was used for the selective dihydroxylation. (Scheme 87).



247 **248** **249**

Scheme 87. *Neipp and Martin's Selective Oxidative Cleavage of Diene* **247**.

The second example used stoichiometric osmium tetroxide for the dihydroxylation, with triethylamine as a tertiary amine ligand to accelerate the reaction. The desired diol **251** was isolated in 76% yield from diene **250**, along with 13% of the undesired diol. Cleavage with sodium periodate proceeded to give ketone **252** (Scheme 88).[139]



250 **251** **252**

Scheme 88. *Selective Oxidative Cleavage of Diene* **250**.

The second system is similar to diene **87**, in that both alkenes are disubstituted. However there is clearly still less bulk around the terminal alkene compared to the (*S*)-zearalenone (**3**) system and in addition the second alkene geometry is *cis*, whereas in diene **87** it is *trans*.

Sharpless *et al.* reported the order of reactivity towards alkene dihydroxylation in the absence of a ligand to be that shown in Figure 25.[140] This would suggest that dihydroxylation of the required terminal alkene is less favoured than that of the *E*-alkene inside the ring. This would also explain why in the two examples discussed, terminal alkenes such as c) are dihydroxylated faster than the *Z*-alkenes b).

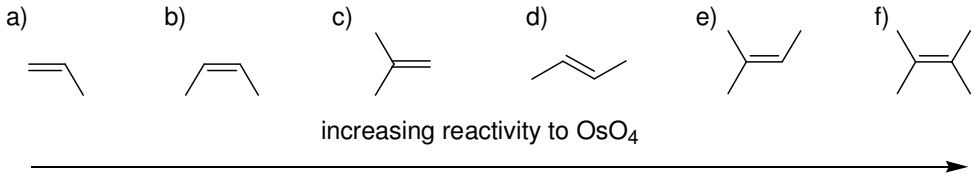
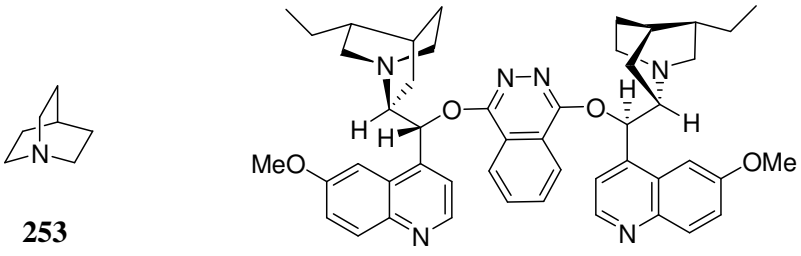


Figure 25. *Order of reactivity of alkenes to dihydroxylation with OsO_4*

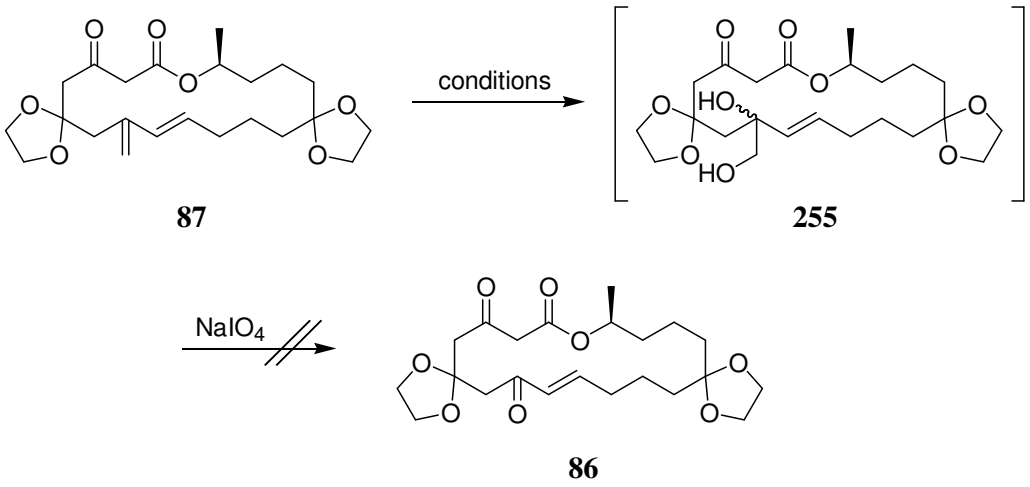
Sharpless also proved that the effects of adding tertiary amine ligands (Figure 26), are an increase in the reaction rate (quinuclidine (**253**) : ~200 fold; $(DHQ)_2PHAL$ (**254**), the ligand in AD-mix-α : ~1400 fold) and an increase in selectivity. The precise tertiary amine ligand used with osmium tetroxide was shown to have an effect on the reaction rates with different alkene geometries.



253 **254**

Figure 26. *Tertiary amine ligands.*

The reaction of diene **87** with osmium tetroxide in the presence of different amine ligands was investigated (Scheme 89, Table 10.)



87 **255** **86**

Scheme 89. *Oxidative Scission by Dihydroxylation.*

Entry	*Reagents and conditions i)*	*Product from Step i)*[†]	*Product from $NaIO_4$ cleavage*[†,*]
1	OsO_4 (1.0 eq.), Et_3N, *t*-BuOH, THF, –78 °C to 23 °C, 18 h	Mono-diol (major product)	Decomposition.
2	OsO_4 (1.0 eq.), quinuclidine (**253**), *t*-BuOH, THF, –78 °C to 23 °C, 18 h	Mono-diol (major product)	Decomposition.
3	AD-mix-α, $MeSO_2NH_2$, *t*-BuOH, H_2O, 23 °C, 18 h	Mono-diol (major product)	Decomposition.

Table 10

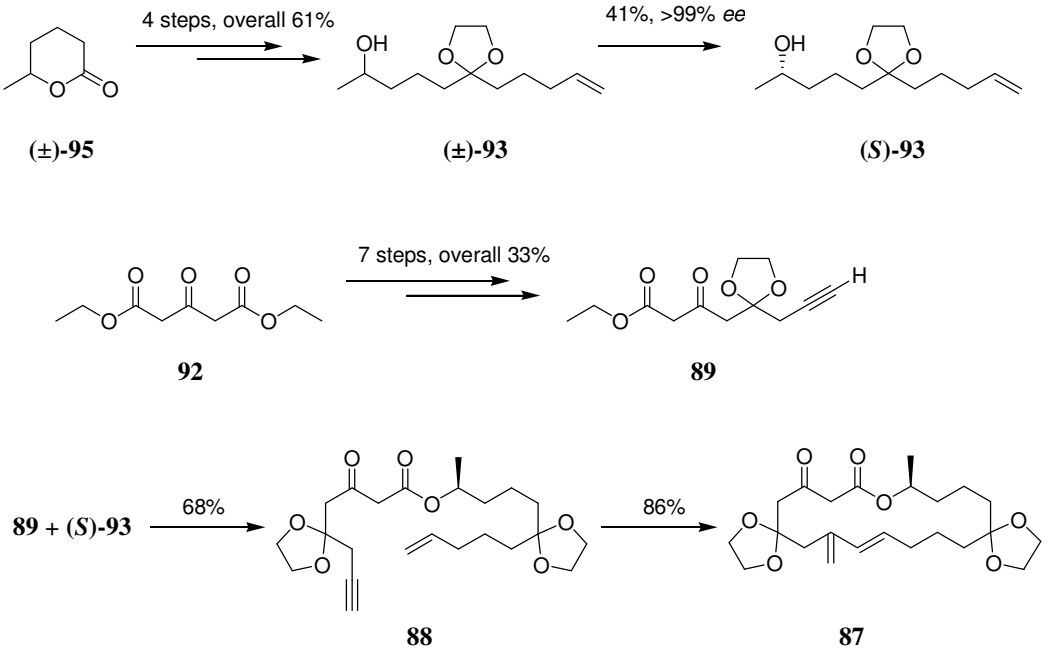
[†]products determined by MS analysis; [*]*Reagents and conditions:* $NaIO_4$, cat. HIO_4, *t*-BuOH : H_2O : THF, 45: 45 : 10, 23 °C, 4 h;

All three sets of reaction conditions showed a product diol, such as diol **255**, by MS ($[M+NH_4^+–H_2O] = 456$), although the they were visibly different by TLC. This suggested different selectivities. In each case the crude mass recovery was low (~40%) and unfortunately when each crude product was treated with sodium periodate, none of the desired cleavage product **86** could be detected. This suggested similar behaviour of diene **87** towards dihydroxylation as previously observed for epoxidation.

At this time, due to difficulties encountered with the selective oxidative cleavage and the fact that no material remained, we decided to pursue an alternative retrosynthesis.

2.6 Conclusions

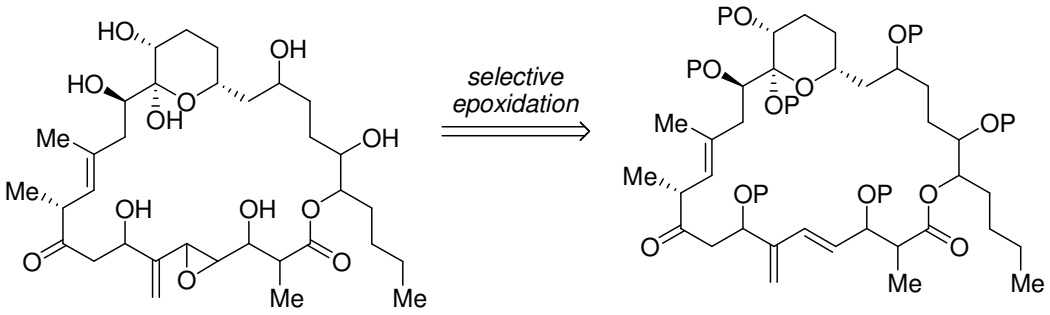
The synthesis of (*S*)-alcohol **93** from (±)-δ-hexanolactone (**95**) was achieved in six steps, including a biocatalysed kinetic resolution to introduce chirality. Synthesis of alkyne ester **89** by a modification of a literature procedure allowed access to gram scale quantities. The coupling of the two fragments by zinc-mediated transesterification and RCEYM enabled macrocyclisation, forming diene **87** in excellent yields (Scheme 90).



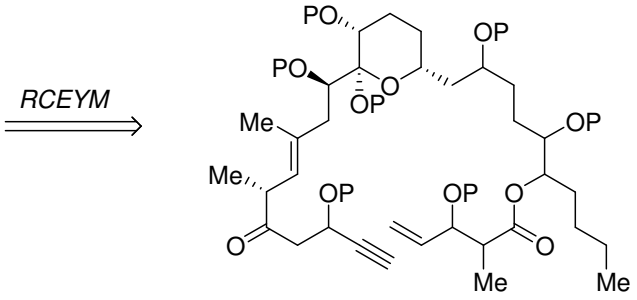
Scheme 90. *Synthesis of Diene* **87** *via RCEYM*

At this point however, the attempted selective oxidative scission of the *exo*-cyclic methylene group to generate enone **86** had been unsuccessful under a variety of conditions. Results indicated a lack of regioselectivity, or undesired regioselectivity as neither starting materials or desired products had been detected from periodate cleavage of either mono-epoxides or mono-1,2-diols.

In 2005 Nicolaou *et al.* attempted the total synthesis of amphidiolide N (**256**) *via* RCEYM of enyne **258** and mono-epoxidation of product diene **257** (Scheme 91).[141]



256 **257**

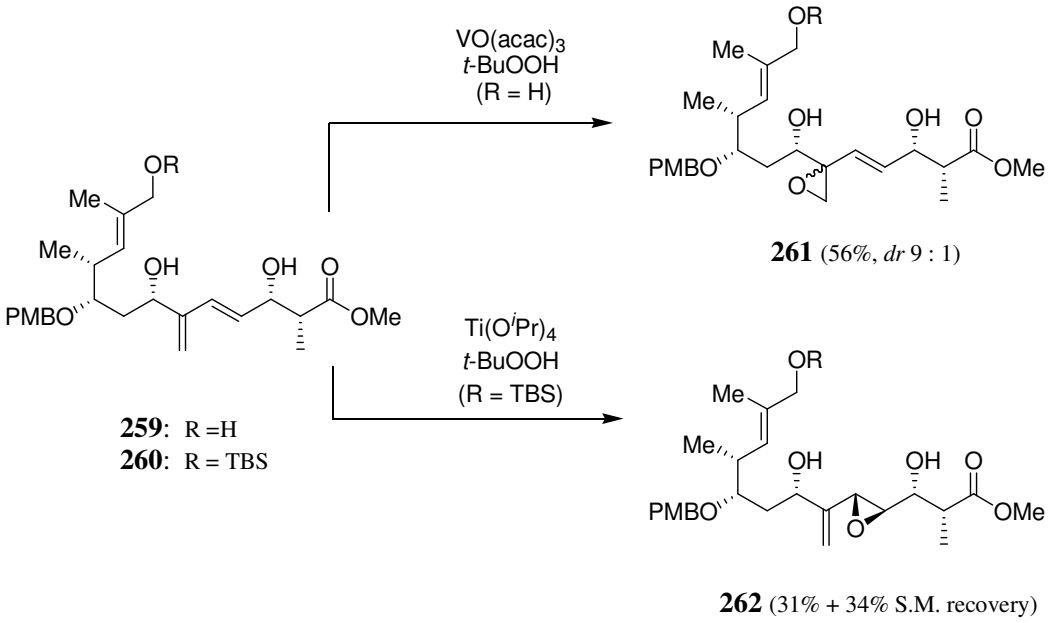


258

Scheme 91. *Nicolaou's Proposed Retrosynthesis of Amphidiolide N.*[141]

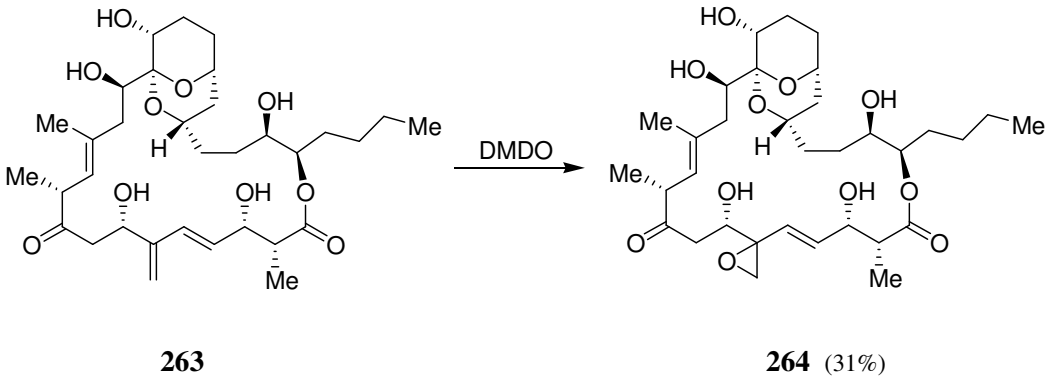
In this example, the desired mono-epoxidation would have the opposite regioselectivity than we wished for in our (*S*)-zearalenone (**3**) system.

Interestingly, Nicolaou's model study on diene **259** produced conflicting results. When alcohol **259** was treated with a vanadium catalyst and *tert*-butyl peroxide, a moderate yield of product **261**, from mono-epoxidation of the terminal alkene function, was observed. However, reacting silyl ether **260** under Katsuki-Sharpless conditions allowed their desired mono-epoxidation with the opposite regioselectivity (and excellent stereoselectivity) to occur in moderate yields, producing the regiomer **262** (Scheme 92). It was also observed both products were susceptible to decomposition on chromatography.



Scheme 92. *Nicolaou's Mono-epoxidation of intermediates* **259** *and* **260**.

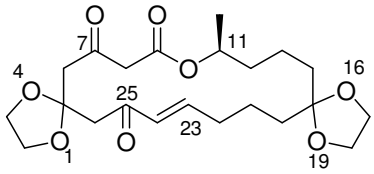
However when the previously successful Katsuki-Sharpless epoxidation was attempted on their real amphidiolide N system, this failed. Under no conditions could they observe their desired regioselectivity. When diene **263** was treated with DMSO, regioisomeric *iso*-epoxy-amphidiolide N **264** was generated as a single undetermined diastereoisomer in 31% yield (Scheme 93). They concluded that the precise three-dimensional conformation of the diene is influential in the epoxidation selectivity.



Scheme 93. *Nicolauo's Mono-epoxidation of Diene* **263**.

These results highlight the non-trivial nature of the mono-epoxidation of conjugated dienes and suggest that the difficulties encountered in our studies were warranted. They also underline the lack of reliability of model studies: indeed our own model study of selective oxidative cleavage had been a success, but the real system proved more troublesome.

With these conclusions, we decided to abandon the RCEYM route to (*S*)-zearalenone (**3**) and to devise an alternative retrosynthesis, avoiding the need for the selective oxidative scission. This would mean having the oxygen at C-25 in place before macrocyclisation (Figure 27).



86

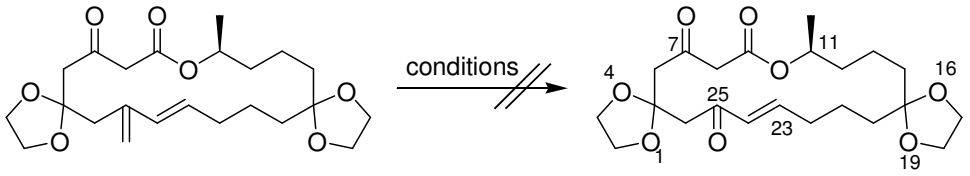
Figure 27. *Primary Target Diketone* **86**.

The next chapter of the results and discussion section details our new disconnection strategy and synthetic work carried out to this end.

Chapter Three: Results and Discussion - RCM Approach to (S)-Zearalenone

3.1 Introduction

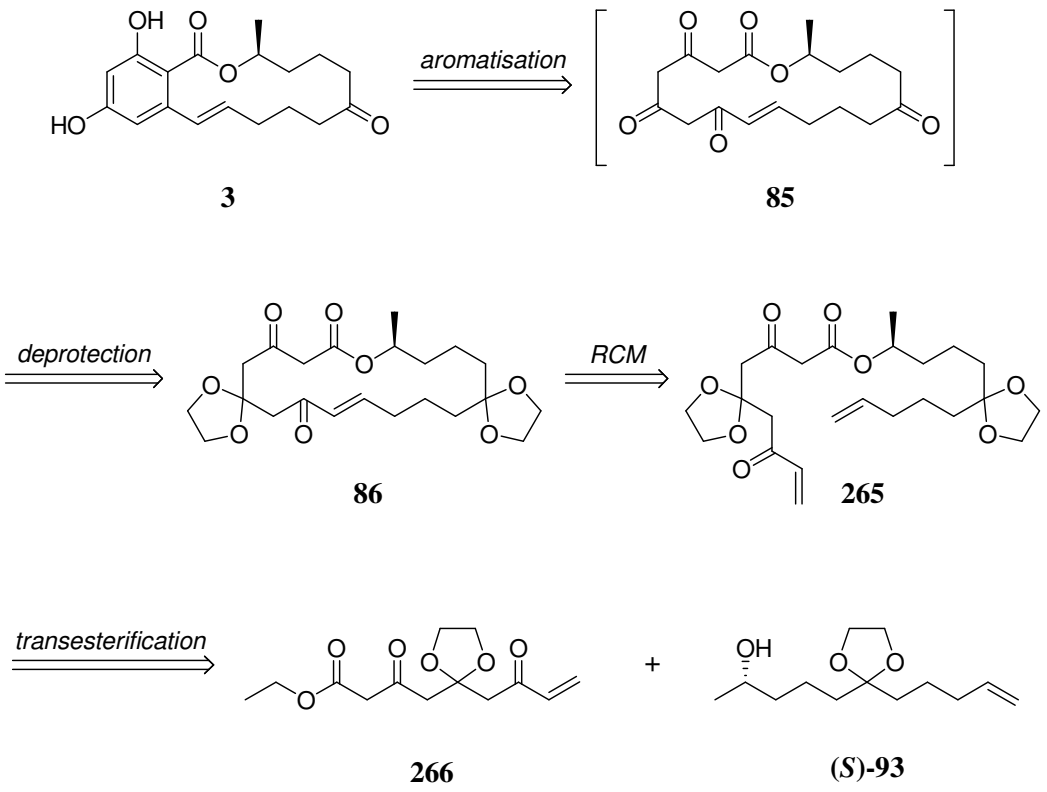
Chapter 2 was concerned with our initial retrosynthetic analysis of (*S*)-zearalenone (**3**), which involved disconnecting the molecule *via* enyne metathesis. This route encountered difficulties in performing the required selective oxidative cleavage of the terminal alkene of intermediate diene **87** (Scheme 94).



87 **86**

Scheme 94. *Failed Selective Oxidative Cleavage.*

In order to avoid this transformation, an alternative retrosynthetic analysis with the oxygen at C-25 already in place at the time of macrocyclisation was necessary. An obvious alternative to RCEYM is ring-closing metathesis (RCM).[142, 143] Disconnection of target diketone **86** by RCM would provide α,β-unsaturated ketone **265**. This in turn could come from the transesterification of (*S*)-alcohol **93**, previously synthesised (see Section 2.2), with vinyl ketone **266** (Scheme 95). This new retrosynthetic analysis identified vinyl ketone **266** as a primary target.



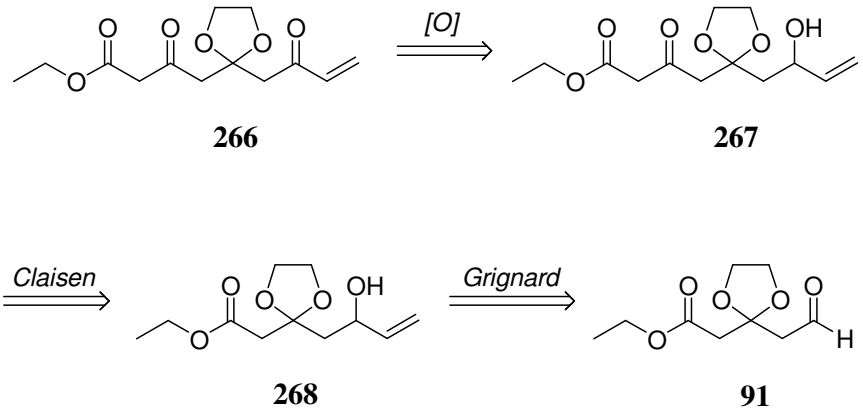
3 **85** **86** **265** **266** **(*S*)-93**

Scheme 95. *Alternative Retrosynthetic Analysis of (S)-Zearalenone* (**3**)

In this chapter, efforts towards this revised synthetic route will be discussed, beginning with the synthesis of vinyl ketone **266**.

3.2 Synthesis of Vinyl Ketone **266**

Further retrosynthetic analysis of target vinyl ketone **266** reveals that this could be prepared by the oxidation of alcohol **267**, which is produced *via* the Claisen condensation of alcohol **268**. This in turn could be generated from aldehyde **91**, a previous intermediate (Section 2.3), by a Grignard addition (Scheme 96).



266 **267**

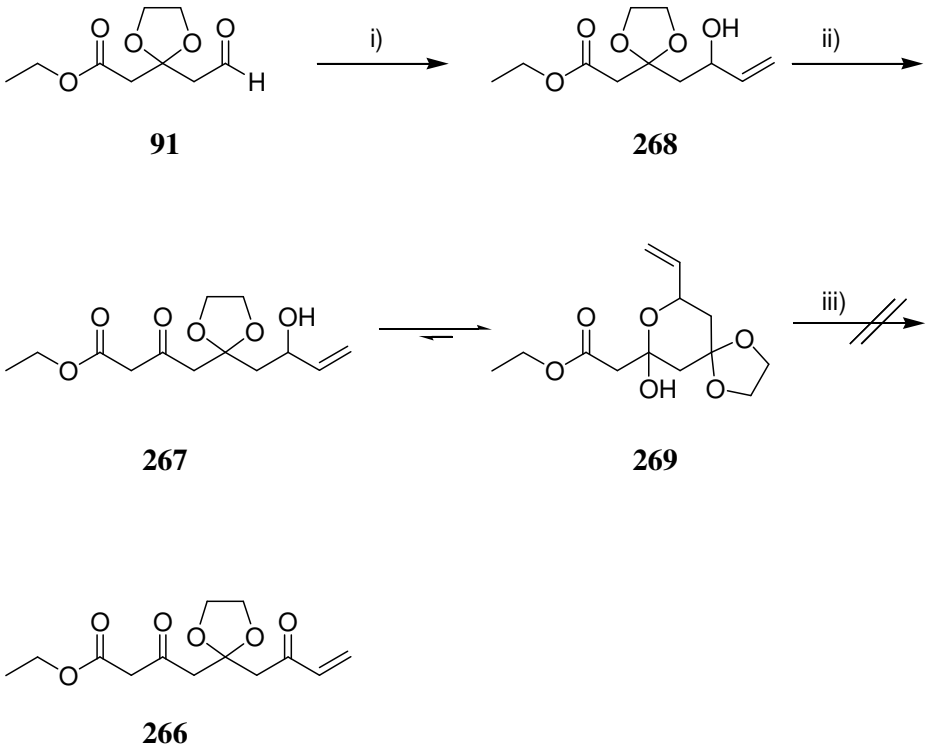
268 **91**

Scheme 96. *Retrosynthetic Analysis of Vinyl Ketone* **266**

It was thought that carrying out the Claisen condensation before the oxidation would prevent competing aldol reactions occurring. Also, if the alcohol moiety was shown to interfere in the reaction, this could be protected.

3.2.1 Grignard Additions to Aldehyde **91**

Dropwise addition of commercial vinylmagnesium bromide was carried out at –78 °C, to ensure reaction at the more reactive aldehyde centre rather than the ester. Alcohol **268** was isolated, albeit in a disappointing 39% yield. The Claisen condensation of alcohol **268** with ethyl acetate (**190**) gave a mixture of products, the major being cyclised hemi-ketal **269** in 29% yield. Unfortunately, the attempted oxidation of hemi-ketal **269** to α,β-unsaturated ketone **266** using mild Dess-Martin periodinane[144] was unsuccessful (Scheme 97).

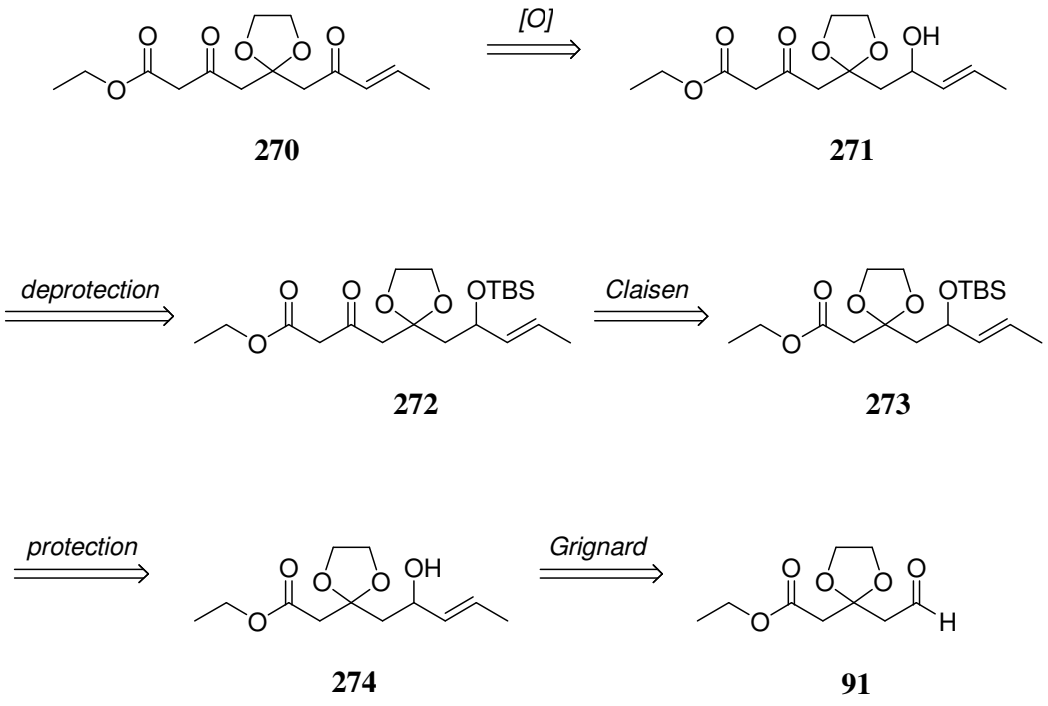


Scheme 97. *Reagents and conditions:* i) Vinylmagnesium bromide, THF, –78 °C, 39%; ii) EtOAc (**190**) (3.0 eq.), LDA (3.0 eq.), THF, –78 °C, 29%; iii) DMP, CH_2Cl_2, 23 °C.

3.2.2 Improvements to the Synthetic Strategy

Two main improvements to the procedure were envisaged: firstly it was hoped that inclusion of a methyl group on the terminal alkene position would improve the yield of the initial Grignard addition, for example by preventing side products from the polymerisation of vinylmagnesium bromide. This methyl group would be cleaved during the RCM process.

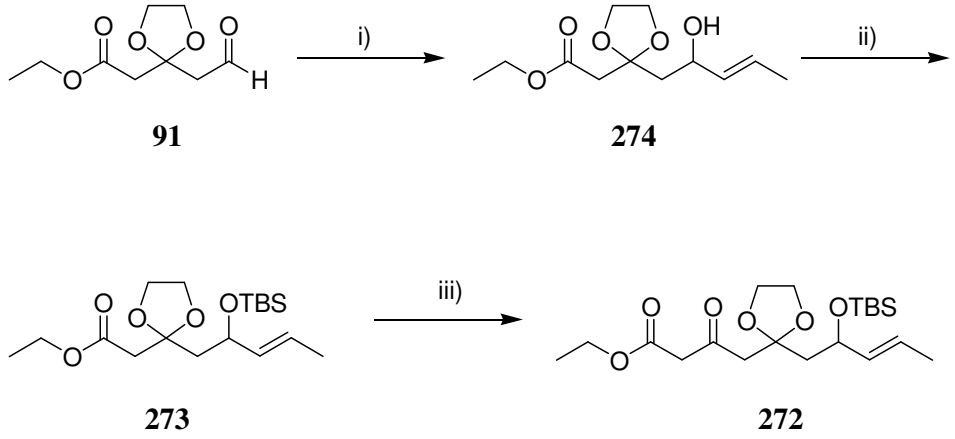
Secondly, to prevent the formation of a 1,5-keto alcohol which would cyclise to a hemi-ketal, a protecting group would be added to the alcohol before the Claisen condensation. A silyl ether protecting group was chosen, as this would be stable to the basic conditions required for the condensation step (Scheme 98).



270 **271** **272** **273** **274** **91**

Scheme 98. *Modified Retrosynthetic Analysis of Transesterification Partner* **270**.

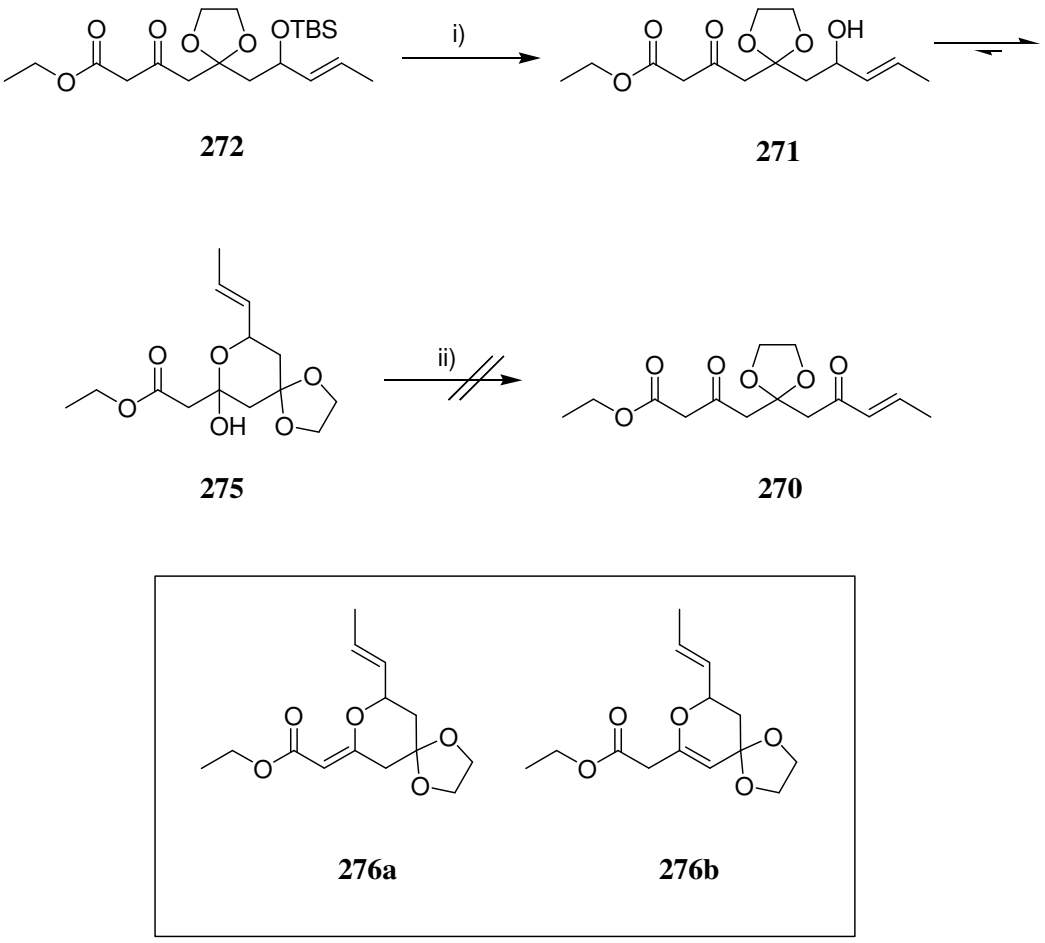
To this end, 1-propenylmagnesium bromide was added dropwise to aldehyde **91** at –78 °C to yield product alcohol **274** in a greatly improved 76% yield. The alcohol was then protected as silyl ether **273** in 96% yield and Claisen condensation with ethyl acetate gave 77% of β-ketoester **272** (Scheme 99).



91 **274** **273** **272**

Scheme 99. *Reagents and conditions:* i) 1-Propenylmagnesium bromide, THF, –78 °C, 76%; ii) TBSCl, DMAP, Imid., DMF, 0 °C to 23 °C, 18 h, 96%; iii) DIPA, *n*-BuLi, THF, 0 °C, 15 min; EtOAc, –78 °C, 30 min; **273**, –78 °C to 23 °C, 4 h, 77%.

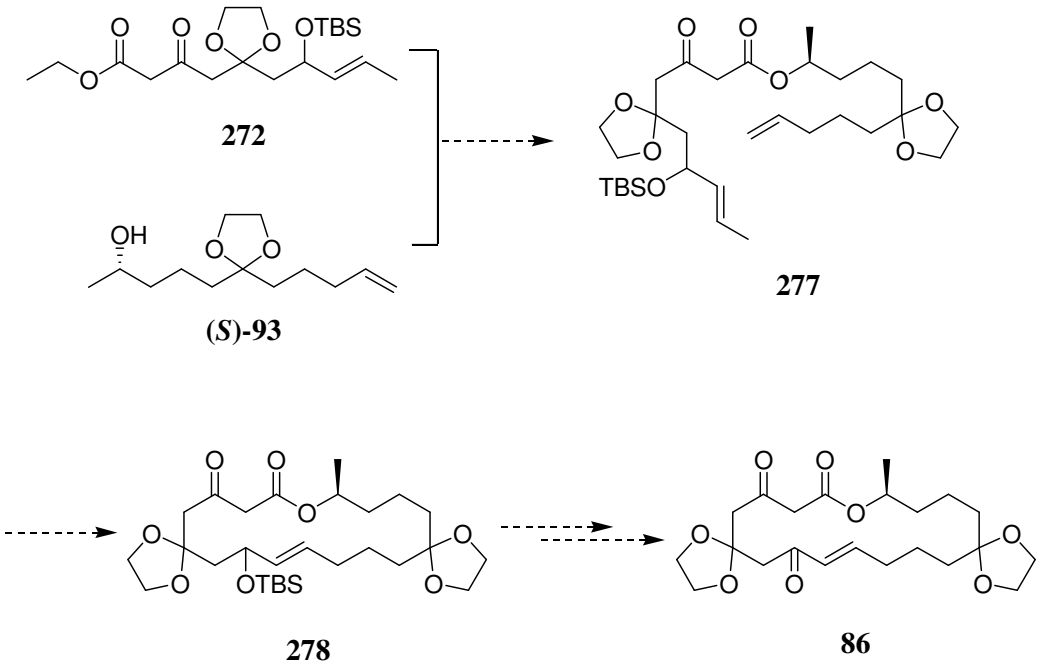
The TBAF deprotection of silyl ether **272** gave a single product, which proved to be hemi-ketal **275**. Oxidation with Dess-Martin periodinane gave no desired product, with only starting material or the possible dehydration products **276** observed by MS (Scheme 100).



Scheme 100. *Reagents and conditions:* i) TBAF (1.0 M in THF, 5.0 eq.), THF, 23 °C, 18 h, 79%; ii) DMP, CH_2Cl_2, 0 °C to 23 °C, 1 h.

3.3 Coupling of Vinyl Ketone **272** with (*S*)-Alcohol **93**

It was decided to couple vinyl ketone **272** to (*S*)-alcohol **93** and to form macrocycle **278** before deprotection of the silyl group and oxidation to target **86**. It was hoped that once the ring was closed, there would be greater hindrance to hemi-ketal formation (Scheme 101).

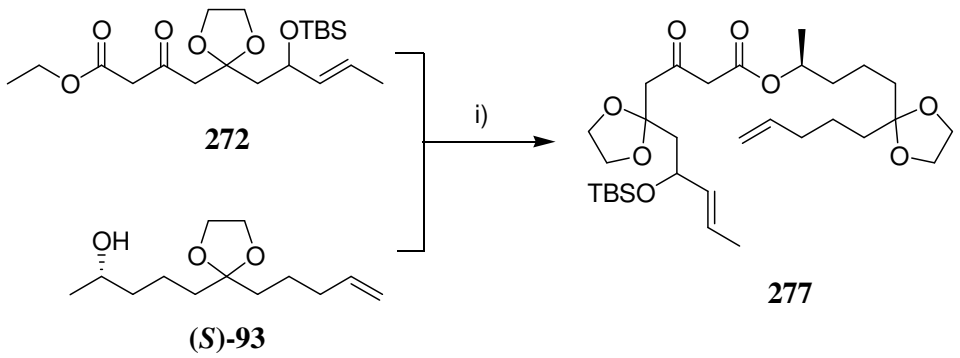


Scheme 101. *Proposed New Synthetic Route.*

Closing the macrocycle would be accomplished firstly *via* transesterification, then RCM and these will now be discussed in turn.

3.3.1 Transesterification

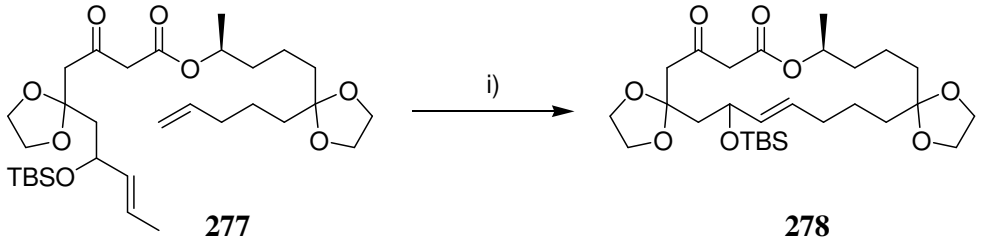
The coupling was carried out in an analogous method to that previously used to couple ester **89** with (*S*)-alcohol **93**: zinc mediated transesterification. As previously, the reaction was carried out at a temperature of 110 °C under a distillation condenser to remove the excess ethanol by-product (see Section 2.4.1.2). Diene **277** was formed in 84%, an improvement on the previous transesterification yield. This was mainly due to simpler chromatography (Scheme 102).



Scheme 102. *Reagents and conditions:* i) Zn dust (20 mol%), PhMe, 110 °C, 18 h, 84%

3.3.2 Ring Closing Metathesis (RCM)

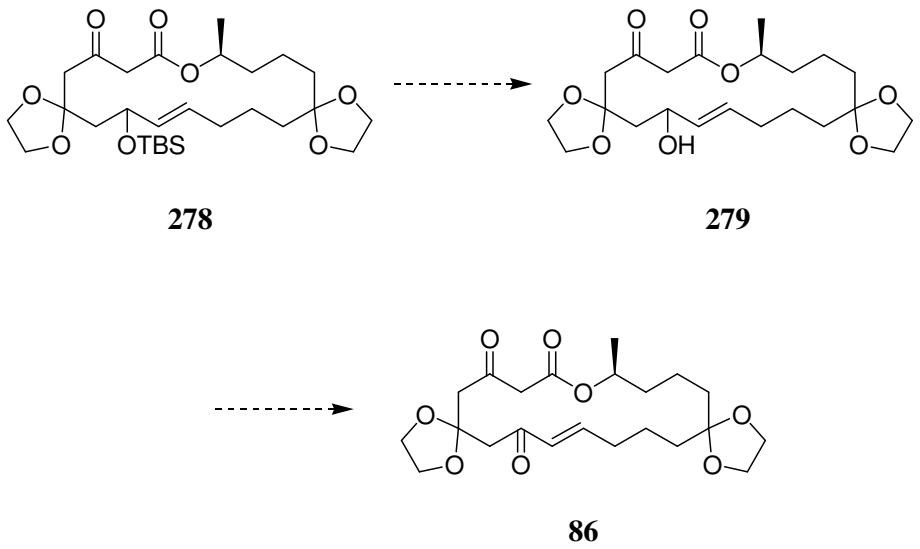
Gratifyingly, when diene **277** was treated with Grubbs' second generation catalyst in toluene at 120 °C under argon for 72 h, spot to spot conversion to a new product was observed. The product was isolated in 88% yield and shown to be the desired ring-closed macrocycle **278** (Scheme 103). This was achieved despite previous literature evidence which suggested that bulky silyl ethers adjacent to alkenes could prevent ring-closing metathesis, presumably from steric effects.[145, 146]



Scheme 103. *Reagents and conditions:* i) Grubbs' II (**196**) (10 mol%), PhMe, 120 °C, 72 h, 88%.

3.4 Elaboration of Macrocyclic Silyl Ether **278** to Diketone **86**

The next synthetic goal was the formation of diketone **86**. From macrocyclic silyl ether **278** this involved silyl deprotection and then oxidation of the product alcohol **279** (Scheme 104).



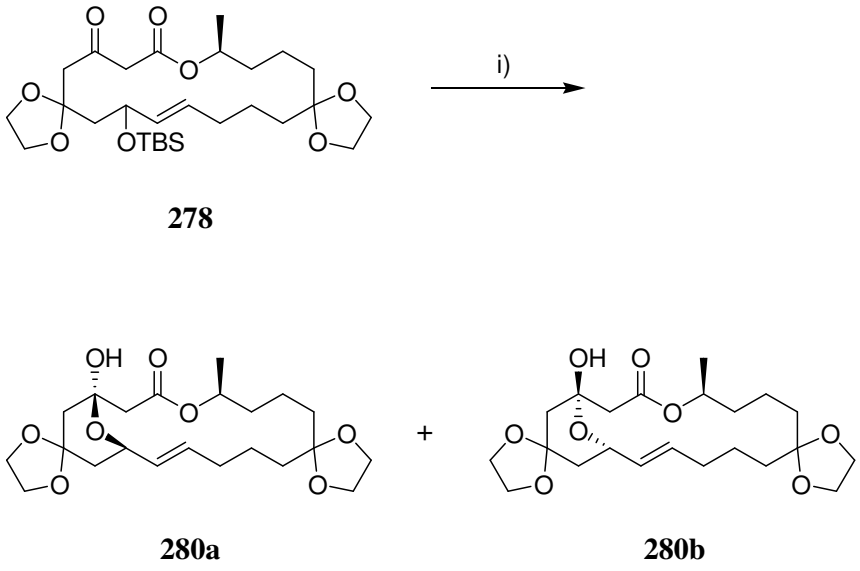
278 **279**

86

Scheme 104. *Synthetic Steps to Diketone* **86.**

3.4.1 Silyl Deprotection of Macrocyclic Silyl Ether **278**

As feared, the TBAF deprotection of macrocyclic silyl ether **278** gave rise to a 1:1 mixture of diastereoisomeric hemi-ketals, **280a** and **280b**, each in 42% yield. Interestingly, one diastereoisomer, **280b**, was crystalline and we were able to obtain a crystal structure of this material in order to assign the configuration as that shown. The open-chain alcohol **279** was not be observed by crude ^{1}H NMR or TLC (Scheme 105).



Scheme 105. *Reagents and conditions:* i) TBAF, THF, 23 °C, 5 d, 84%.

The crystal structure clearly shows an intramolecular hydrogen bond between the alcohol proton and ester carbonyl oxygen, whilst also unambiguously confirming the 14-membered macrocycle is in place (Figure 28).

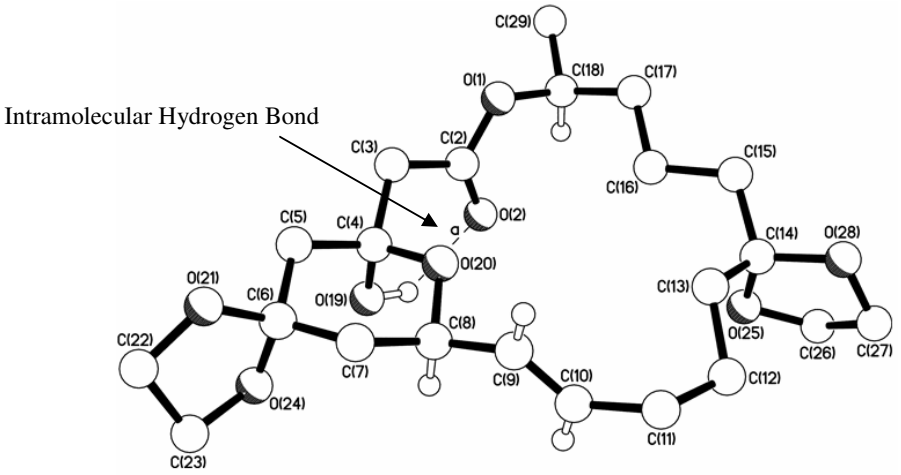
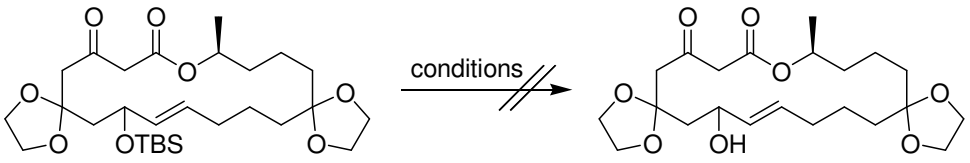


Figure 28. *Crystal Structure of Hemi-Ketal* **280b**

The TBAF deprotection of macrocyclic silyl ether **278** was slow (5 days), hence investigations into alternative and possibly milder deprotection conditions were made (Scheme 106, Table 11). Disappointingly however, no improvements were found.



278 **279**

Scheme 106. *Attempted Silyl Deprotection.*

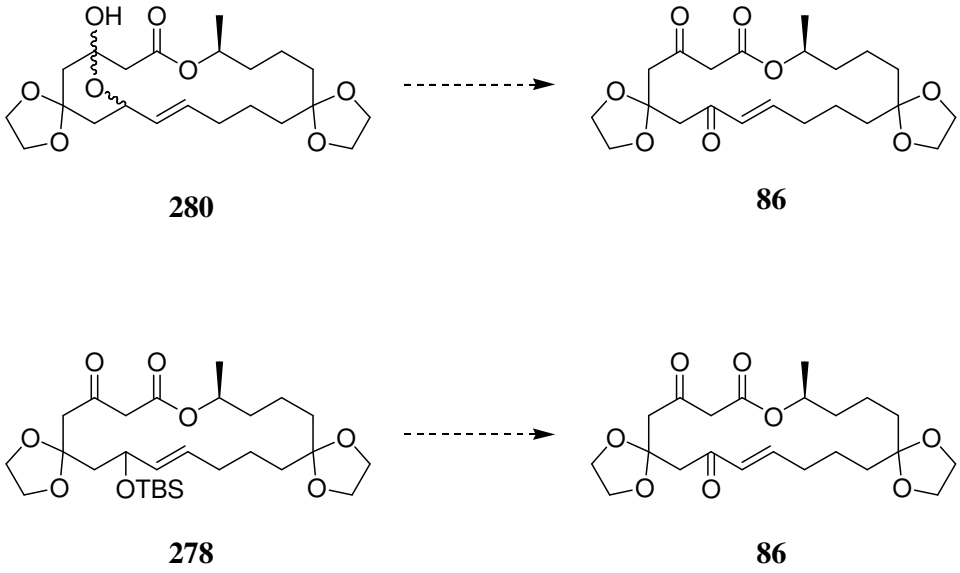
Entry	*Reagents and conditions*	*Products*[†]
1	TBAF (3.0 eq.), THF, 24 h	S.M.
2	TBAF (10 eq.), THF, 5 d	Hemi-ketals **280**
3	$Zn(BF_4)_2$ (3.0 eq.), H_2O, THF, 24 h[147]	S.M.
4	CAN (1.0 eq.), MeOH, 0 ºC, 3 h [148]	Decomposition

Table 11

[†]products determined by MS and ^{1}H NMR analysis.

3.4.2 Oxidation

To complete the synthesis of diketone **86**, oxidation was necessary. Based on the principle that hemi-ketals **280** will be in equilibria with the open chain alcohol **279**, it should be possible to oxidise this directly. Failing this, macrocyclic silyl ether **278** may potentially be oxidised directly to diketone **86** (Scheme 107).



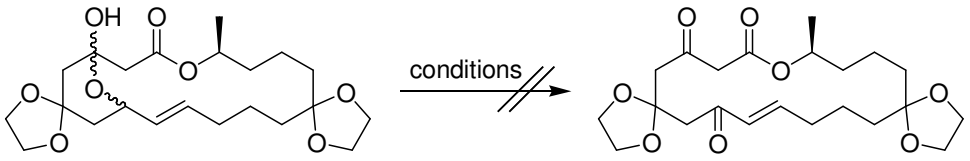
280 **86**

278 **86**

Scheme 107. *Possible Oxidations to form Diketone* **86.**

3.4.2.1 Oxidation of Hemi-Ketals **280a** *and* **280b**

Investigations into the oxidation of hemi-ketals **280a** and **280b** failed to isolate any desired product dione **86**, despite a wide range of conditions being attempted (Scheme 108, Table 12). It is interesting to note that hemi-ketal **280a** and hemi-ketal **280b** behave slightly differently under the same conditions (Entries 1, 2, 5 & 8-10).



280 **86**

Scheme 108. *Attempted Oxidation of Hemi-Ketals* **280**.

Entry	*Hemi-ketal*	*Reagent and conditions*[†]	*Products*[*]
1	**a**	DMP[144]	S.M.
2	**a**	DMP, pyr.[149]	S.M.
3	**a**	TPAP, NMO, 4Å m.s.	S.M.
4	**a**	PCC, $MgSO_4$, celite[150]	S.M.
5	**a**	PCC, NaOAc, 4Å m.s.[151]	S.M.
6	**a**	*t*BuOCl, pyr. [152, 153]	Dehydration
7	**a**	PhSNH*t*Bu (10 mol%), NCS, DBU[154]	S.M.
8	**b**	DMP	S.M.
9	**b**	DMP, pyr.	Dehydration
10	**b**	PCC, NaOAc, 4Å m.s.	S.M.

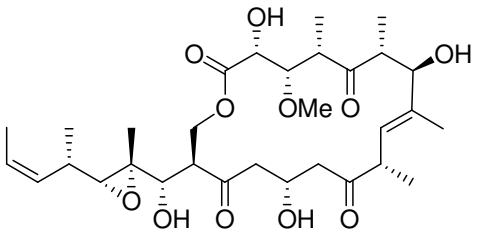
Table 12

[†]reactions carried out in CH_2Cl_2 at 23 °C for 5 h; [*]products determined by MS and ^1H NMR analysis.

Both the difficulty observed in the oxidation of hemi-ketals **280** and also the absence of detection of any free alcohol **279** during silyl deprotection, suggest that the hemi-ketal forms are extremely stable with respect to the open chain alcohol. Most of these oxidation procedures would rely on the oxidation of the small amount of free

alcohol present in equilibria. Neither basic conditions (Entries 2, 6 and 7) or acidic conditions (Entry 4) seemed to promote the hemi-ketal opening.

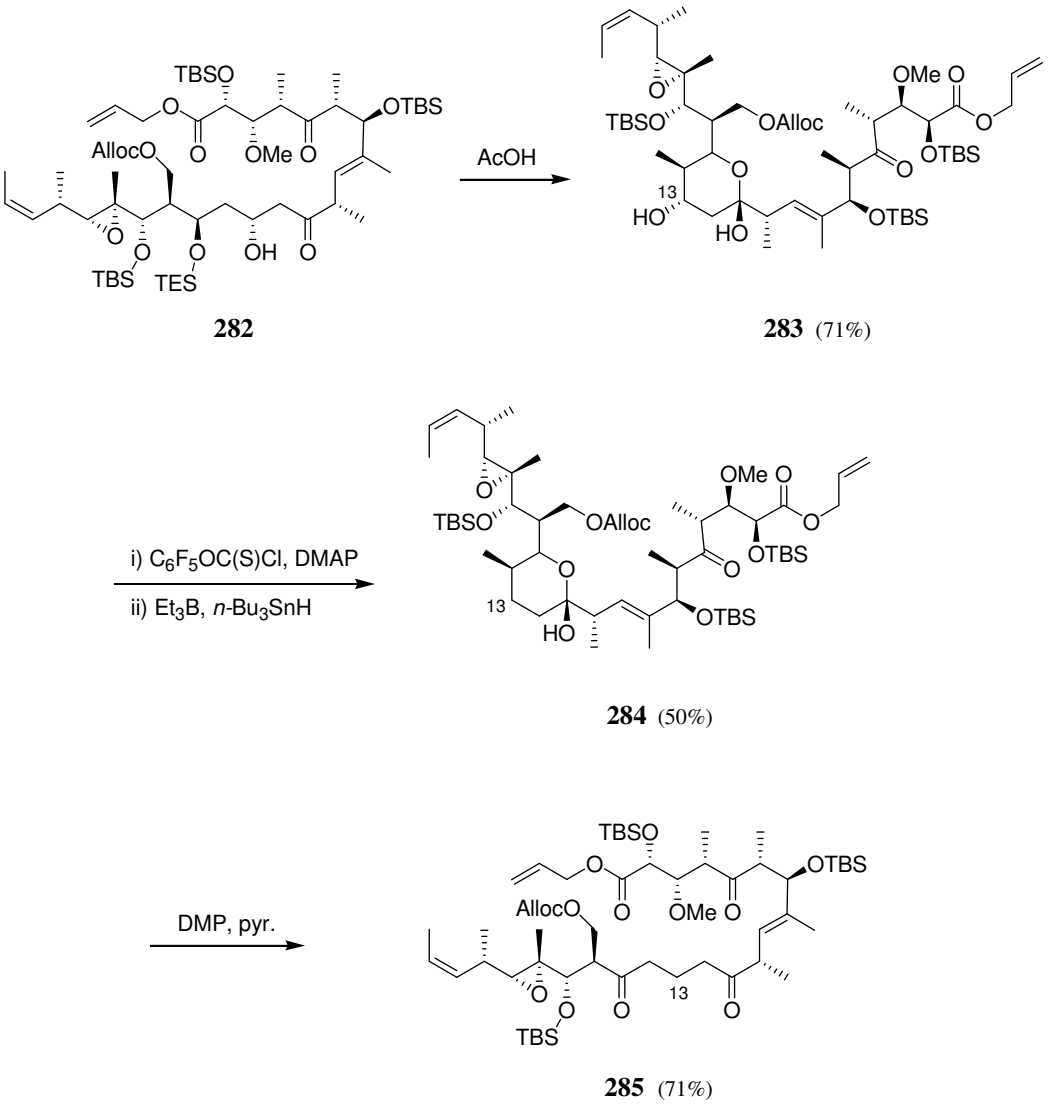
A similar effect was observed by Julian *et al.* during their attempted synthesis of (+)-tedanolide (**281**) (Figure 29).[149]



281

Figure 29 (+)-*Tedanolide* (**281**)

Upon deprotection of their TES ether intermediate **282** they observed facile hemi-ketal formation and then were unable to oxidise product **283**. They attributed the increased stability of the closed hemi-ketal with respect to its open chain form to the Thorpe-Ingold effect[155] of the presence of substituents on the newly formed six-membered ring. In their example there is an alcohol moiety at the C-13 position and indeed, when they remove this group they are able to oxidise deoxygenated hemi-ketal **284** under mild conditions to diketone **285** in 71% yield (Scheme 109).



282

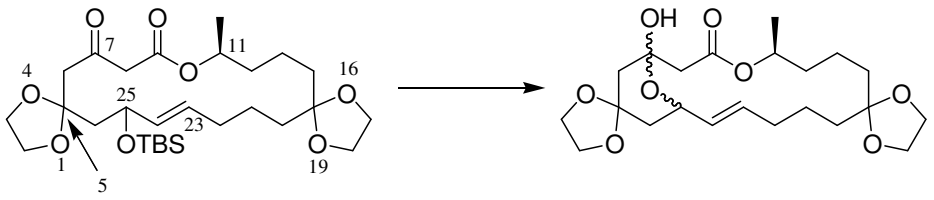
283 (71%)

284 (50%)

285 (71%)

Scheme 109. *Julian et al.'s Synthesis of Diketone* **285**.

This suggests that the presence of the tertiary carbon at C-5 of macrocyclic silyl ether **278** is key in shifting the equilibrium from the open-chain alcohol to favour hemi-ketal **280**, as this tertiary carbon becomes positioned within the new six-membered ring (Scheme 110).



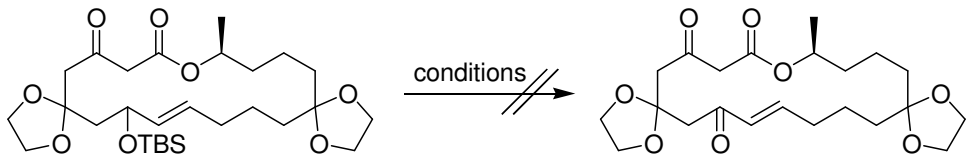
278 **280**

Scheme 110. *Hemi-Ketal Formation.*

Unfortunately in our case, synthesis of a resorcylate natural product analogue would not be possible without the presence of this ketal, as the carbonyl at this position is necessary for the late-stage aromatisation.

3.4.2.2 Direct Oxidation of Macrocyclic Silyl Ether **278**

Several literature procedures for direct oxidation of macrocyclic silyl ether **278** were endeavoured, however in no case was the desired product diketone **86** identified (Scheme 111, Table 13).



278 **86**

Scheme 111. *Attempted Direct Oxidation of Macrocyclic Silyl Ether* **278.**

Entry	*Reagents and conditions*	*Products*[†]
1	Jones' Reagent, KF, acetone, 0 °C, 18 h[156]	Decomposition
2	PCC, celite, $MgSO_4$, CH_2Cl_2, 23 °C, 5 d[150]	S.M.
3	NHPI, $Co(Ac)_2$, 1 atm $O_{2\ (g)}$, CH_3CN, 23 °C, 20 h[157]	S.M
4	$(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C, 3 h[158]	Decomposition
5	DDQ, pH 7 buffer, CH_2Cl_2, 23 °C, 2 h[159]	S.M.
5	DDQ, CH_2Cl_2, 40 °C, 18 h	S.M.
6	DDQ, *hν*, CH_2Cl_2, CH_3CN, 3 h[160]	S.M.

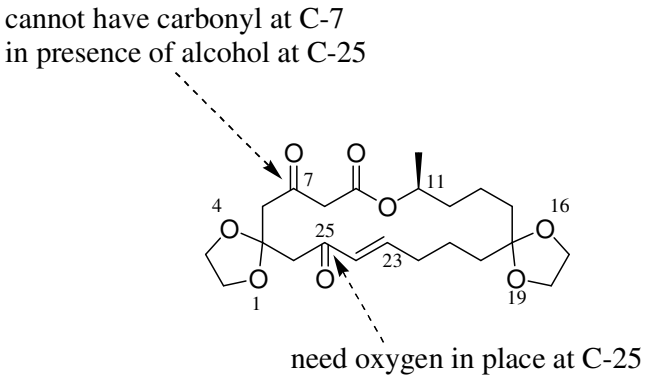
Table 13

[†] products determined by crude MS and ^1H NMR analysis.

The failure of both the oxidation of hemi-ketals **280**, or macrocyclic silyl ether **278** meant a modification of our strategy was necessary.

3.4.3 Protection Strategies

Thus far our synthetic work towards diketone **86** has proven firstly that we must have an oxygen in place at C-25 (failure of selective oxidative scission) and secondly that any 1,5-hydroxy-ketone intermediate must be avoided at all costs (failure of hemi-ketal oxidation, Figure 30).

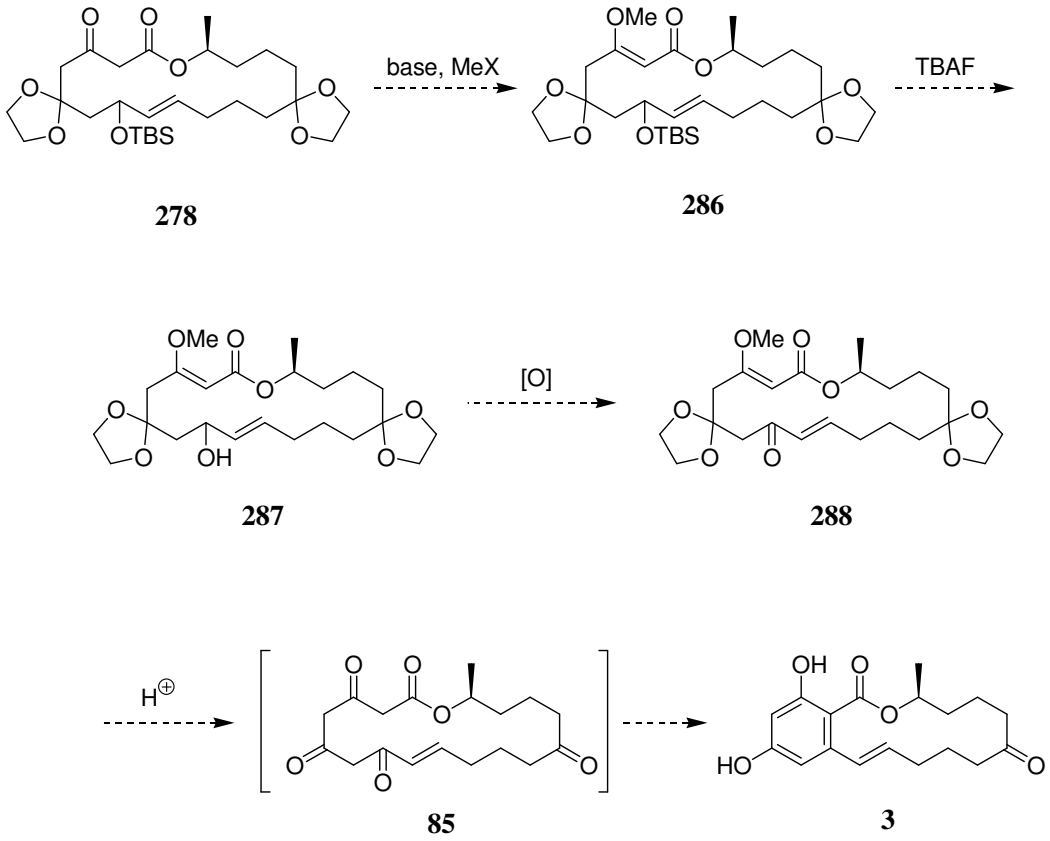


86

Figure 30. *Summary of Synthetic Discovery.*

Our RCM disconnection strategy could still be viable, provided we fulfil these criteria. This implied the need to modify our protecting group strategy and our efforts in this area will now be described.

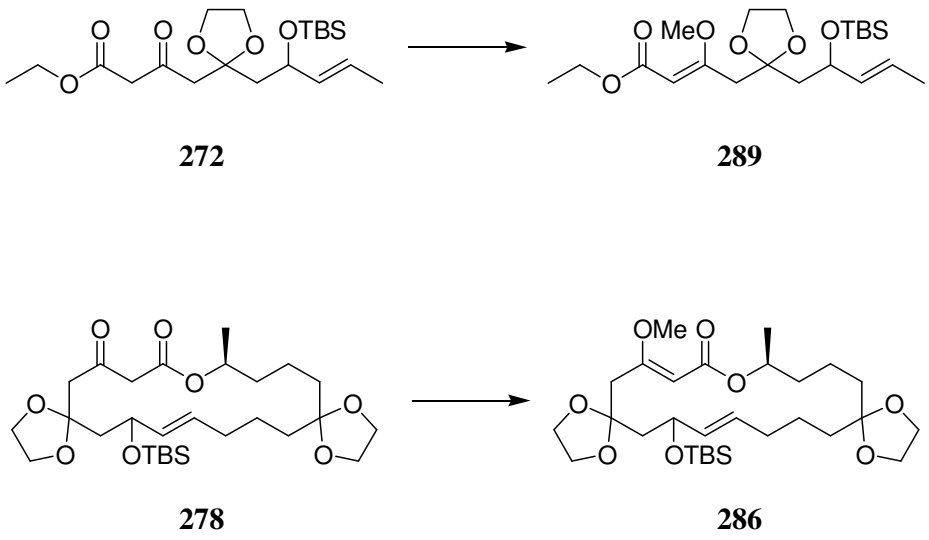
With macrocyclic silyl ether **278** in hand, it was resolved to protect the carbonyl at C-7. This would preclude attack by the C-25 alcohol. Although ketalisation with ethylene glycol would mean that the three ketals could be removed in one step, we guessed that the equilibriating ketalisation conditions would result in simultaneous deprotection and therefore a mixture of several different ketal products. Instead, we recognised the potential to protect C-7 as an enol ether, due to the adjacent acidic protons. This would require only mildly basic conditions, leaving existing protecting groups intact whilst only adding one step to the planned synthesis (Scheme 112).



278 **286** **287** **288** **85** **3**

Scheme 112. *Strategy for Protecting β-Ketoester* **278** *as an Enol Ether.*

As acyclic silyl ether **272** was also in hand, methyl enol ether protection was simultaneously carried out on this substrate (Scheme 113, Table 14).



272 **289**

278 **286**

Scheme 113. *Enol Ether Protections.*

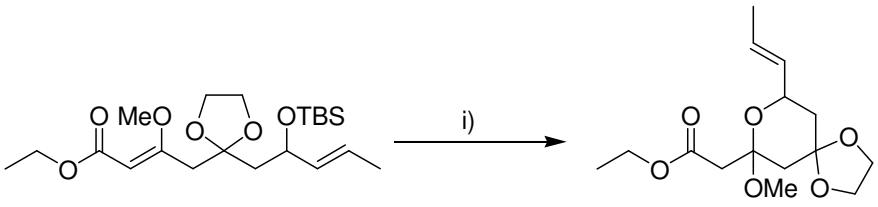
Entry	*β-Ketoester*	*Reagents and conditions*[†]	*Products*[*]
1	**272**	Me_2SO_4, K_2CO_3, 18-crown-6, CH_2Cl_2[161]	Product: C-alkylation: unknown 1 : 2 : 1
2	**272**	$TMSCHN_2$, DIPEA, CH_3CN : MeOH, 9 : 1[162, 163]	Product: C-alkylation: unknown 1 : 1 : 2
3	**278**	$TMSCHN_2$, DIPEA CH_3CN : MeOH, 9 : 1	Product: C-alkylation: unknown 1 : 2 : 4

Table 14

[†]reactions carried out at 23 °C for 18 h; [*]ratio determined by crude ^{1}H NMR analysis.

Reactions were low yielding, with side-products formed as well as the desired product. One identified side-product seemed to be that from competing C-alkylation. The isolated yields from the TMS-diazomethane procedure were 10% for the open chain enol ether **289** and just 5% for the macrocyclic product **286**.

Open chain enol ether **289** was subjected to TBAF and disappointingly, the only isolated product was ketal **290**, in an isolated 69% yield as a 5 : 3 mixture of diastereoisomers (Scheme 114).



289 **290**

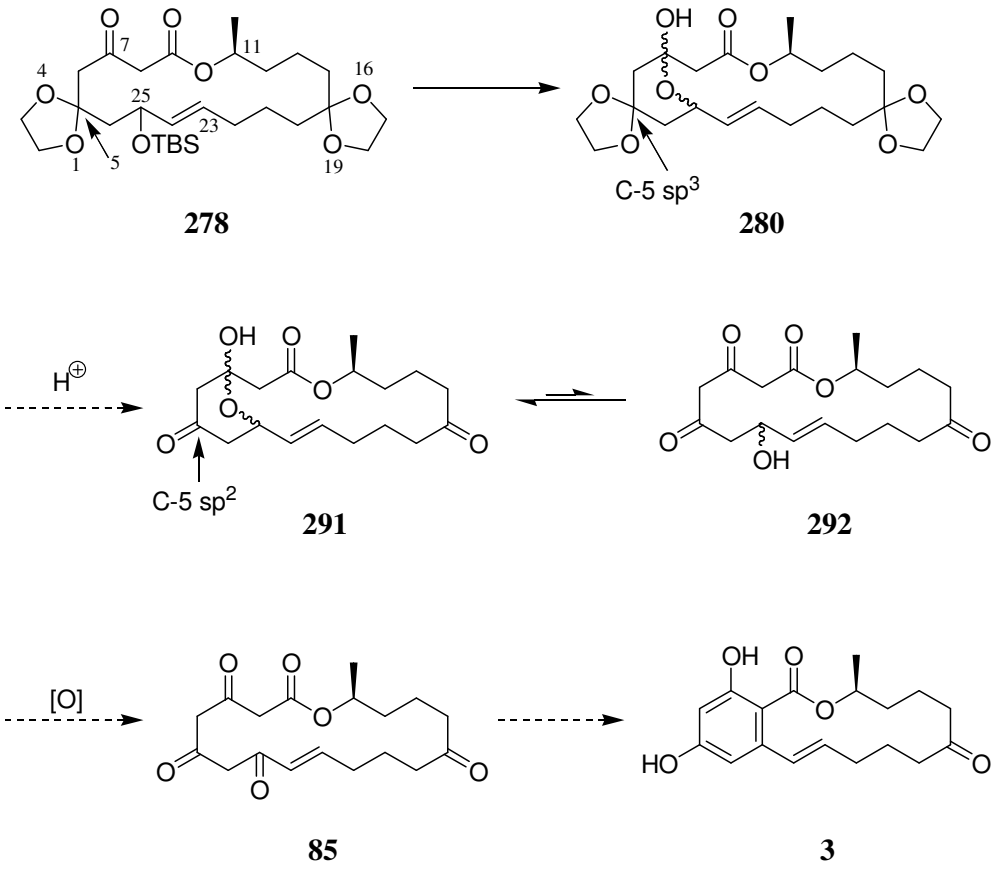
Scheme 114. *Reagents and conditions:* i) TBAF, THF, 23 °C, 3 d.

It was concluded that enol ether formation provided no protection from cyclisation and hence the route was abandoned.

At this time it appeared that a complete new retrosynthetic route would be necessary. One proposal was to simply replace the TBS group with an oxidisable protecting group, such as the *ortho*-bromobenzyl group which is known to undergo oxidation under radical conditions *via* 1,5-hydrogen atom transfer.[164] However before beginning the synthesis again, we first wished to make sure that all other possibilities from the materials in hand were exhausted.

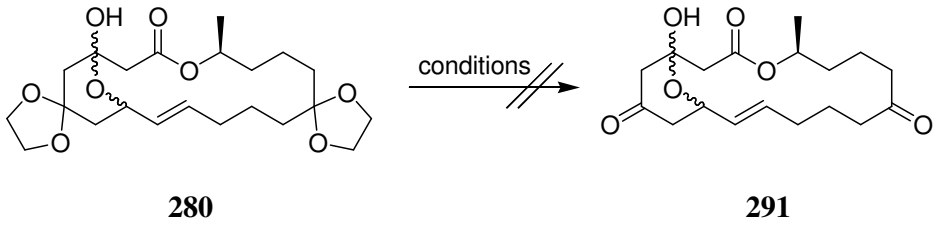
3.4.4 Ketal Deprotection of Hemi-Ketals **280**

As discussed in section 3.4.2.1, facile hemi-ketal formation was attributed to the presence of the ketal group at C-5, according to the Thorpe-Ingold effect. It was decided to try to deprotect the ketal groups of hemi-ketals **280**. It was thought that changing the bond angle around C-5 from sp^3 to sp^2 could influence the equilibria between hemi-ketal **291** and open-chain alcohol form **292**, thus potentially allowing oxidation to occur, generating aromatisation precursor **85** (Scheme 115).



Scheme 115. *Planned Ketal Deprotections*

The ketal deprotections of hemi-ketals **280** and also macrocyclic silyl ether **278** under mild conditions (PPTS in acetone and H_2O) were first explored (Scheme 116, Table 15).



Scheme 116. *Attempted Ketal Deprotections.*

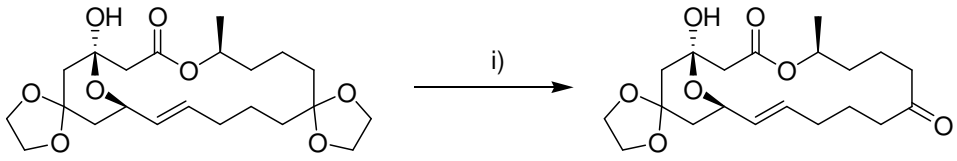
Entry	*Starting material*[†]	*Product(s)*[*]
1	**280a**	Mixture of mono- and di-ketal deprotection. Evidence of dehydration.
2	**280b**	Single product: mono-deprotected ketal **293** (94%)
3	**278**	Full silyl deprotection. Mixture of mono- and di-ketal deprotection. Evidence of dehydration.

Table 15

[†] *Reagents and conditions:* PPTS, Acetone, H_2O, 23 °C, 18 h;

[*] products determined by crude ^1H NMR analysis.

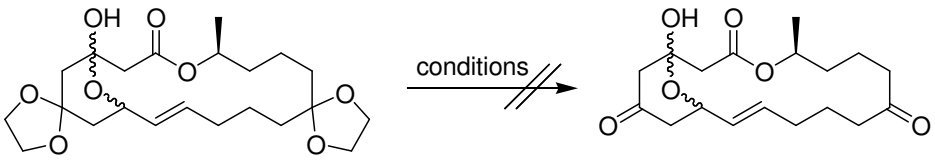
Interestingly, the two diastereoisomers gave different results under the same conditions. A mixture of partial deprotection and full deprotection was observed for diastereoisomer **280a**, (Table 15, Entry 1) whilst the crystalline diastereoisomer **280b** gave only one product, ketal **293** (Entry 2, Scheme 117). Macrocyclic silyl ether **278** underwent full TBS-deprotection under the reaction conditions, resulting in a mixture of hemi-ketals **280a** and **280b**, plus their ketal deprotection products (Entry 3).



280b **293**

Scheme 117. *Reagents and conditions:* i) PPTS, Acetone, H_2O, 23 °C, 18 h, 94%.

Harsher deprotection conditions were also investigated, namely sodium perchlorate in acetic acid. These conditions had been utilised in a study by Yamaguchi *et al.*,[61] to facilitate the aromatisation of polycarbonyl compounds to resorcylates (Section 1.3). It was hoped that these deprotection conditions would also encourage spontaneous aromatisation (Scheme 118, Table 16).



280 **291**

Scheme 118. *Attempted Ketal Deprotections.*

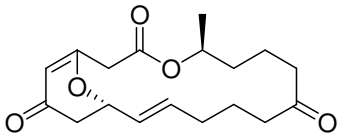
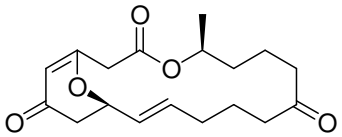
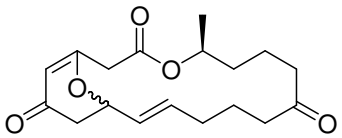
Entry	*Starting material*[†]	*Product(s)*	*Yield*[*]
1	**280a**	 **294a**	97%
2	**280b**	 **294b**	99%
3	**278**	 **294**	71%

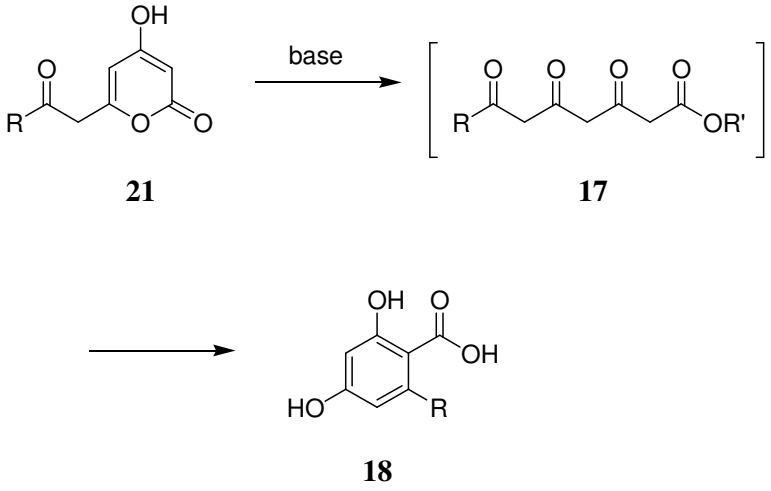
Table 16

[†] *Reagents and conditions:* $NaClO_4$, AcOH, 23 °C, 18 h, 97-99%; [*] isolated product yields.

In all three cases, complete ketal deprotection occurred, along with dehydration to form the dihydropyrones **294** in excellent yields. For macrocyclic silyl ether **278**, this meant five operations occurring in one pot: TBS deprotection, hemi-ketal formation, dehydration and two ketal deprotections.

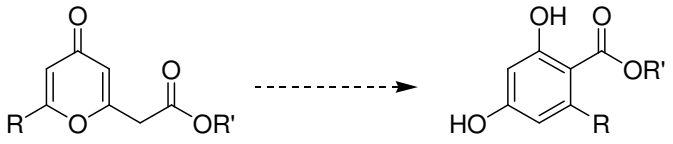
Dihydropyrones **294** pose a problem in the synthesis of (*S*)-zearalenone (**3**), as no literature examples could be found where similar systems have been converted to resorcylates. Oxidation of the dihydropyrone is likely to provide the 4-pyrones, which are alternative aromatisation products from β-triketo esters to resorcylates (see Section 1.2).

In order to convert 4-pyrones to resorcylates, a novel reaction protocol would need to be developed. As discussed in Section 1.3, 2-pyrones such as pyrone **21** are known to rearrange to resorcylates **18**, *via* open chain β-triketo ester **17**, by the use of a base (Scheme 119).



Scheme 119. *Base-catalysed Rearrangement of 2-Pyrones* **21** *to Resorcylates* **18**.

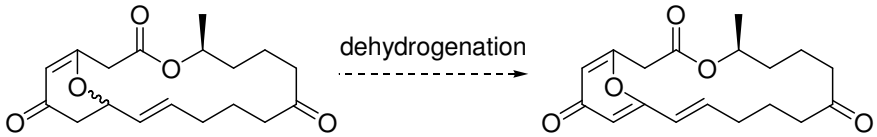
Thus we anticipated that 4-pyrones **20** might also be encouraged to rearrange, under the right conditions, presuming that resorcylates **18** are the thermodynamically most stable β-triketo ester aromatisation product (Scheme 120). Lack of literature support for the hypothesis could be due the fact that only few examples 4-pyrones **20** have been reported.



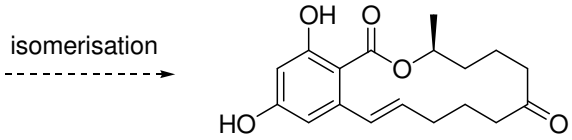
20 **18**

Scheme 120. *Possible Rearrangment/Isomerisation of 4-Pyrones* **20** *to Resorcylates* **18**

Before the isomerisation investigations however, it was necessary to dehydrogenate dihydropyrones **294** to 4-pyrone **295** (Scheme 121).



294 **295**



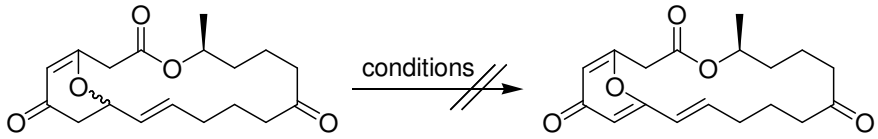
3

Scheme 121. *Possible Synthetic Strategy from Dihydropyrones* **294**

3.4.4.1 Attempts towards the Synthesis of 4-Pyrone **295**

4-Pyrones are scarce in the literature and indeed, only very few simple 4-pyrones with adjacent carbonyl groups have been synthesised.[37] 4-Pyrone **295** not only represents a novel structural class of compounds, but is also an isomer of the natural product (*S*)-zearalenone (**3**), thus could be of biological importance.

Despite a range of dehydrogenation/oxidation conditions being applied, 4-pyrone **295** has thus far proved elusive. Both diastereoisomers have been used, and in neither case has any product been detected (Scheme 122, Table 17).



294 **295**

Scheme 122. *Attempted Dehydrogenation of Dihydropyrones* **294**.

Entry	*Reagents and conditions*	*Product*[†]
1	DDQ (1.8 eq.), CH_2Cl_2, 23 °C, 6 h	S.M.
2	DDQ (2.0 eq.), CH_2Cl_2, 40 °C, 6 h	S.M.
3	DDQ (1.5 eq.), PhMe, 80 °C, 6 h	S.M.
4	DDQ (1.5 eq.), PhMe, 120 °C, 24 h	S.M.
5	IBX (2.0 eq.), DMSO : PhMe, 1 : 2, 65 °C, 4 h	S.M.
6	IBX (Fresh batch, 2.0 eq.), DMSO : PhMe, 2 : 1, 65 °C, 6 h	S.M.
7	HIO_3 (1.0 eq.), DMSO, 80 °C, sealed tube, 18 h[165]	S.M.
8	I_2O_5, (1.0 eq.), H_2O, 18 h[166]	S.M.
9	CAN (3.0 eq.), CH_3CN:H_2O, 5 : 1, 23 °C, 18 h	S.M.

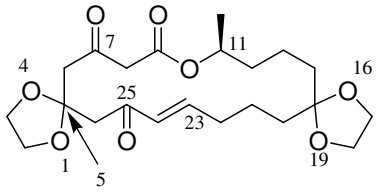
Table 17

[†]products determined by crude MS and ^{1}H NMR analysis.

The range of conditions tolerated by dihydropyrones **294** imply that they are robust and chemically stable. It was decided instead to screen the biological activity of these compounds as they are structurally similar in size to RALs, however regrettably at the time of writing no results have yet been obtained. Our focus instead returned to devising an alternative retrosynthesis of the resorcylate target, completely avoiding hemi-ketal formation and consequent problems.

3.4.5 Revised Retrosynthetic Analysis of (*S*)-Zearalenone (**3**)

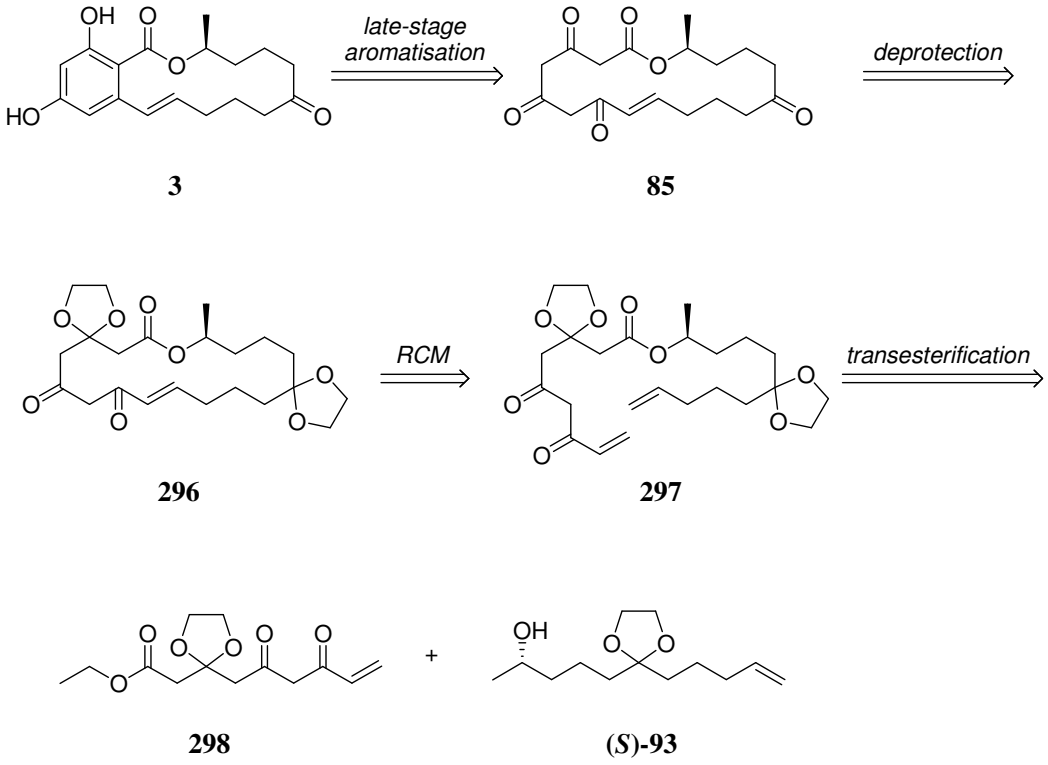
As discussed in section 3.4.3, in order to form target diketone **86** a synthetic strategy avoiding the simultaneous presence of a carbonyl at C-7 and alcohol at C-25 was necessary (Figure 31).



86

Figure 31. *Target Diketone* **86**.

A completely new retrosynthetic analysis was devised in order to initially protect the carbonyl at C-7, rather than the carbonyl at C-5. Thus the desired aromatisation precursor would be macrocyclic diketone **296** instead of diketone **86**. Macrocyclisation would still be accomplished by RCM, this time from diene **297**. This in turn would come from the transesterification of alcohol (*S*)-alcohol **93** (see Section 2.2) with vinyl ketone **298** (Scheme 123).



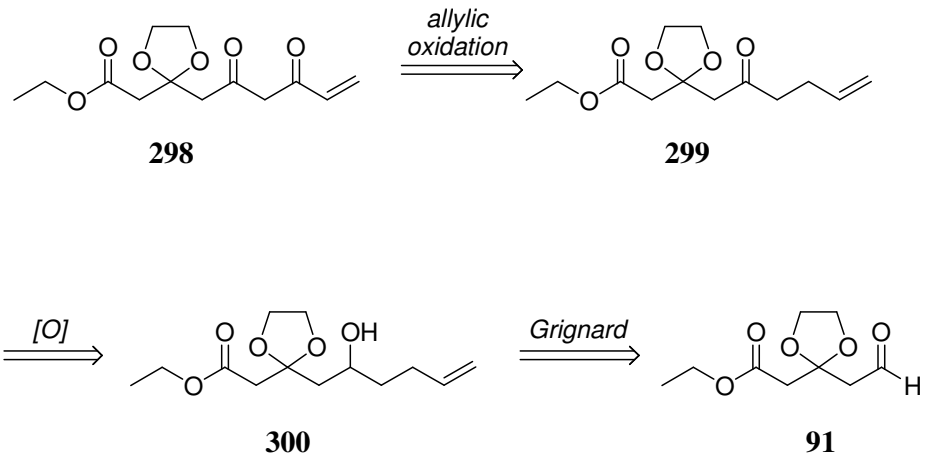
3 **85** **296** **297** **298** **(*S*)-93**

Scheme 123. *New Retrosynthetic Analysis to Protect the Carbonyl at C-7.*

This new retrosynthetic analysis gave vinyl ketone **298** as a primary target.

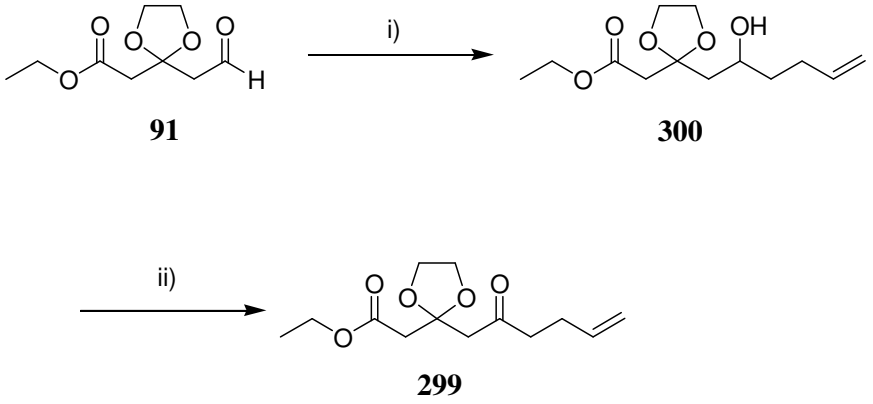
*3.4.5.3 Towards the Synthesis of Vinyl Ketone **298***

Further analysis of target vinyl ketone **298** yielded an allylic oxidation of ketone **299**. This could be obtained from a Grignard addition onto aldehyde **91** (see Section 3.2) and oxidation of the resultant alcohol **300** (Scheme 124).



Scheme 124. *Retrosynthetic Analysis of Vinyl Ketone* **298**

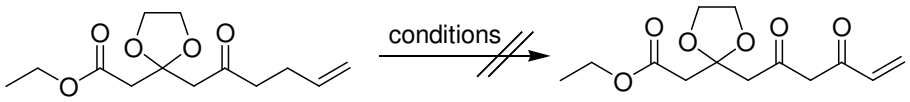
The Grignard reaction of aldehyde **91** with 4-pentenylmagnesium bromide (**96**) afforded only poor conversion to desired alcohol **300**, which proved difficult to separate from remaining aldehyde **91**. Instead the crude mixture was oxidised with Dess-Martin periodinane, allowing ketone **299** to be isolated in a disappointing 11% yield over the two steps (Scheme 125). Enough material was obtained however, to enable investigations to be made into the allylic oxidation step.



91 **300** **299**

Scheme 125. *Reagents and conditions:* i) a) **96**, THF, –78 °C, 2.5 h; ii) DMP, CH_2Cl_2, 0 °C to 23 °C, 1h, 11% over two steps.

Endeavours towards the allylic oxidation of ketone **299** proved unsuccessful (Scheme 126, Table 18).



299 **298**

Scheme 126. *Attempted Allylic Oxidation of Ketone* **299**.

Entry	*Reagents and conditions*	*Product*[†]
1	SeO_2, EtOH, 23 °C, 6 h[167]	S.M.
2	SeO_2, EtOH, 80 °C, 18 h	S.M.
3	$Mn(OAc)_3 \cdot 2H_2O$ (0.1 eq.), O_2, *t*-BuOOH (5.0 eq.), nonane, EtOAc, 23 °C, 36 h[168]	S.M.
4	SeO_2 (0.5 eq.), *t*-BuOOH (2.0 eq.), CH_2Cl_2, 23 °C, 18 h	S.M.
5	PDC (15 eq.), CH_2Cl_2, 23 °C, 18 h	S.M.
6	MnO_2 (15 eq.), CH_2Cl_2, 23 °C, 18 h	S.M.

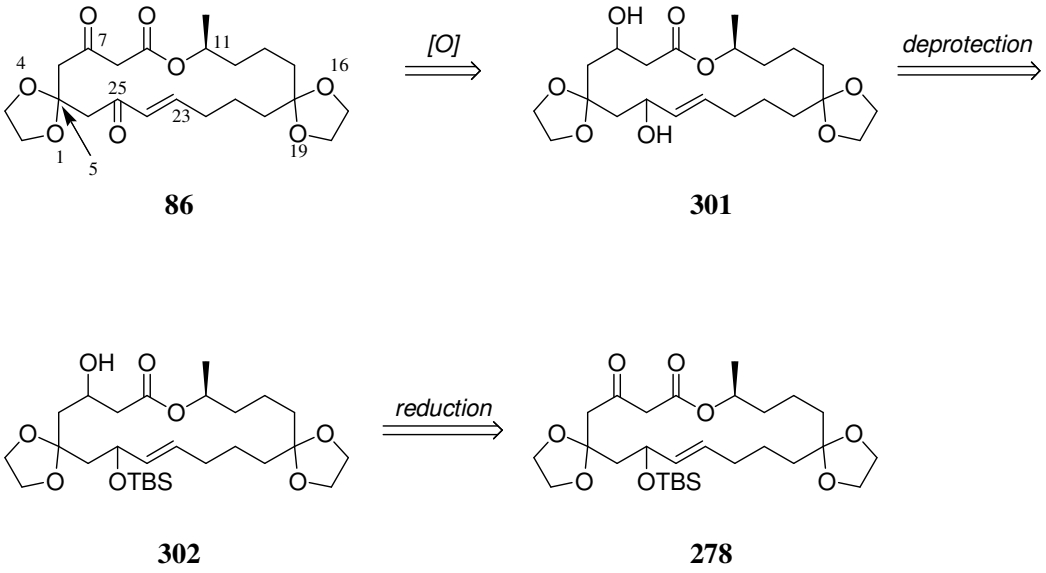
Table 18

[†]products determined by crude MS and ^{1}H NMR analysis.

Fortunately, at this time an alternative route was shown to be successful, so work in this area was discontinued.

3.4.6 Successful Method: Reduction-Oxidation Strategy

A method thus-far overlooked which would prevent the simultaneous presence of a carbonyl at C-7 and alcohol at C-25, was to carry out the selective reduction of the ketone at C-7 of macrocyclic silyl ether **278** before deprotection of silyl ether **302**, producing diol **301** (Scheme 127).

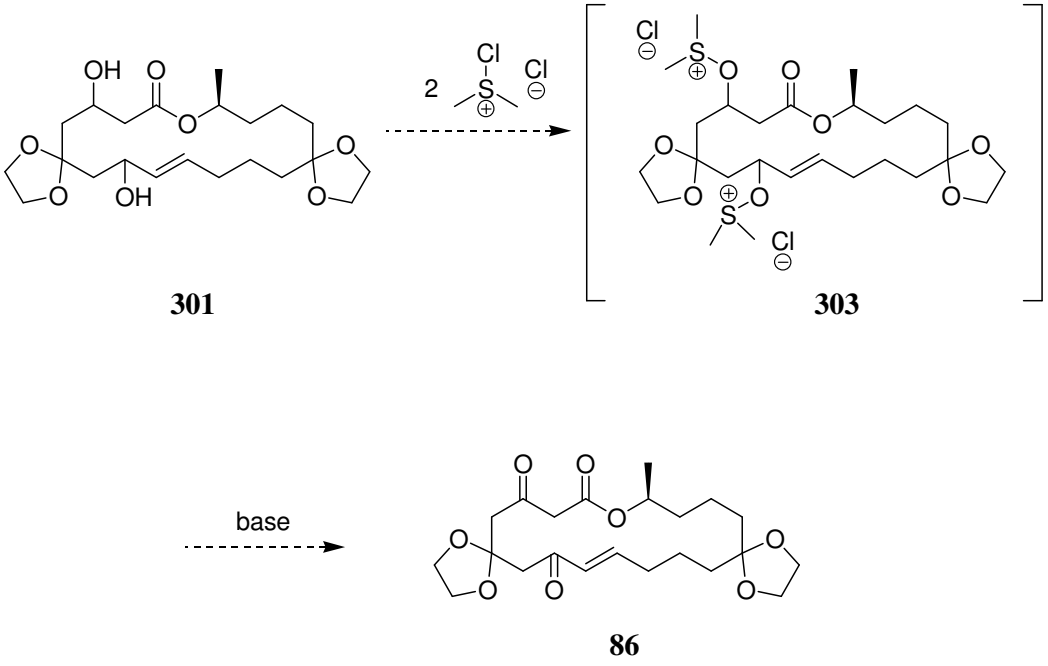


86 **301**

302 **278**

Scheme 127. *Synthetic Strategy via Reduction of Ketone at C-7 of Macrocyclic Silyl Ether* **278**.

It was anticipated that after silyl deprotection, oxidation of the diol **301** *via* a Swern oxidation would avoid any hemi-ketal formation,[169] for the reason that the mechanism would proceed with complete formation of dialkoxysulfonium ion **303** before base-promoted elimination to the ketone in a separate step (Scheme 128).

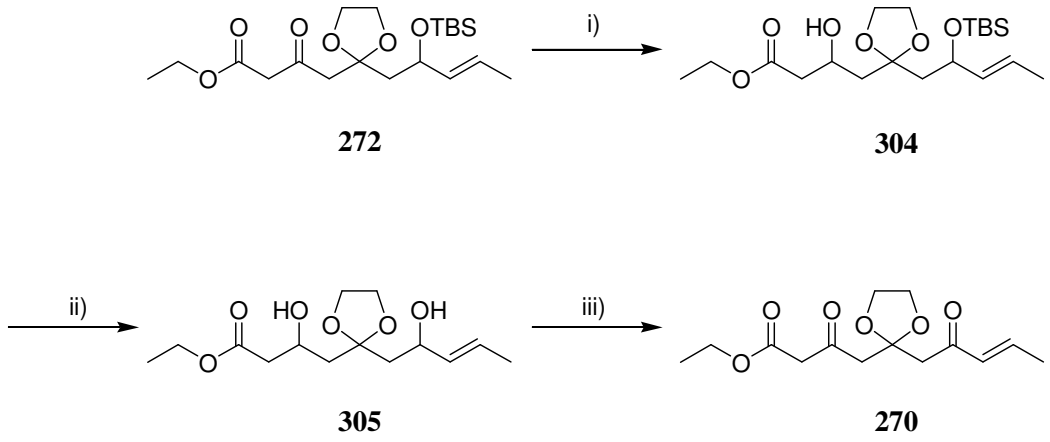


301 **303**

86

Scheme 128. *Mechanism of Swern Oxidation of Diol* **301.**

To model the system, the reduction of the ketone at C-7 was first carried out on the open chain silyl ether **272** which was in hand. The use of sodium borohydride at 0 °C allowed the selective reduction of the more reactive ketone in the presence of the ester group in excellent yield, producing alcohol **304**. TBAF deprotection allowed diol **305** to be isolated. The key double-Swern reaction proved more troublesome, with the crude reaction mixture containing several spots. Unfortunately, column chromatography failed to isolate enough material to characterise due to the small scale of the reaction, however the desired product **270** was detected in the crude mixture by MS (Scheme 129).

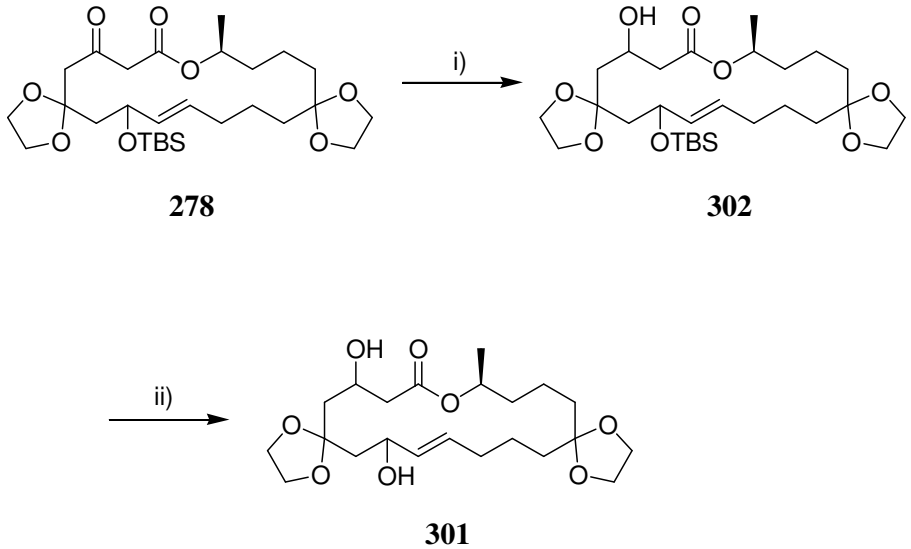


272 **304**

305 **270**

Scheme 129. *Reagents and conditions:* i) $NaBH_4$, EtOH, 0 °C, 20 min, 89%; ii) TBAF (1.0 M in THF), THF, 23 °C, 18 h, 47%; iii) a) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 1 h, b) Et_3N, –78 °C to 0 °C, 1h.

In light of these encouraging results, the reduction of macrocyclic silyl ether **278** was also carried out, yielding 88% of alcohol **302**. Silyl deprotection afforded diol **301** quantitatively (Scheme 130).



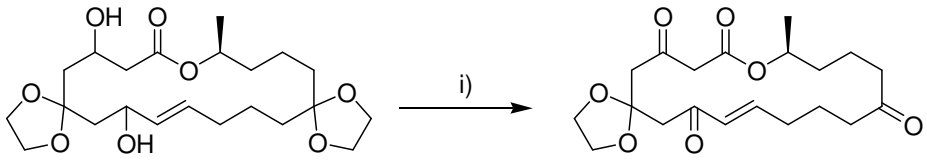
278 **302**

301

Scheme 130. *Reagents and conditions:* i) $NaBH_4$, EtOH, 0 °C, 20 min, 88%; ii) TBAF (1.0 M in THF), THF, 23 °C, 18 h, 99%.

The double-Swern oxidation of diol **301** was attempted and desired product **86** was observed in the crude MS spectrum. Disappointingly, decomposition was observed during column chromatography and diketone **86** could not be isolated. Instead, the

major product identified was ketal deprotected triketone **306** in 15% yield, as evidenced by only one ketal and three ketone signals in the ^{13}C NMR spectrum data (Scheme 131). It would be expected that if the western ketal had been deprotected, the resultant β-triketo ester would exist in a mixture of enol forms hence show increased complexity in the ^{1}H and ^{13}C NMR spectra.

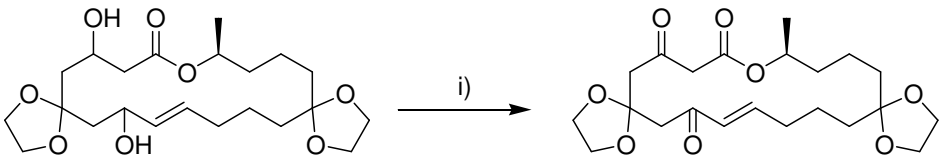


301 **306**

^{13}C NMR: δ 192.2, 197.0, 210.4

Scheme 131. *Reagents and conditions:* i) a) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 1 h, b) Et_3N, –78 °C to 0 °C, 1h, 15%.

Gratifyingly, when the procedure was repeated with minimal exposure to silica gel (increased polarity eluent), desired diketone **86** was isolated in a excellent yield (Scheme 132). This time both ketals and only the two expected ketones were evident in the ^{13}C NMR spectrum.



301 **86**

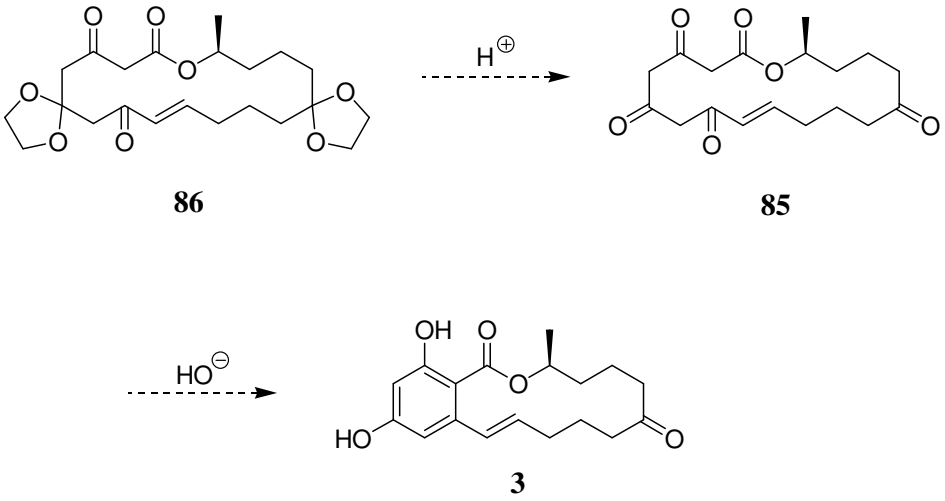
^{13}C NMR: δ 191.4, 197.5

Scheme 132. *Reagents and conditions:* i) a) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 1 h, b) Et_3N, –78 °C to 0 °C, 1h, 91%.

Finally, we had completed the synthesis of diketone **86**, which meant we were close to testing our key aromatisation step. These investigations will be discussed in the following section.

3.5 Aromatisation Studies of Diketone **86**

The final goal in the synthesis of (*S*)-zearalenone (**3**) was ketal deprotection and aromatisation of diketone **86** (Scheme 133). It was expected that the aromatisation of β-triketo ester **85** would be optimal in basic conditions, although it was possible that polyketide intermediate **85** could aromatise spontaneously under the acidic ketal deprotection conditions.[45]



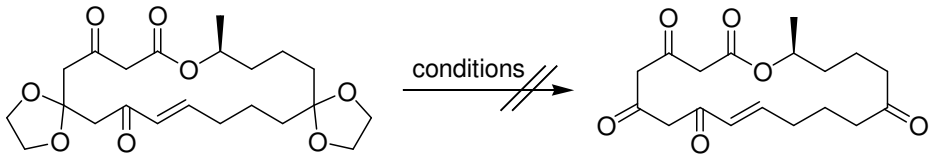
86 **85** **3**

Scheme 133. *The Final Steps for (S)-Zearalenone (***3***) Synthesis.*

The primary goal was examination of the ketal deprotection conditions.

3.5.1 Diketone **86** Under Acidic Conditions.

Due to the fact that deprotection of the eastern ketal group of diketone **86** had already been observed simply upon exposure to silica gel, along with evidence from the attempted ketal deprotection investigations of hemi-ketals **280 (**see Section 3.4.4), it was postulated that the western ketal would be more robust than the eastern. At this stage material was valuable, hence initial attempts were carried out on a small scale and MS spectra examined for evidence of products or starting materials (Scheme 134, Table 19)



86 **85**

Scheme 134. *Attempted Deprotection of Diketone* **86** *Under Acidic Conditions.*

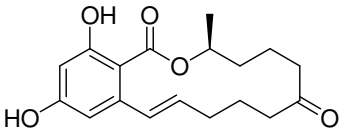
Entry	*Reagents and conditions*	$[M+H]^+$ †	*Suggested Product*
1	PPTS, acetone, H_2O, 23 °C, 72 h	381	Mono-deprotection
2	$NaClO_4$, AcOH, 23 °C, 72 h[61]	319	Dehydration of desired product
3	$Ni(OAc)_2$, AcOH, 80 °C, 6 h[61]	425	S.M.
4	3 M HCl, THF, 23 °C, 18 h	425	S.M.
5	1.25 M HCl in MeOH, 23 °C, 72 h	425	S.M.
6	*c*. HCl (2 drops), CH_2Cl_2, 40 °C, 2 h	425 + 381	S.M. and mono-deprotection
7	85% aq. TFA, 50 °C, 18 h	*	Decomposition

Table 19

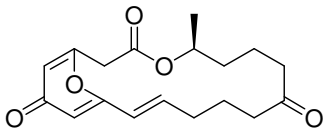
† determined from crude MS analysis; * no obviously identifiable products.

Surprisingly, under several sets of conditions only starting material was recovered (Table 19, Entries 3-5), despite our previous findings of the instability of diketone **86** to acidic silica. Desired β-triketo ester **85** (expected MS (CI) *m/z* 337 $[M+H]^+$) was not observed under any attempted conditions. However, the subsequent dehydration product was observed with sodium perchlorate in acetic acid (MS (CI) *m/z* 319 $[M+H]^+$, Entry 2). Interestingly, this is the same mass of the natural product, (*S*)-zearalenone (**3**). Unfortunately however, both the crude ^1H NMR spectrum and TLC analysis revealed many products and the natural product could not be identified. This suggests other undesired aromatisations may be occurring.

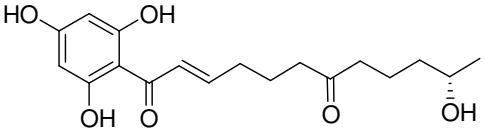
As discussed in section 1.2, there are four major aromatisation pathways for β-triketo esters. In addition, acidic conditions have been demonstrated by Harris *et al.* to favour *O*-cyclisations or Claisen condensations over aldol condensations. Thus aromatisation of β-triketo ester **85** may have occurred spontaneously under the acidic ketal deprotection conditions, to give an alternative product or a mixture of products. Alternative aromatisation products include 4-pyrone **295**, Claisen product **307** or 2-pyrone **308** (Scheme 135).



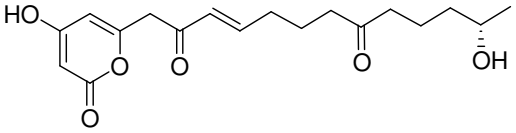
3
resorcylate (aldol)



295
4-pyrone



307
acylphloroglucinol (Claisen)

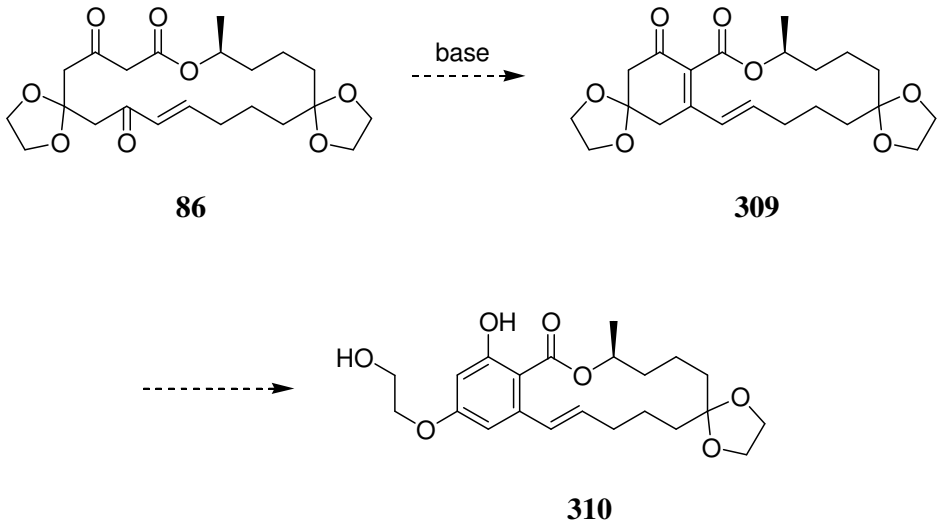


308
2-pyrone

Scheme 135. *Possible Aromatisation Products of β-Triketo ester* **85**

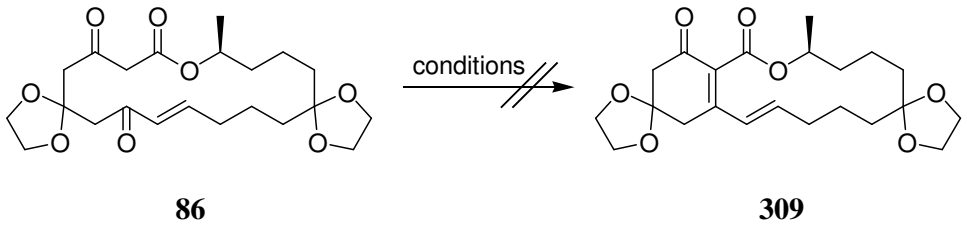
3.5.2 Diketone **86** Under Basic Conditions.

The desired resorcylate forming aromatisation occurs *via* an aldol-type pathway, with the attack of the β-keto ester carbon to the vinyl ketone. It was postulated that an intramolecular Knöevenagel reaction of precursor diketone **86** under basic conditions could be utilised to control the regioselectivity of the condensation.[170] This would promote selectively by the mild base deprotonating only the most acidic β-keto ester proton, generating diketal **309** as an intermediate. We postulated that aromatisation of diketal **309** would also occur under the reaction conditions, *via* enolisation, to generate (*S*)-zearalenone analogue **310** (Scheme 136).



Scheme 136. *Proposed Knöevenagel Condensation of Diketone* **86.**

Our initial Knöevenagel studies were carried out on small scale and this time crude ^{1}H NMR spectra were examined for evidence of products or starting materials (Scheme 137, Table 20).



Scheme 137. *Attempted Knöevenagel Condensation of Diketone* **86.**

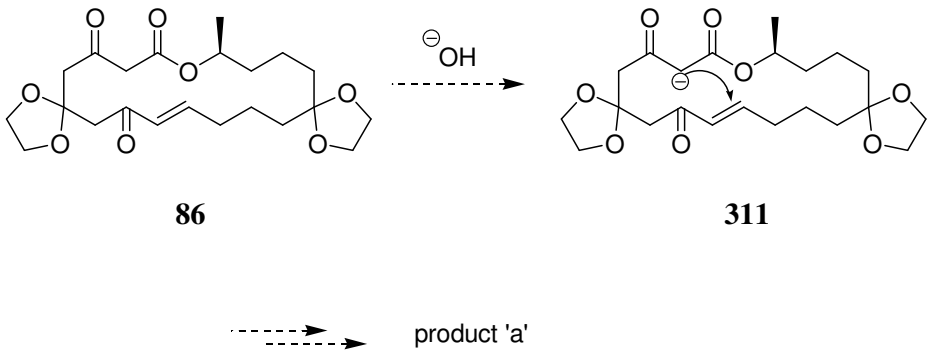
Entry	*Reagents and conditions*	*Product*[†]
1	DBU (1.1 eq.), PhMe, 65 °C, 18 h[170]	Many products
2	*t*-BuOK (0.95 eq.), *t*-BuOH, 50 °C, sealed vial, 6 h	Many products
3	0.1 M KOH in MeOH, 23 °C, 18 h	Unknown product 'a'
4	K_2CO_3, *i*-PrOH, CH_2Cl_2, 50 °C, 5 h[65]	Many products
5	K_2CO_3, *i*-PrOH, CH_2Cl_2, 23 °C, 24 h then 1 M HCl in MeOH, 2 h	Unknown product 'b'

Table 20

[†] products determined by crude ^{1}H NMR analysis.

Disappointingly, neither diketal **309** or aromatised product **310** could be detected from standard Knöevenagel reaction conditions, only a complex mixture of products which could not be identified (Table 20, Entries 1 and 2).

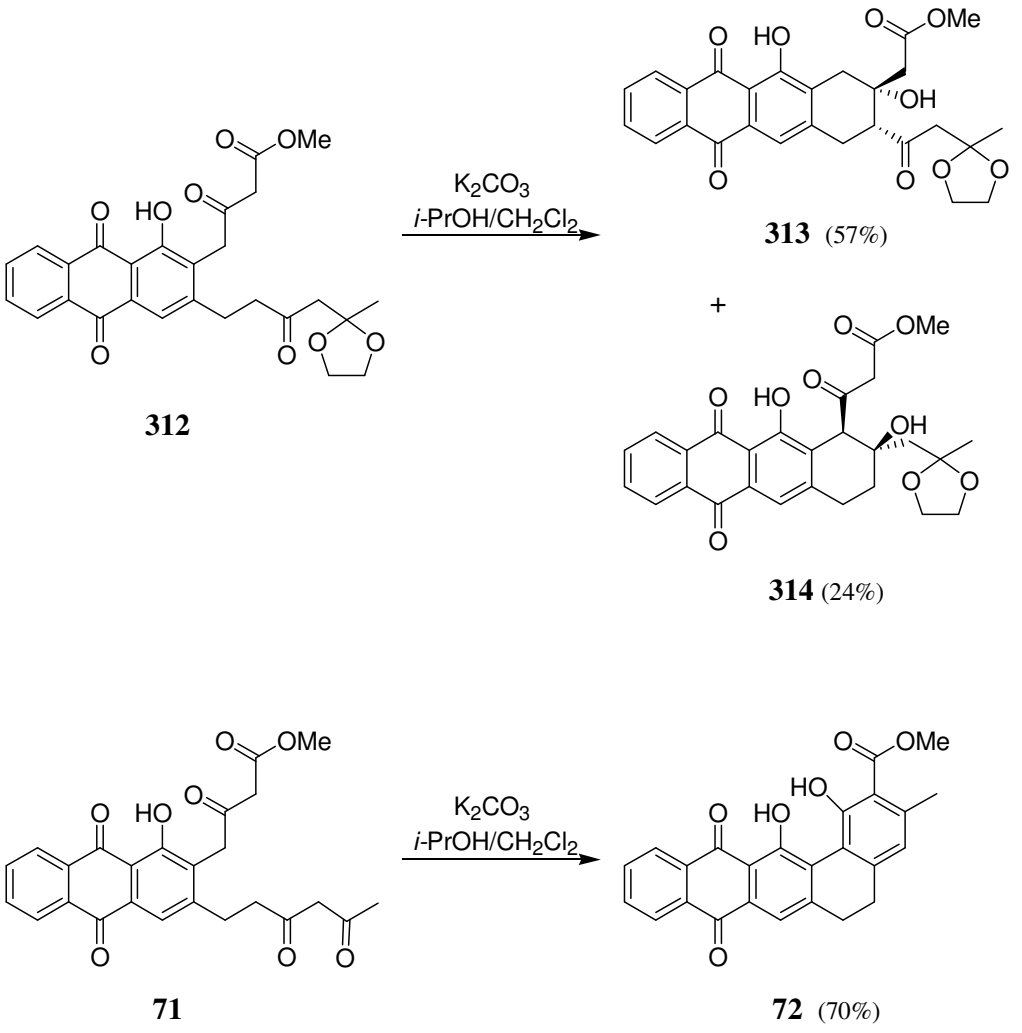
The use of methanolic potassium hydroxide had previously been demonstrated within our group to instigate aromatisation (see Chapter 4), however employing these conditions to diketone **86** led to the formation of unexpected product 'a'. Mysteriously, this product had no protons in the alkene or aromatic region of the ^{1}H NMR spectrum, and only two carbonyl peaks, at 169.9 and 206.1 respectively, in the ^{13}C NMR spectrum. The two ketals looked to have remained intact. This led us to suspect possible transannular additions from intramolecular attack of anion **311** on the conjugated enone (Scheme 138).



Scheme 138. *Postulated Intramolecular Transannular Additions of Diketone Anion* **311**

Unfortunately, insufficient quantity of unknown product 'a' was isolated to allow precise characterisation and speculation at the structure could not be confirmed.

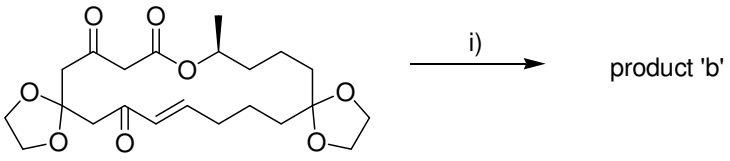
At this time, we were reminded of Krohn *et al.*'s report of a mild base-catalysed biomimetic aldol reaction used in the synthesis of benzo[*a*]naphthacenequinones (see Section 1.3).[65] When diketone **312** had been subjected to the reaction conditions, a mixture of two regioisomeric products **313** and **314** had been obtained in 57% and 24% yields respectively. However, ketal deprotected β-triketo ester **71** had given only a single regioisomer **72** in 70% yield (Scheme 139).



Scheme 139. *Krohn et al's Synthesis of benzo[a]naphthacenequinones.*

These findings suggest that the presence of ketals can affect the regioselectivity of condensations occurring under basic conditions.

Krohn's conditions were attempted on our system, resulting in many products (Table 20, Entry 4). However, when the reaction temperature was lowered and the time extended, after acidification a single product was recovered with 80% mass recovery (Entry 5). Fascinatingly, yet again it was an unidentified product, product 'b' (Scheme 140).



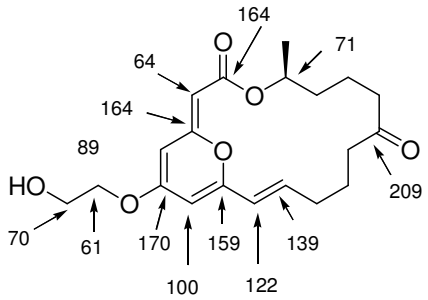
86

Scheme 140. *Reagents and conditions:* i) K_2CO_3, *i*-PrOH, CH_2Cl_2, 45 °C, 80% by mass.

The ^{1}H NMR spectrum of product 'b' clearly showed two coupling triplets integrating for 2H at approximately 4 ppm, which suggested that the western ketal had partially deprotected, possibly due to aromatisation. There were six protons above 5 ppm, three of which appeared as singlets. Significantly, the two alkene protons did not have greatly altered chemical shifts from starting diketone **86**, suggesting that they were still next to an unsaturated carbon joined to oxygen.

The ^{13}C NMR spectrum proved equally puzzling, with four peaks at around 160-170 ppm, two at 120-140 ppm (assigned as the carbon-carbon double bond) and two at 90-100 ppm. Importantly, comparison to the spectra of (*S*)-zearalenone (**3**) and other literature analogues indicated that product 'b' was not a resorcylate, as the chemical shifts of the aromatic and styrene protons did not match those expected.

31 mg (80% by mass) of product 'b' was isolated in excellent purity, allowing careful examination of 2-D correlation spectra (see Appendix 3). This culminated in our tentative assignment of product 'b' as the highly conjugated *O*-cyclised lactone **315** (Figure 32 and Figure 33).



315

Figure 32. *Postulated Structure of Product 'b' with labelled ^{13}C NMR Shifts (in ppm).*

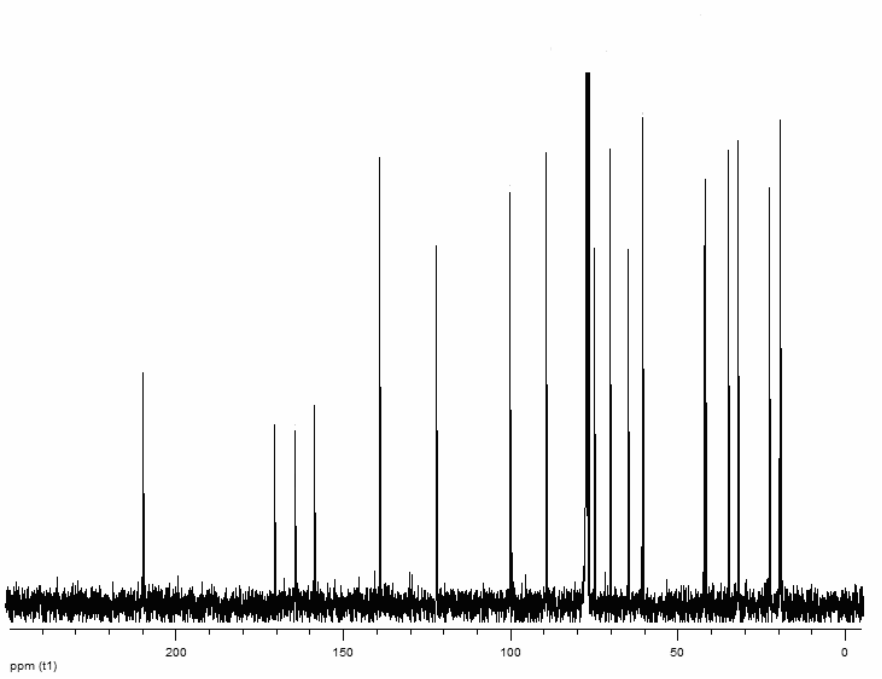


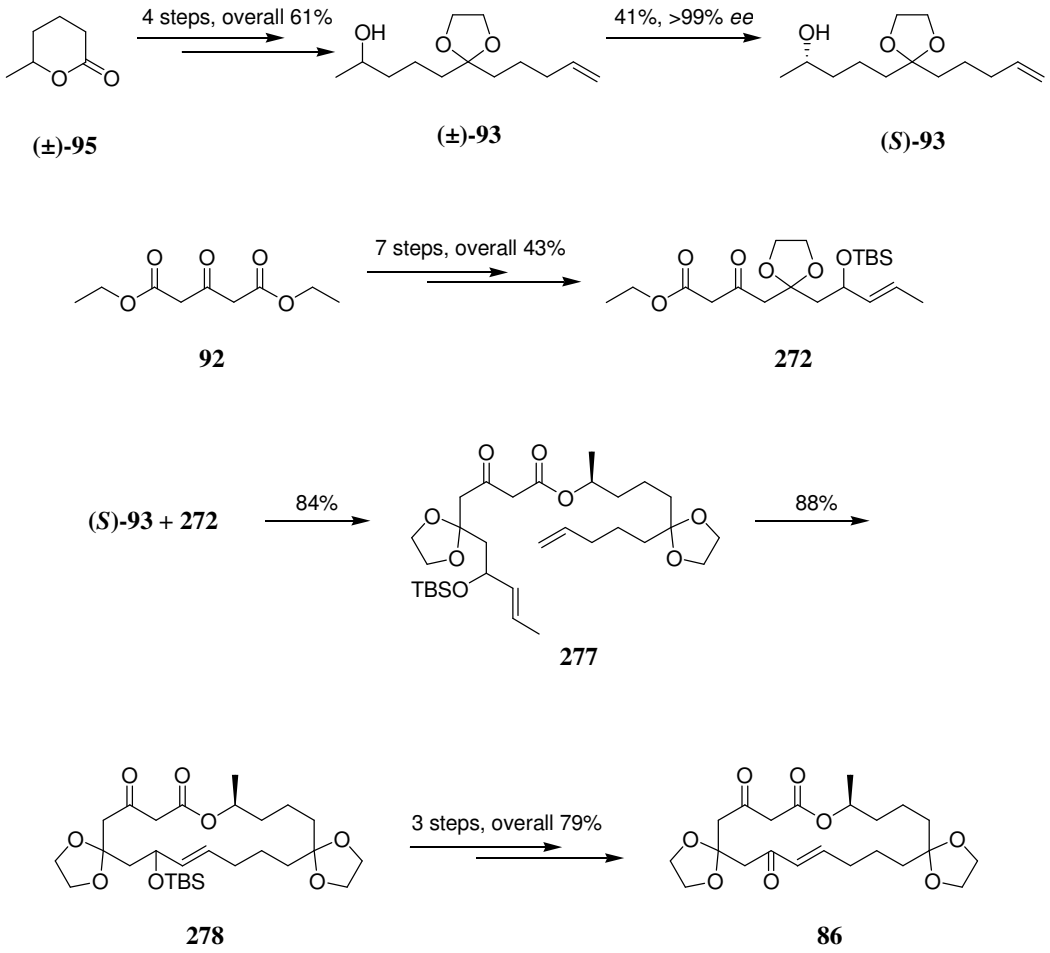
Figure 33. *^{13}C NMR Spectrum of Product* **315.**

Although product 'b' could not be confirmed as lactone **315** by MS, microanalysis was obtained to verify the molecular formula. Sadly, product 'b' is not crystalline hence absolute confirmation by X-ray crystallography was not possible. It is hoped that the biological activity of product 'b' will be tested once its identity can be authenticated.

Unfortunately, at this time all material had been exhausted hence investigations into the aromatisations of diketone **86** could not continue. Our initial attempts had, however, indisputably demonstrated the sensitivity of our poly-β-carbonyl system to variations in reaction conditions, whilst underlining the need for precise optimisation to discover the prerequisite conditions for desired aromatisation to (*S*)-zearalenone (**3**).

3.6 Conclusions

The second retrosynthetic analysis of (*S*)-zearalenone (**3**) discussed in this chapter had been a definite improvement on the first. Although the RCM strategy for macrocyclisation had been comparable to the previous RCEYM, the new route had enabled the synthesis of the elusive diketone **86** to be accomplished in three steps from silyl ether **278** (Scheme 141).



Scheme 141. *Synthesis of Diketone* **86** *via RCM.*

Diketone **86** proved sensitive to both acidic and basic conditions, undergoing partial ketal-deprotection on silica gel and being prone to a variety of condensations and decomposition pathways upon treatment with strong acid or base.

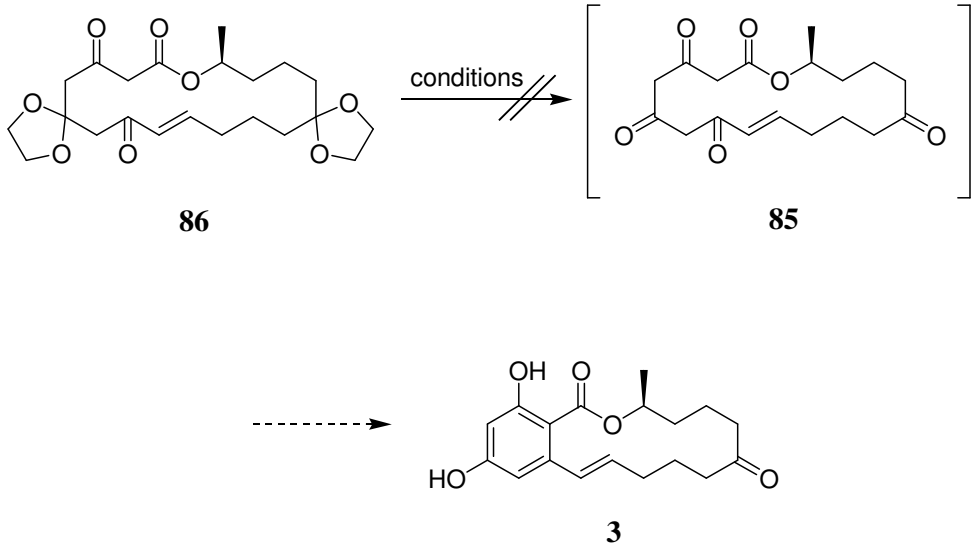
Whilst with unlimited time and resources conditions could probably be established to optimise the aromatisation of diketone **86** to (*S*)-zearalenone (**3**), it would be by no means certain that the same conditions would work for other resorcylate systems. This study illustrates the power of biosynthesis *via* the polyketide pathway: the levels of organisation demonstrated by enzymes is phenomenal and reproducing this control under laboratory conditions is no mean feat.

We concluded from this work that in order to discover a reliable and general biomimetic synthesis of resorcylates it will be necessary to introduce control into the system. This could be possible either by the introduction of directing groups for the condensation, or masking groups for the β-triketo ester functionality which do not require acid or strong base in order to remove. This has become the new focus of our group's synthetic studies and our new general strategies will be discussed briefly in the next and final chapter, Chapter 4.

Chapter Four: Results and Discussion – Dioxinone Strategy for the Synthesis of Resorcylates

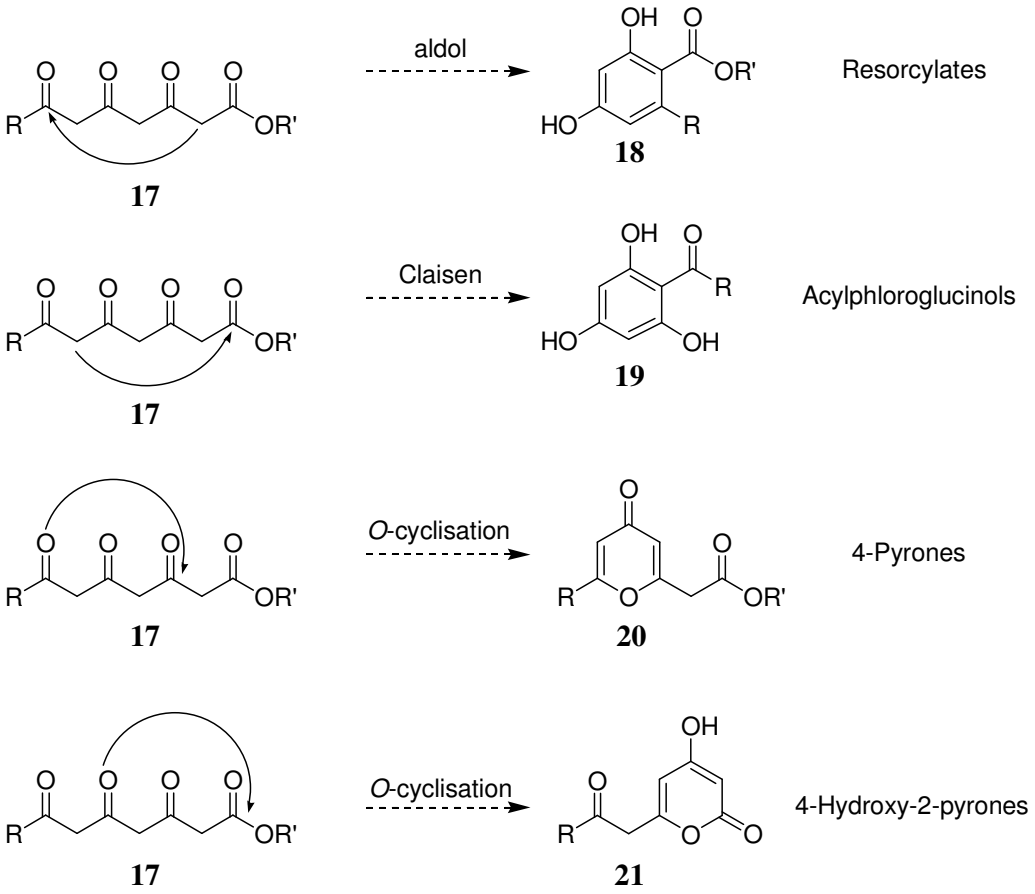
4.1 Introduction

Our studies into the biomimetic synthesis of (*S*)-zearalenone (**3**) *via* a late-stage aromatisation strategy discussed in the previous two chapters had concluded that the key aromatisation step required an element of control in order to become feasible. It had initially been hoped that deprotection of the ketals of diketone **86** would provide β-triketo ester **85**, which would aromatise to the resorcylate natural product under the correct conditions. Unfortunately this approach proved unsuccessful (Scheme 142).



Scheme 142. *Unsuccessful Strategy for the Synthesis of (S)-Zearalenone* (**3**)

The aromatisation of a β-triketo ester to form a resorcylate occurs *via* an intramolecular aldol-dehydration reaction. The problem is that β-triketo esters can also undergo Claisen condensations or *O*-cyclisations to form a variety of different aromatic products. Controlling which of these various aromatisations occurs is essential for our approach to be a success (Scheme 143).

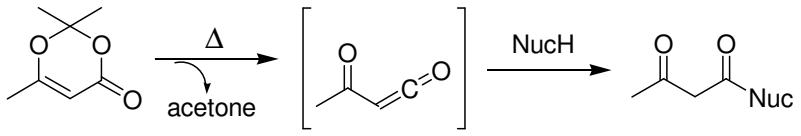


Scheme 143. *Potential Aromatisations of β-Triketo esters* **17**.

This chapter examines new strategies devised to regulate the condensations of β-triketo esters and generate resorcylates.

4.1.1 Dioxinones as β-Ketoester Synthons

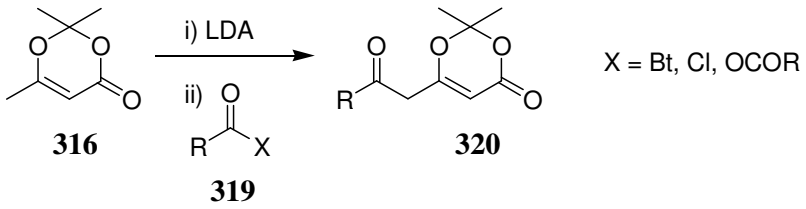
The diketene-acetone adduct, 2,2,6-trimethyl-4H-1,3-dioxin-4-one (**316**), can be opened at elevated temperatures with nucleophiles such as alcohols, amines and thiols to provide β-keto esters, β-keto amides or β-keto thio esters respectively. This reaction occurs *via* the pyrolysis of dioxinone **316** to form acetylketene **317**, which then reacts with the nucleophile to give the desired product **318** (Scheme 144).[171-173]



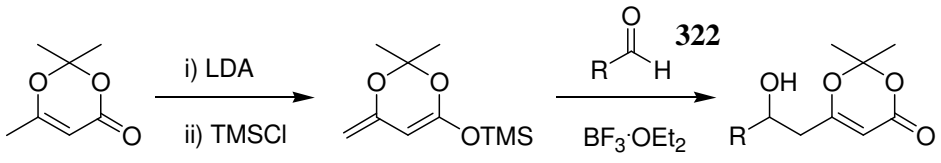
316 **317** **318**

Scheme 144. *Nucleophilic Opening of Dioxinone* **316**.

Dioxinones such as **316** can also be acylated with activated carbonyl derivatives **319** to generate acyl dioxinone derivatives **320**.[174, 175] Silyl enol ethers such as **321** can also be made from dioxinones such as **316**, and then employed in vinylogous Muikayama aldol reactions[176] with aldehydes **322** to generate alcohols **323** (Scheme 145).



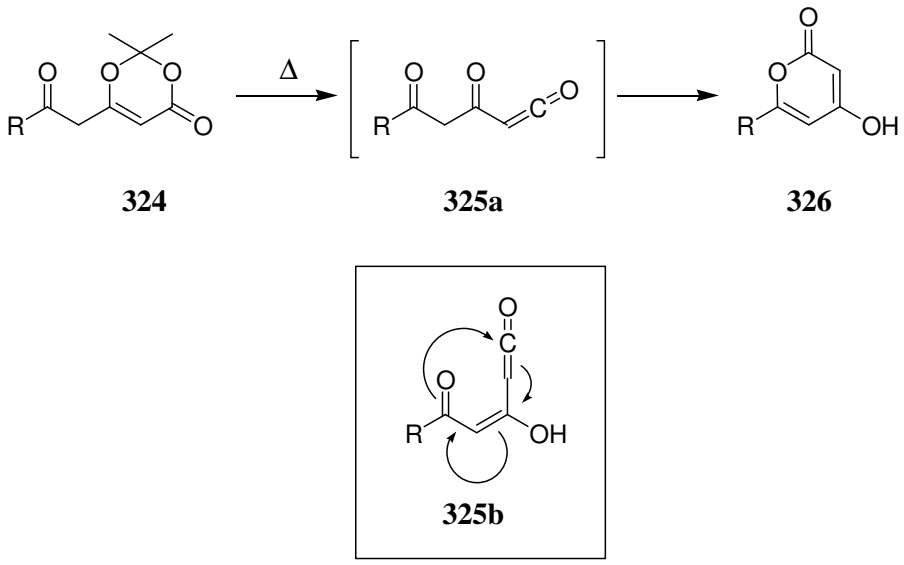
316 **319** **320**



316 **321** **323**

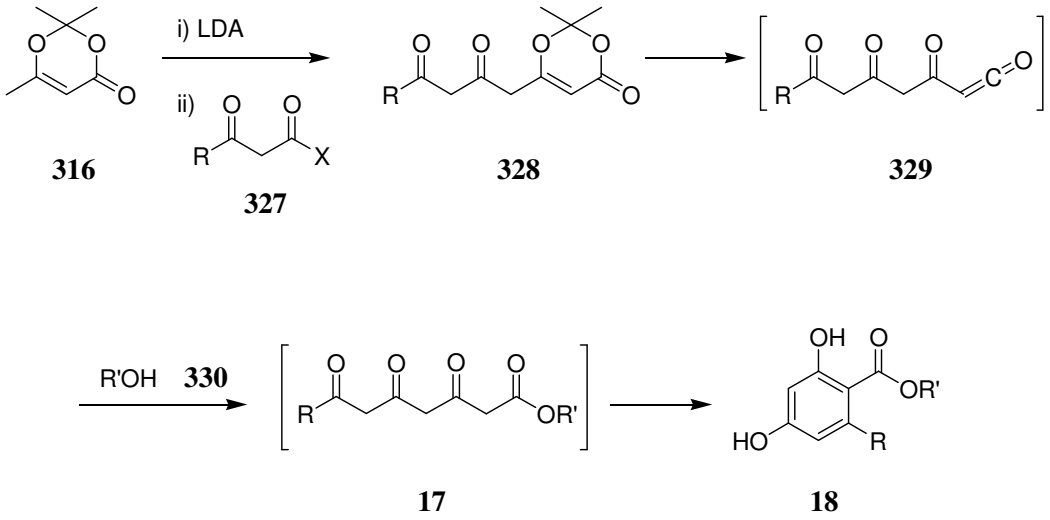
Scheme 145. *Acylation of Dioxinone* **316** (Bt = benzo[1,2,3]triazole).

In 2005, Katritzky *et al.* carried out investigations into applications of dioxinone **316** in polyketide chemistry and found that acyl dioxinone derivatives **324** will rearrange to 2-pyrones **326** by thermolysis, in the absence of nucleophiles. The mechanism involves intermediate **325** (Scheme 146).[175]



Scheme 146. *Thermolysis of Acyl-dioxinones* **324**

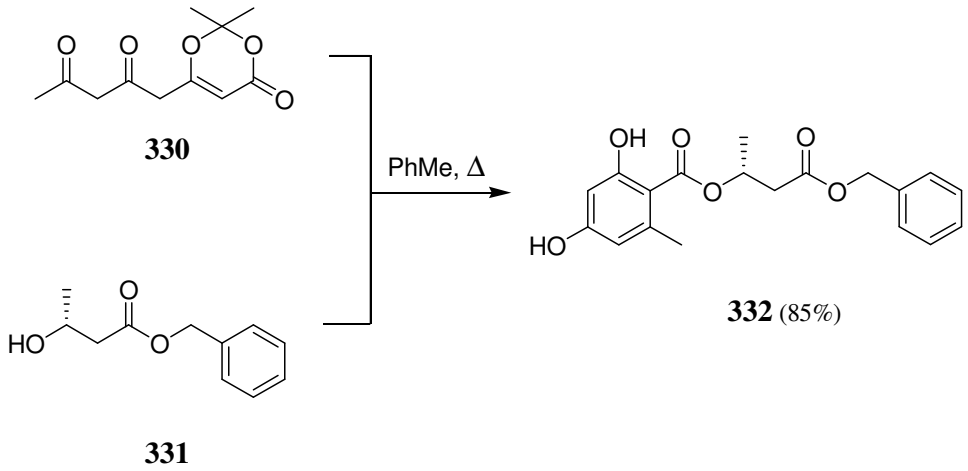
We became interested in dioxinone chemistry since the acylation of dioxinone **316** with a β-keto acid derivative **327** could potentially generate dioxinone analogue **328**. This could act as a masked β-triketo ester equivalent. It was hoped that the thermolysis of a dioxinone analogue **328** in the presence of an alcohol **330** could result in *in situ* β-triketo ester **17** generation, which could be followed by aromatisation to form the resorcylate **18** without the need for additional acid or base (Scheme 147).



Scheme 147. *Proposed use of Dioxinones to Generate Resorcylates.*

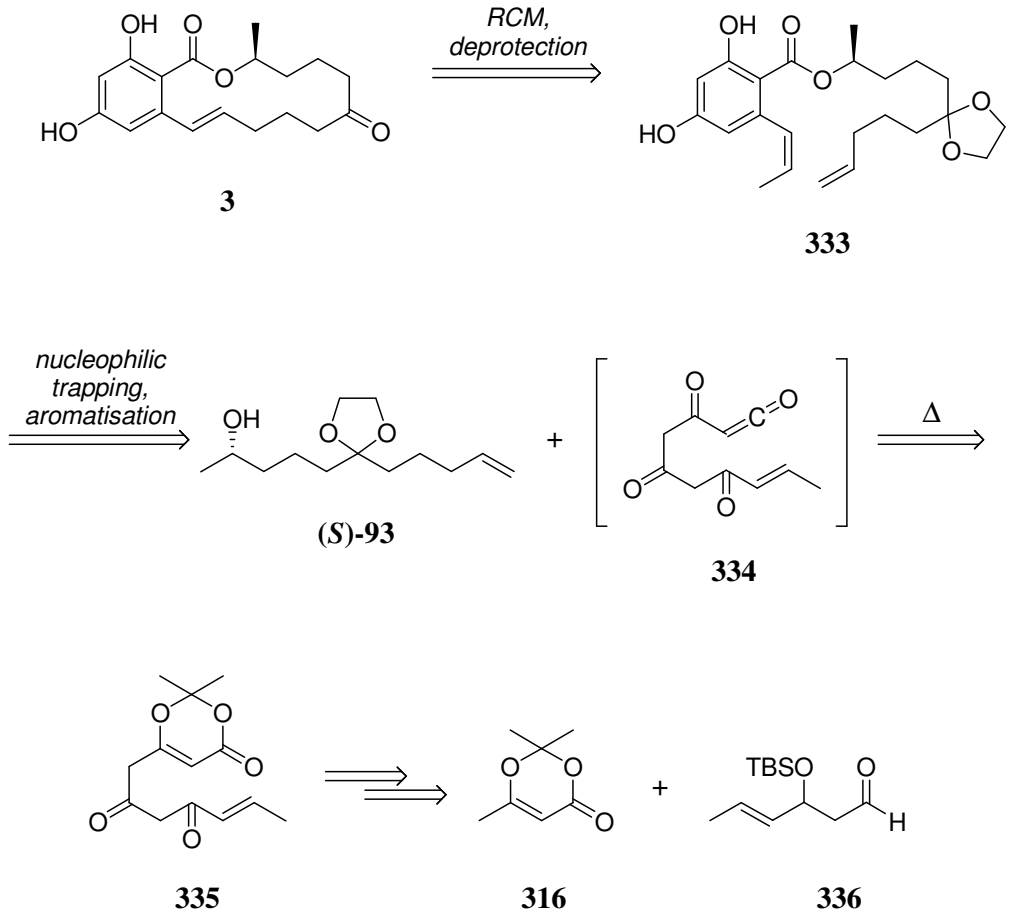
4.1.2 Previous Unpublished Synthetic Work Within Our Group

Initial results within our group[66] had proven extremely encouraging: when dioxinone analogue **330** was heated with alcohol **331** in toluene at 100 °C, the only observed product was resorcylate **332** in 85% yield (Scheme 148). Neither the 2-pyrone nor the Claisen product, which could result from thermolysis and rearrangement (see Scheme 146), were detected.



Scheme 148. *Previous Demonstration of Aromatisation Utilising Dioxinone Analogue* **330**.

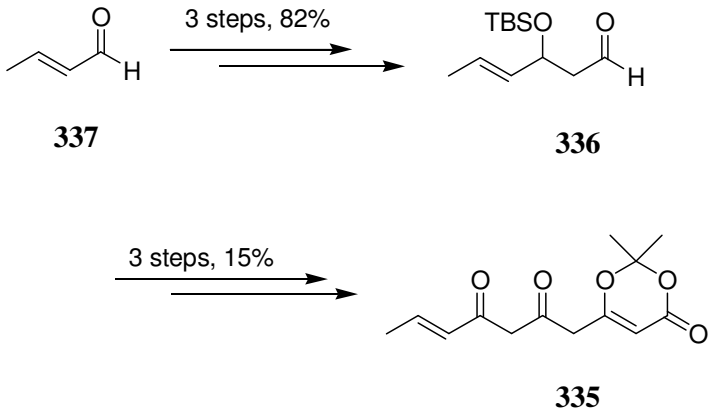
Following on from this lead, studies had commenced into employing dioxinone in the total synthesis of our primary resorcylate target, (*S*)-zearalenone (**3**). Retrosynthetic analysis by RCM gave target diene **333**, formed from the pyrolysis of dioxinone **335** and trapping of intermediate ketene **334** with previously synthesised (*S*)-alcohol **93** (see Section 2.2). Our previous investigations had advocated better overall yields from the vinylogous Muikayama aldol procedure with aldehyde **336** followed by oxidation, rather than direct acylation of dioxinone **316** (Scheme 149).[66]



3 **333** **(*S*)-93** **334** **335** **316** **336**

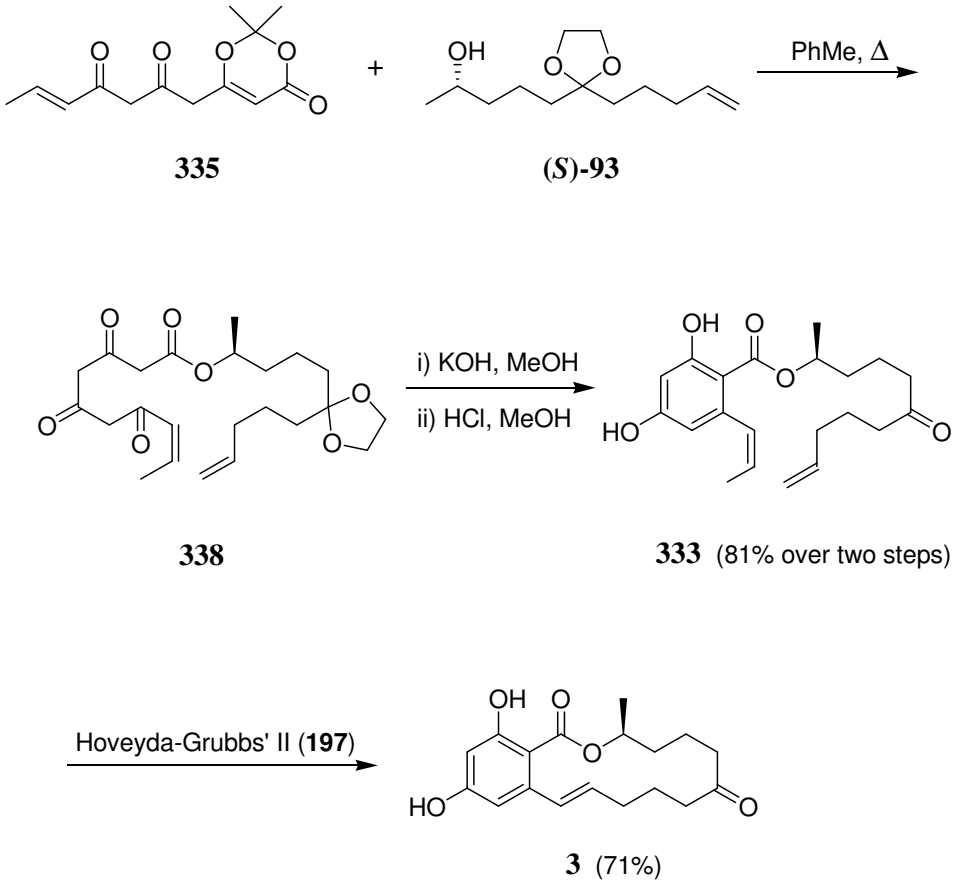
Scheme 149. *Retrosynthetic Analysis of (S)-Zearalenone Employing Dioxinone* **316** *and RCM.*

Aldehyde **336** has recently been synthesised within our group[177] in three steps with overall 82% yield, from crotonaldehyde (**337**) and ethyl acetate (**190**). The vinylogous Muikayama aldol reaction was moderate yielding, however allowed dioxinone analogue **335** to be obtained in four further steps, with overall 15% yield (Scheme 150).



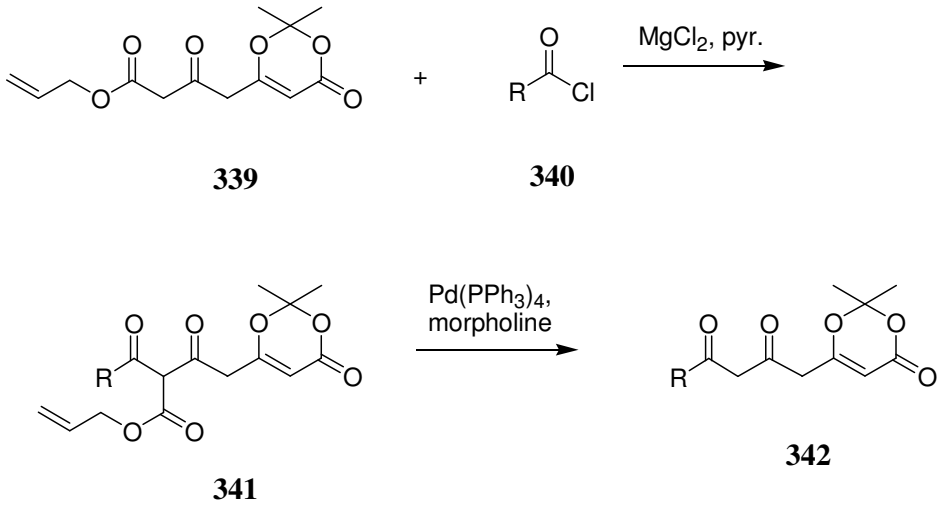
Scheme 150. *Synthesis of Dioxinone Analogue* **335**.

Crucially, reaction of dioxinone analogue **335** with (*S*)-alcohol **93** in toluene at 100 °C was shown to provide non-aromatic β-triketo ester **338**, which existed as a mixture of tautomeric forms. Treatment of the crude product with excess potassium hydroxide in methanol, followed by acidification with methanolic HCl, resulted in ketal deprotection with concomitant aromatisation to afford resorcylate product **333** in an excellent 81% over the two steps. Ring-closing metathesis with Hoveyda-Grubbs' second generation catalyst (**197**) was successful, constituting our first complete synthesis of the natural product, (*S*)-zearalenone (**3**) (Scheme 151).



Scheme 151. *Summary of Successful (S)-Zearalenone* (**3**) *Synthesis.*

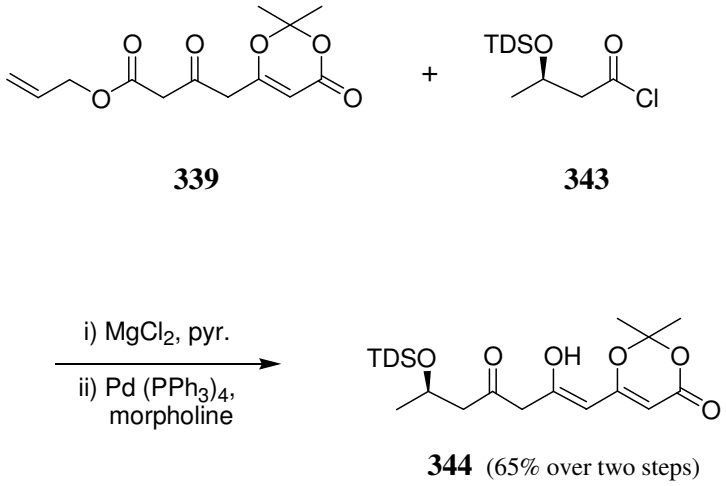
A second avenue of investigation[178] has led to an improved procedure for acylation of dioxinones. Treatment of dioxinone analogue **339** with an acid chloride **340**, followed by mild palladium-catalysed deallylation and decarboxylation of products **341**, generated dioxinone analogues **342** in improved yields to the Muikayama procedures previously utilised (Scheme 152).



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

Scheme 152. *Improved protocol for Dioxinone Analogues* **342** *Synthesis*

For example, following this procedure β-triketo ester equivalent **344** was synthesised from dioxinone analogues **339** and acid chloride **343** in excellent yields (Scheme 153).



339 **343** **344** (65% over two steps)

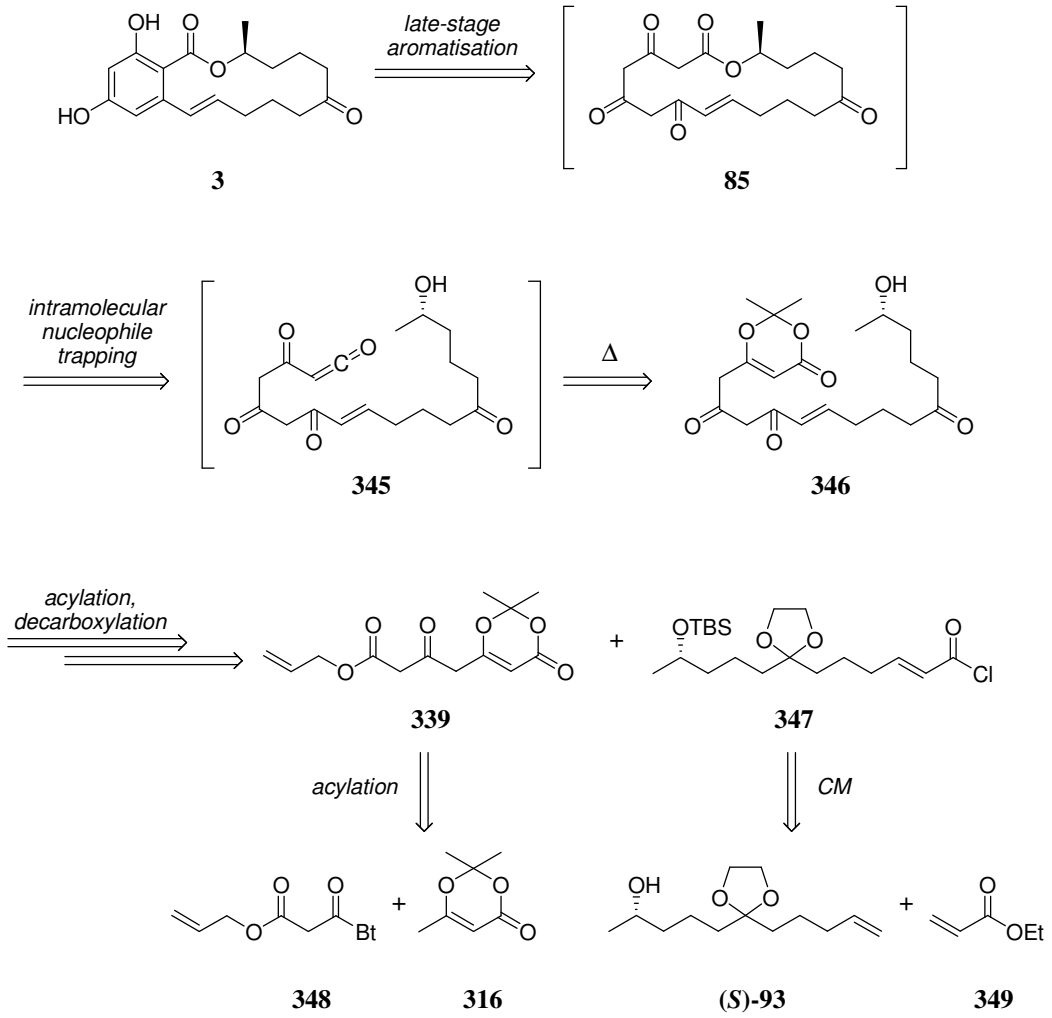
Scheme 153. *Example of Dioxinone Analogue* **344** *Synthesis.*

With these two recent key discoveries in mind, our attention turned to improving our procedure and the possibility of performing an intramolecular dioxinone-opening macrolactonisation-aromatisation.

4.2 Investigations Towards An Intramolecular Macrolactonisation-Aromatisation Procedure.

During the aforementioned synthesis of (*S*)-zearalenone (**3**) (see Section 4.1.2), difficulties had initially been encountered during the RCM procedure. It was found that Grubbs' second generation catalyst (**196**) was inactive in this system, which was attributed to the presence of phenol groups in the substrate.[80] Eventually, the more robust Hoveyda-Grubbs' second generation catalyst (**197**) (see Section 2.4.2, Figure 16) had successfully provided (*S*)-zearalenone (**3**), but with an *E/Z* ratio of 85 : 15.

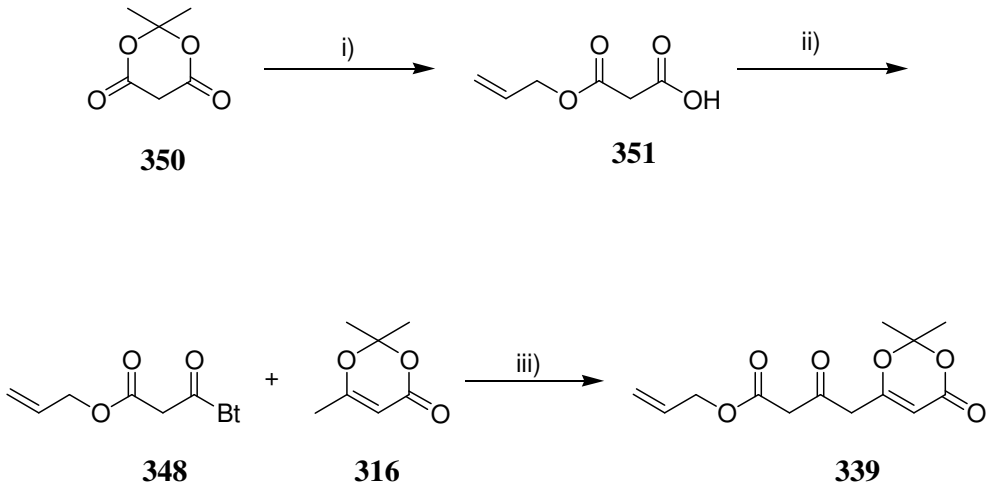
It was hypothesised that reversing the order of the two key disconnections, metathesis and dioxinone pyrolysis, could result in improved overall efficiency. The modified retrosynthetic analysis envisaged thermolysis and intramolecular aromatisation of alcohol **346**, through intermediate **345**. It was anticipated the alcohol functionality would need to be masked during the alkylation of dioxinone analogue **339** with alkene **347**. Alkene **347** could be made from cross-metathesis (CM) of a protected derivative of (*S*)-alcohol **93** and ethyl acrylate (**349**) (Scheme 154).



Scheme 154. *Retrosynthetic Analysis of (S)-Zearalenone* (**3**) *Employing CM and Intramolecular Dioxinone Opening.*

4.2.1 Synthesis of Dioxinone Analogue **339**.

The synthesis of dioxinone analogue **339** commenced from allylic ester **351**, which was formed from the opening of Meldrum's acid (**350**)[179] with allylic alcohol. Activation of ester **351** as the benzotriazole derivative **348** enabled acylation of dioxinone **316** to provide target **339** in good yield[175] (Scheme 155).

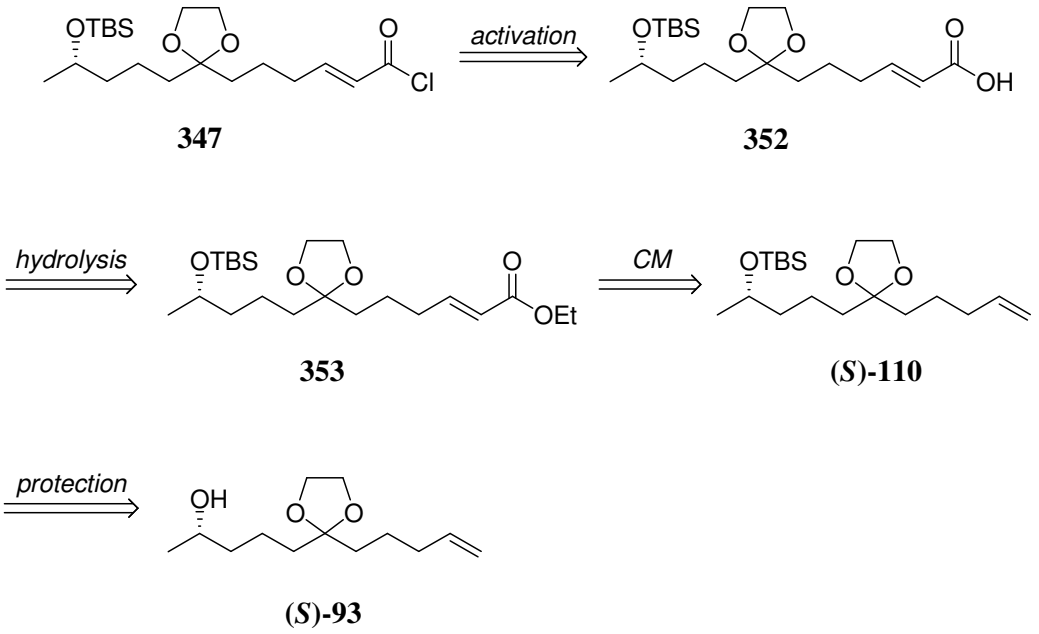


Scheme 155. *Reagents and conditions:* i) allylic alcohol, 100 °C, 6 h, 62%; ii) 1*H*-benzotriazole, $SOCl_2$, CH_2Cl_2, 23 °C, 4 h, 60%; iii) a) *n*-BuLi (4.0 eq.), HMDS (4.0 eq.), –78 °C, 30 min; b) **316** (4.0 eq.), –78 °C, 1.5 h; c) **348**, –78 °C to 23 °C, 18 h, 65%.

Acyl benzotriazole **348** was difficult to separate from dioxinone analogue **339** and also found to be partially hydrolysed upon column chromatography, which is reflected in the moderate isolated yields.

4.2.2 Synthesis of the Acylation Partner

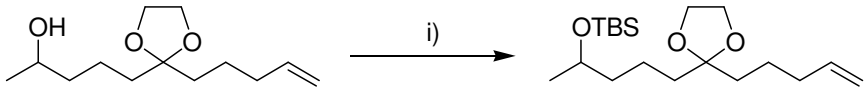
Retrosynthetic analysis of acid chloride **347** proceeded *via* the activation of acid **352**, which would be obtained from the hydrolysis of ester **353**. This could be produced from CM of (*S*)-silyl ether **110** with ethyl acrylate (**349**) and in turn, (*S*)-silyl ether **110** would be formed from silyl protection of (*S*)-alcohol **93** (Scheme 156).



347 **352** **353** **(*S*)-110** **(*S*)-93**

Scheme 156. *Retrosynthetic Analysis of Acid Chloride* **347**.

The protection of (±)-alcohol **93** to hand as a TBS ether was first investigated. It was found that standard conditions of TBSCl with imidazole catalysis failed, hence Corey's improved protocol using TBS-triflate and 2,6-lutidine[180] was attempted and found to be a considerable improvement, yielding 86% of (±)-silyl ether **110** (Scheme 157).



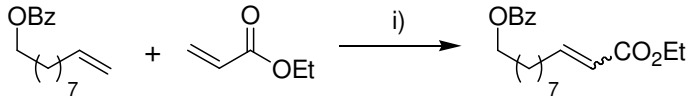
(±)-93 **(±)-110**

Scheme 157. *Reagents and conditions:* i) TBSOTf, 2,6-lutidine, CH_2Cl_2, 23 °C, 20 min, 86%.

Intermolecular metathesis of olefins has long been regarded as inferior to intramolecular procedures, however the evolution of new catalysts has allowed improvement of the selectivity and efficiency of CM procedures.[181] The major drawback of CM is the competing dimerisation or self-metathesis reactions, which cause by-products and lowered yields.

The field of CM has been revolutionised by the advent of Grubbs' and Hoveyda-Grubbs' second generation catalysts (**196** and **197**, see Section 2.4.2, Figure 16), which are tolerant to conjugated electron-deficient olefins. These olefins exhibit an extremely slow rate of dimerisation, meaning that they are able to be used in excess as cross-coupling partners, resulting in increased selectivity for the crossed product.

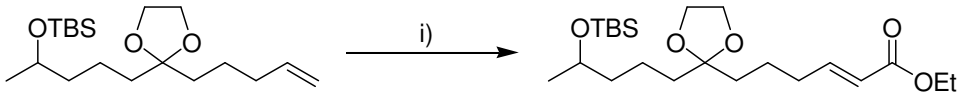
Grubbs and co-workers observed that CM reactions between α,β-unsaturated esters, aldehydes and ketones with simple terminal olefins proceeded in excellent yields with impressive *E*-selectivity. For example, CM of ethyl acrylate (**349**) and alkene **354** generated alkene **355** with and *E/Z* ratio of 4.5 : 1, one of the lower selectivities reported amongst the examples (Scheme 158).[182]



354 **349** **355**

Scheme 158. *Reagents and conditions:* i) Grubbs' II (**196**) (5 mol%), CH_2Cl_2, 45 °C, 91%, *E/Z* 4.5 : 1.

With this in mind, the cross-metathesis of (±)-silyl ether **110** with ethyl acrylate (**349**) was attempted, following Grubbs' protocol.[182] To our delight, spot-to-spot conversion was observed and alkene ester **353** was isolated in 77% yield. Furthermore, alkene **353** was observed to have an alkene coupling constant of 15.5 Hz and no evidence of the *cis*-isomer could be detected (Scheme 159).

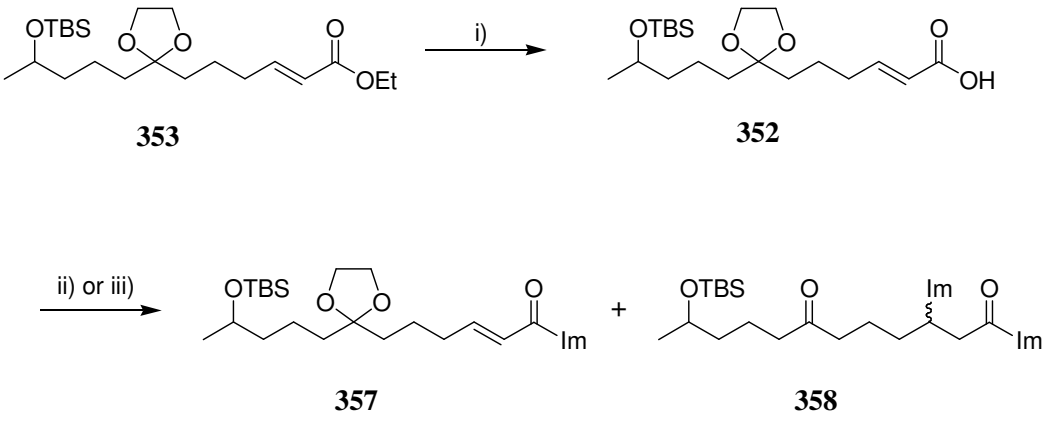


(±)-110 **353**

Scheme 159. *Reagents and conditions:* i) **349**, Hoveyda-Grubbs' II (**197**) (5 mol%), CH_2Cl_2, 45 °C, 2.5 h, 77%, *E/Z* >99 : 1.

Saponification of ester **353** with sodium hydroxide yielded acid **352**, however subsequent attempts to activate the acid as an imidazole derivative resulted in a

mixture of products. The desired product **357** and product **358** resulting from conjugate addition, were both indicated by crude MS and ^{1}H NMR analysis (Scheme 160).

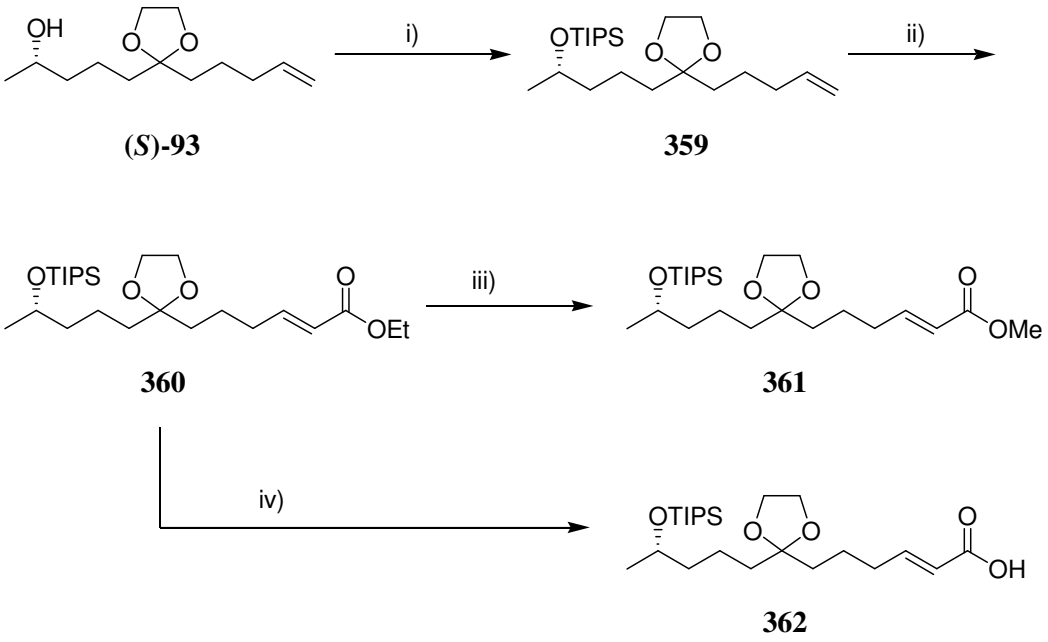


353 **352** **357** **358**

Scheme 160. *Reagents and conditions:* i) 2.0 M NaOH, EtOH, 18 h, 78%; ii) CDI (1.5 eq.), DMAP, CH_2Cl_2, 23 °C, 3 h; iii) EDC·HCl (1.1 eq.), Imid. (1.0 eq.), DMF, 23 °C, 72 h.

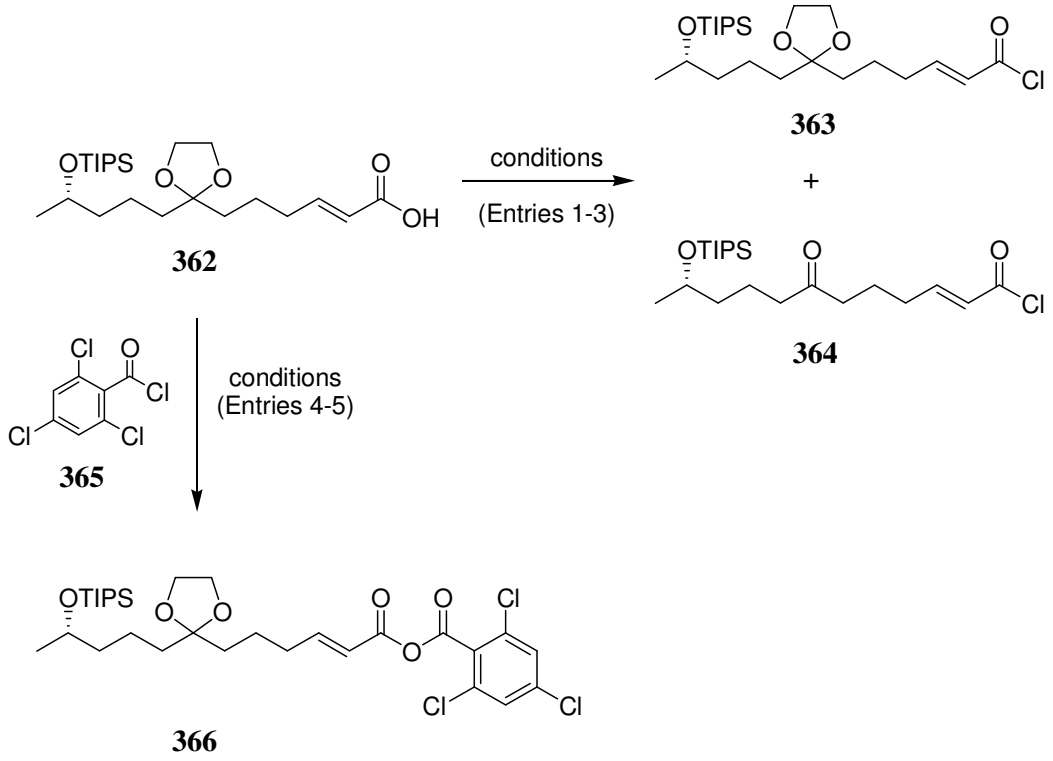
At this time, the supply of material was exhausted. During the re-synthesis of materials it was decided to replace the TBS ether with the more robust TIPS group. This was due to observations within our group that TBS ethers were prone to deprotection during the conditions employed for dioxinone analogue **339** alkylation.[178]

The analogous TIPS acid **362** was formed from (*S*)-alcohol **93** in three steps. Once again, excellent *E*-selectivity was observed during the CM of silyl ether **359** and ethyl acrylate (**349**). Curiously, difficulties were initially encountered during the saponification of ester **360** in ethanol, which were attributed to solvent impurities. Switching to methanol as a solvent yielded firstly transesterification product **361**, however it was discovered that was due to solubility problems and increasing the amount of methanol allowed formation of desired acid **362** in 96% (Scheme 161).



Scheme 161. *Reagents and conditions:* i) TIPSCl, Imid., CH_2Cl_2, 18 h, 23 °C, 99%; ii) **349**, Hoveyda-Grubbs' II (**197**) (5 mol%), CH_2Cl_2, 45 °C, 2.5 h, 78%, *E/Z* >99 : 1; iii) 2.0 M NaOH, MeOH, 23 °C, 18 h, 58%; iv) 2 M aq. NaOH, MeOH, 23 °C, 18 h, 96%.

With acid **362** in hand, various conditions for activation were investigated. Activation as the corresponding acid chloride **363** was first attempted as it was hoped the harder chloride ion nucleophile would have an increased preference for direct (1,2) over conjugate (1,4) addition. Activation as the Yamaguchi mixed anhydride **366**[183, 184] was also explored (Scheme 162, Table 21).



Scheme 162. *Activation of Acid* **362**.

Entry	*Reagents and conditions*[†]	*Product(s)*[*]
1	$(COCl)_2$ (1.3 eq.), cat. DMF, CH_2Cl_2	**363** : **364**, 1 : 3
2	$(COCl)_2$ (1.0 eq.), CH_2Cl_2	**363** : **362**, 2 : 1
3	$SOCl_2$ (1.2 eq.), pyr. (0.1 eq.), CH_2Cl_2	Decomposition
4	**365** (2.5 eq.), Et_3N (3.0 eq.), THF	**366**, excess **365**
5	**365** (1.0 eq.), Et_3N (1.2 eq.), THF	**366** : **362**, 2 : 1 excess **365**

Table 21

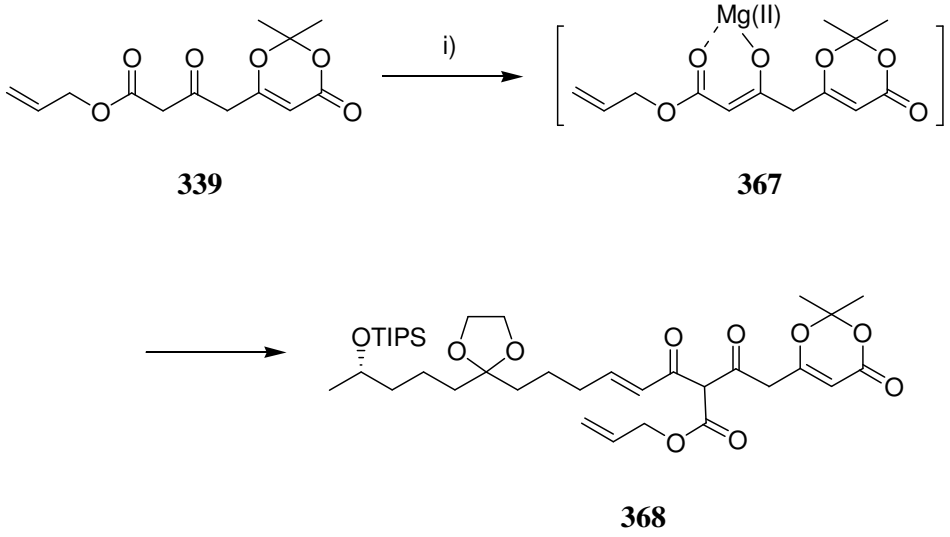
[†] reactions carried out at 23 °C for 3h; [*] products determined by crude MS + ^{1}H NMR analysis.

Excess oxalyl chloride with catalytic DMF resulted in partial ketal deprotection to generate acid chloride **364** under the acidic conditions (Table 21, Entry 1). Reduction in the number of oxalyl chloride equivalents and removal of DMF resulted in clean acid chloride **363** formation, however starting acid **362** remained and acid chloride **363** was not stable to the purification methods attempted (Entry 2). Thionyl chloride with catalytic pyridine resulted in a complex mixture of products (Entry 3).

Conversion to the Yamaguchi mixed anhydride **366** was successful, however excess Yamaguchi acid chloride **365** remained (Entry 4). Reducing the number equivalents of acid chloride **365** led to a mixture of starting material **362** and product **366**, which was chromatographed on silica to yield mixed anhydride **366** in approximately 90% purity. It was decided to attempt the acylation of ester **339** with this material and try to isolate the acylation product, dioxinone analogue **368**.

4.2.3 Acylation of Dioxinone Analogue **339** with Mixed Anhydride **366**

The conditions for the alkylation of dioxinone analogue **339** required pre-treatment of the dioxinone with pyridine and magnesium chloride to form magnesium enolate **367**. Mixed anhydride **366** was then added and gratifyingly, after 3 h crude MS analysis showed the correct mass of product dioxinone analogue **368** as a major product (MS (ESI$^+$) *m/z* 679 [M+H]$^+$, 701 [M+Na]$^+$, Scheme 163).



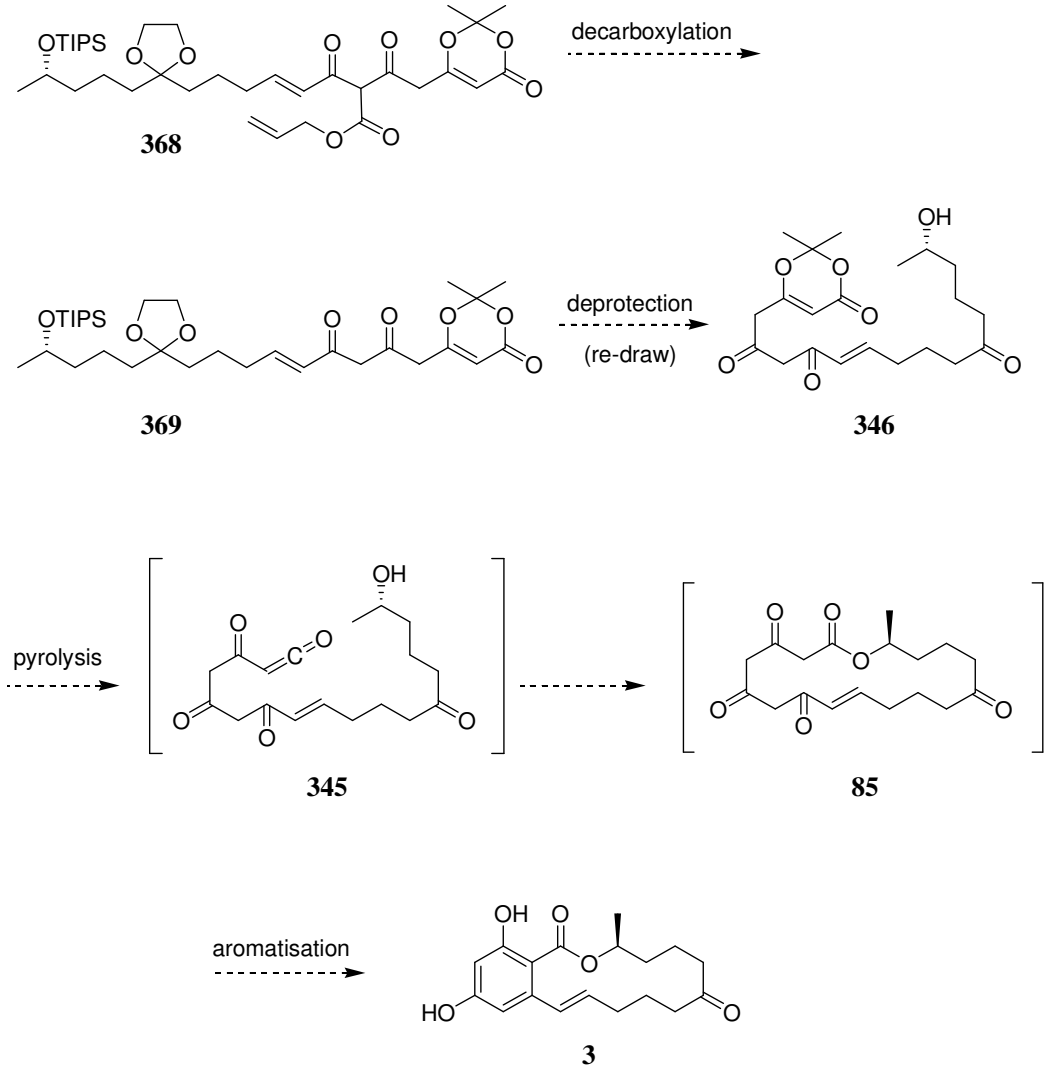
339 **367** **368**

Scheme 163. *Reagents and conditions:* i) a) $MgCl_2$ (1.1 eq.), pyr. (2.1 eq.), 0 °C, 30 min, b) **366**, 23 °C, 3 h.

Regrettably, due to time constraints the synthesis could not be completed. This work is currently being finished by others within the Barrett group.

4.3 Future Work

To complete this synthesis of (*S*)-zearalenone (**3**), four steps remain after the purification of dioxinone analogue **368**: firstly decarboxylation under palladium catalysis, which has already been proven on similar substrates,[178] to form dioxinone analogue **369** and then deprotection of the ketal and silyl groups to afford alcohol **346**. Finally, the key intramolecular macrolactonisation-aromatisation of alcohol **346** to provide the natural product target can be tested (Scheme 164).

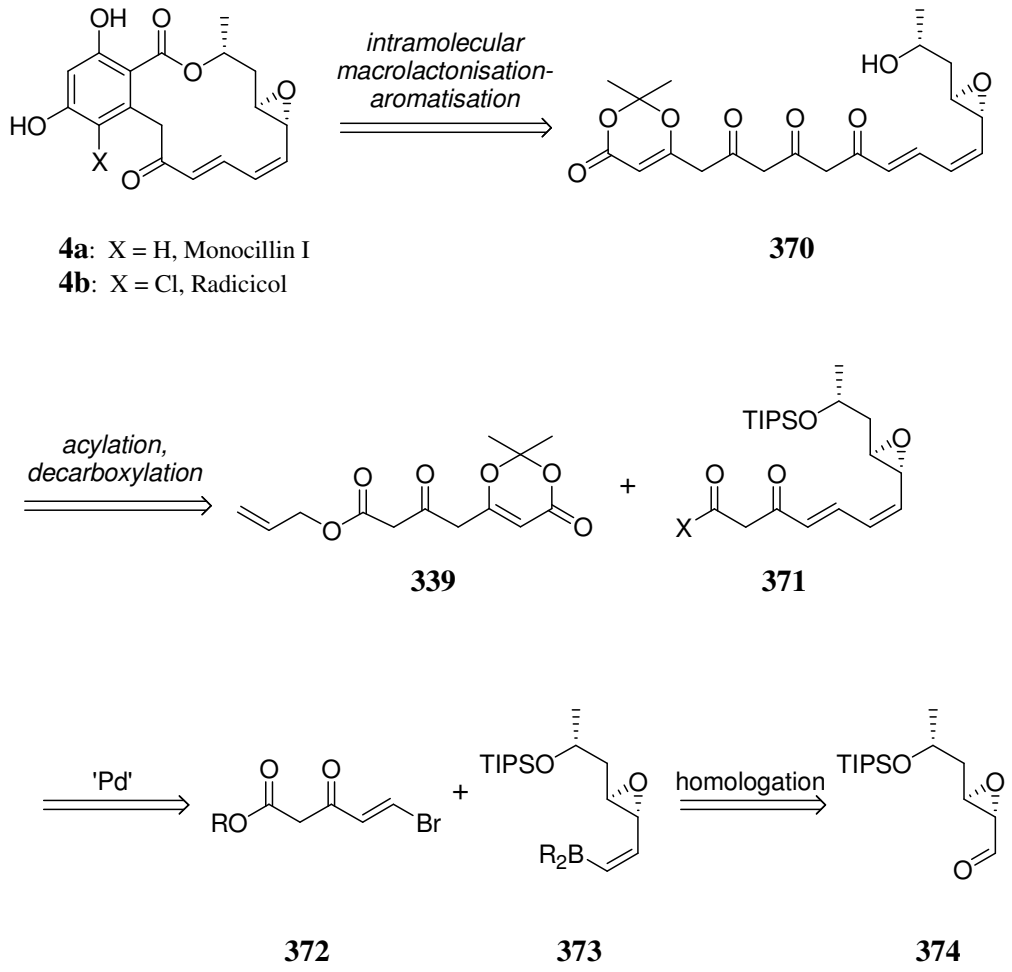


Scheme 164. *Remaining Steps to Synthesise (S)-Zearalenone* (**3**).

Once completed, this route will prove whether the overall procedure is preferable with CM followed by macrolactonisation-aromatisation, or with intermolecular esterification-aromatisation followed by RCM. One point of note from this synthetic route is the advantageous complete *E*-selectivity (*E/Z* ratio of >99 : 1) observed in the CM of alkene **359** with ethyl acrylate (**349**), compared with the *E/Z* ratio of 85 : 15 from the RCM procedure of diene **333** (see Scheme 151).

The CM yields were 77% and 78% for silyl ethers **(±)-110** and **359** respectively, which are comparable with the RCM yield of 71%. Therefore, any improvement to the previously observed 81% yield of the intermolecular esterification-aromatisation of dioxinone analogue **335** and (*S*)-alcohol **93** (Scheme **151**), will prove the intramolecular lactonisation-aromatisation a superior route.

More significantly, if the intramolecular lactonisation-aromatisation reaction is successful, this will pave the way for other resorcylate syntheses utilising a variety of different methods to build up the macrocyclic portion. For example, we envisage that the use of palladium couplings, Wittig reactions or other carbon-carbon bond forming chemistry will be compatible with this new methodology. This is illustrated by our proposed synthesis of monocillin I (**4a**) and radicicol (**4b**) (Scheme 165).

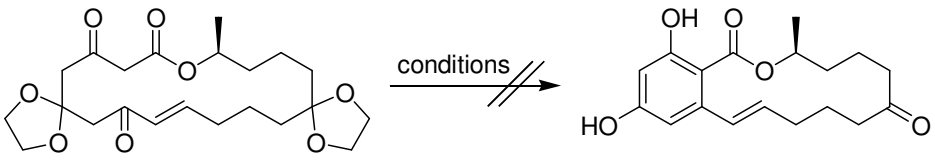


Scheme 165. *Proposed Synthesis of Monocillin I* (**4a**) *and Radicicol (***4b**)

Radicicol (**4b**) can be prepared from monocillin I (**4a**) by chlorination.[80] Disconnection of monocillin I (**4a**) *via* our late-stage intramolecular lactonisation-aromatisation procedure would give alcohol **370**, which could come from acylation of previously prepared dioxinone analogue **339** with protected alcohol **371**. This in turn can be derived from a palladium cross-coupling of bromide **372** with organoborane **373**. Organoborane **373** can be formed from aldehyde **374** by firstly homologation to an alkyne (Corey-Fuchs) and then hydroboration.

4.4 General Conclusions

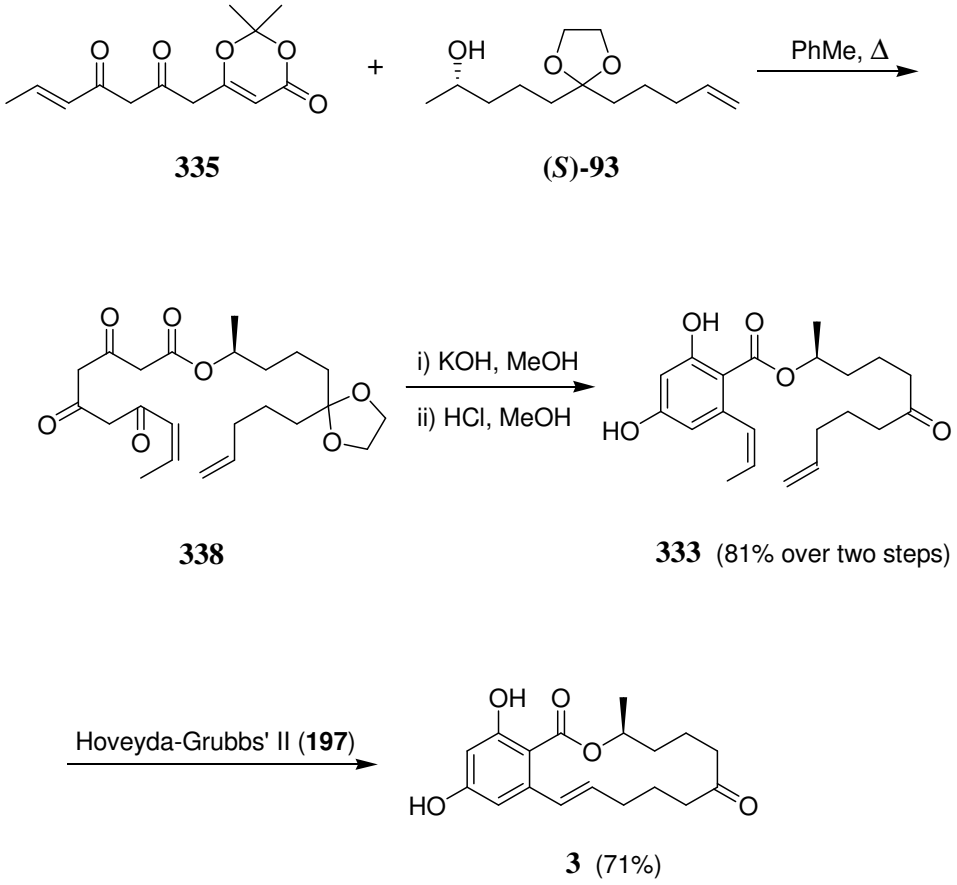
Although our initial strategies towards the synthesis of (*S*)-zearalenone (**3**) discussed in Chapters 2 and 3 were unsuccessful (Scheme 166), they demonstrated the level of control necessary for the aromatisation of β-triketo esters and the dependence upon the nature of the aromatisation substrate on the outcomes.



86 **3**

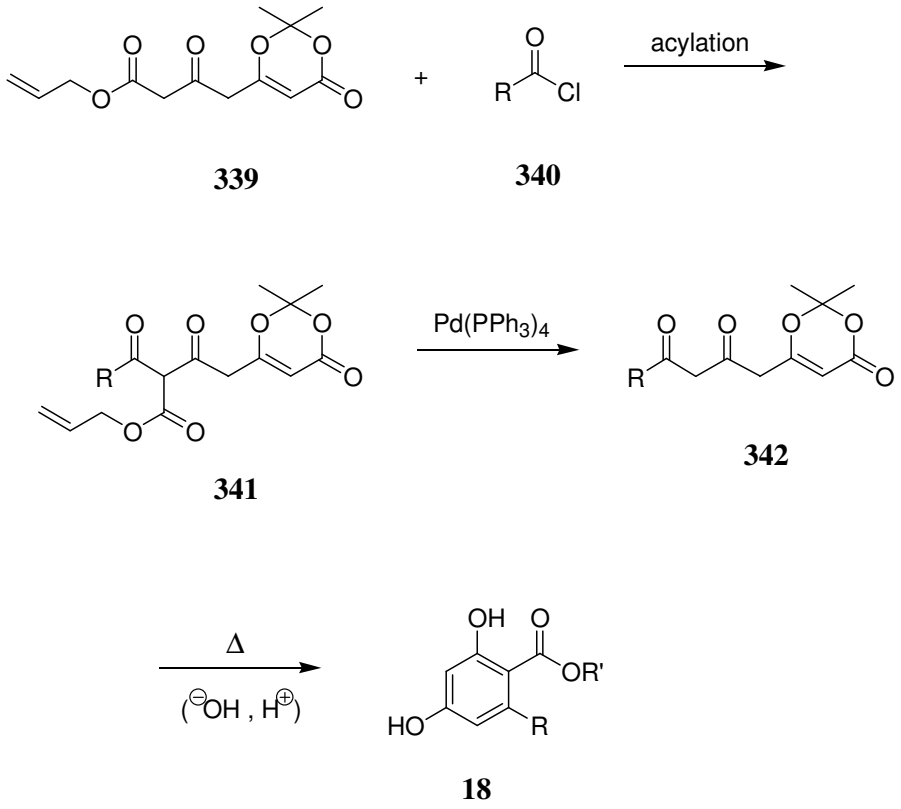
Scheme 166. *Initial Unsuccessful Strategy for the Synthesis of (S)-Zearalenone* (**3**)

Our revised dioxinone strategy discussed in this chapter has finally accomplished a selective aromatisation, with resorcylate **333** being formed from β-triketo ester precursor **338** in excellent yield (81% over two steps). This result clearly demonstrated the feasibility of late-stage aromatisation as a strategy for resorcylate synthesis and allowed synthesis of the natural product (*S*)-zearalenone (**3**) (Scheme 167).



Scheme 167. *Successful Selective Resorcylate Synthesis.*[177]

An improved method of generating dioxinone analogues **342**, β-triketo ester equivalents and aromatisation precursors to resorcylates **18**, has also been developed. Dioxinone analogue **339**, which is available in three steps from commercial materials, can be acylated with activated acid derivates such as acid chlorides **340**. The product allyl esters **341** can then be decarboxylated with palladium to generate targets **342** (Scheme 168).



Scheme 168. *Successful Strategy for Resorcylate Synthesis.*

Our future aim is to optimise these reaction conditions further and to produce a general method which can be applied in resorcylate synthesis. One particular goal is to validate the potential intramolecular dioxinone analogue opening macrolactonisation-aromatisation reaction. It is hoped this will lead to an improved aromatisation protocol, compatible with a range of chemistry which will be used to synthesise resorcylate side-chains or macrocycles.

As discussed in the introduction, before undertaking this work few aromatisations to form simple resorcylates had been employed in the literature, with the most recent reported being in 1988.[62] Also, interest in these resorcylates has recently been rekindled by the discovery that some members of the RAL family are potent kinase inhibitors and inhibitors of the molecular chaperone Hsp90, thus may have potential applications in chemotherapy.[14] We believe that our work will therefore provide a gateway to a new synthetic area and allow fast access to not only a range of natural products but also novel resorcylate derivatives.

Chapter Five: Experimental

5.1 General Procedures

5.1.1 Instrumental Procedures

Melting points: obtained using a Reichert-Thermovar melting point apparatus and are uncorrected. ***Infrared spectra:*** obtained using a Mattson 5000 FTIR apparatus with automatic background subtraction. Indicative features of each spectrum are given with adsorptions (ν_{max}) reported in wavenumbers (cm^{-1}). Samples were prepared on sodium chloride plates. ***Proton magnetic resonance spectra* (^{1}H NMR)*:*** recorded at 300 or 400 MHz on Bruker DRX-300 or Bruker DRX-400 spectrometers respectively, or at 500 MHz on a Bruker AM 500 spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) and referenced to the residual solvent peak (7.26 ppm for $CDCl_3$). Coupling constants (*J*) recorded in Hertz (Hz) and quoted to the nearest 0.5 Hz. ***Carbon magnetic resonance spectra* (^{13}C NMR):** recorded at 75 or 100 MHz on Bruker DRX-300 or Bruker DRX-400 spectrometers respectively, or at 125 MHz on a Bruker AM 500 spectrometer. Chemical shifts (δ) are quoted in ppm and referenced to the residual solvent peak (77.0 ppm for $CDCl_3$). Spectra recorded at 500 MHz (^{1}H NMR) and 125 MHz (^{13}C NMR) were carried out by the Imperial College Department of Chemistry NMR Service. ***Gas chromatography mass spectrometry* (GCMS):** recorded on a Hewlett-Packard 5890 series 2 gas chromatograph. ***Mass spectrometry:*** low and high resolution mass spectra (EI, CI, ESI) were recorded by Imperial College Mass Spectrometry Service using a Micromass Platform II and Micromass AutoSpec-Q spectrometer. ***Microanalysis:*** determined by the University of North London Analytical Service. ***Optical Rotations:*** recorded at 25 °C on a Perkin-Elmer 241 Polarimeter with a path length of 1 dm, using the 589.3 nm D-line of sodium. Concentrations (c) are quoted in g/100 mL. ***X-ray Diffraction:*** X-ray diffraction data were recorded by the Imperial College Department of Chemistry X-ray diffraction service.

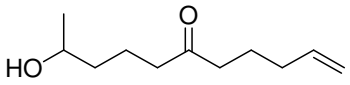
5.1.2 General Experimental Procedures

Reaction Procedures: All reactions were carried out in flame-dried or oven-dried glassware in an atmosphere of dry nitrogen or argon unless otherwise stated. For the purpose of this thesis, ambient temperature was taken as 23 °C where no external heating or cooling was applied and temperatures other than this were recorded as the bath temperature unless otherwise stated. Prolonged periods of vessel cooling were attained by the use of CryoCool apparatus. ***Solvents and reagents:*** All solvents and reagents were obtained from commercial suppliers and used without further purification unless otherwise stated. The following reaction solvents were distilled under nitrogen: Et_2O and THF from sodium benzophenone ketyl; PhMe from sodium; CH_2Cl_2 and Et_3N from CaH_2. MeOH was dried by refluxing over magnesium turnings and iodine, followed by distillation from CaH_2 under nitrogen. H_2O refers to distilled H_2O. ***Chromatography:*** Flash column chromatography was performed using BDH silica gel 60, particle size 40-63 mm unless otherwise stated. Thin layer chromatography (TLC) was performed on pre-coated aluminium backed or glass backed plates (Merck Kieselgel 60 F_{254}), visualisation was accomplished by either UV light (254 nm) or chemical staining using basic potassium permanganate ($KMnO_4$), or acidic vanillin stains as deemed appropriate.

5.1.3 Conventions Adopted in Experimental Section

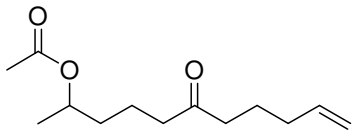
All compounds reported herein are either novel or are known compounds which have been synthesised by modification of the literature experimental procedure. In the latter case, these have been referenced and the data obtained is consistent with the literature. Reported compounds are in sequential, rather than numerical order, to help readers follow the synthetic pathway. All compounds have been reported according to the *J. Org. Chem.* format. In cases where diastereoisomeric/regioisomeric compounds were observed, judgement was used to either report signals for the major isomer, the entire mixture of isomers or each isomer separately, depending upon the ease of analysis.

(±)-10-Hydroxyundec-1-en-6-one (94)[84]



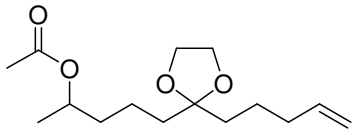
To a suspension of Mg powder (2.45 g, 101 mmol) in Et_2O (100 mL) was added two crystals of I_2 and the resultant mixture was sonicated for 10 min before heating to 60 °C, at which point the reaction mixture turned from brown to colourless. 5-Bromo-1-pentene (12.0 mL, 101 mmol) was added dropwise and after a further 1 h at 60 °C, the reaction mixture was cooled to 23 °C. The resulting crude 4-pentenyl magnesium bromide (**96**) solution was transferred *via* canula to a solution of δ-hexanolactone (**47**) (13.3 g, 92.3 mmol) in THF (200 mL) at −78 °C and the ensuing reaction mixture was stirred for 2 h at that temperature before quenching by addition of sat. aq. NH_4Cl (60 mL) and H_2O (100 mL). The aqueous layer was extracted with Et_2O (3 × 100 mL) and the combined organic extracts washed with H_2O (2 × 50 mL) and dried (Na_2SO_4). Concentration *in vacuo* afforded (±)-alcohol **94** (16.5 g) as a pale yellow oil which was used in the next step without purification: R_f 0.50 (EtOAc : hexanes, 1 : 1); IR (film) ν_{max} 3444, 1732, 1711, 1068 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.19 (d, J = 6.0 Hz, 3H, CH_3), 1.39 – 1.99 (m, 6H, CH_2), 2.02 – 2.10 (m, 2H, CH_2CH=CH_2), 2.39 – 2.48 (m, 4H, CH_2CO), 3.74 – 3.80 (m, 1H, CHOH), 4.96 – 5.04 (m, 2H, CH_2=CH), 5.74 – 5.79 (m, 1H, CH=CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 22.8, 23.4, 29.6, 33.1, 38.6, 42.6, 67.5, 115.2, 138.0, 211.3; MS (CI) *m/z* 185 $[M+H]^+$, 202 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{11}H_{21}O_2$ $[M+H]^+$; 185.1542, found: 185.1546.

Acetic acid 1-methyl-5-oxodec-9-enyl ester (98)



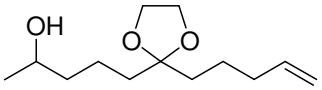
A mixture of crude (±)-10-hydroxyundec-1-en-6-one (**94**) (5.0 g, 27 mmol), acetic anhydride (30 mL) and pyridine (30 mL) was heated to 60 °C. After 24 h the reaction mixture was cooled to 0 °C, quenched by addition of MeOH (40 mL) and concentrated *in vacuo*. The residue was taken up in H_2O (30 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with brine (30 mL) and dried (Na_2SO_4). Concentration *in vacuo* was followed by flash column chromatography (EtOAc : hexanes, 1 : 4) to afford ketone **98** (4.92 g, 71% over two steps) as a colourless oil: R_f 0.30 (EtOAc : hexanes, 1 : 3); IR (film) ν_{max} 2941, 1733, 1451, 1372, 1247, 1019 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.13 (d, J = 7.0 Hz, 3H, CH_3CH), 1.12 – 1.20 (m, 2H, CH_2) 1.37 – 1.65 (m, 4H, CH_2), 1.95 (s, 3H, CH_3CO_2R) 1.97 – 2.01 (m, 2H, CH_2), 2.31 – 2.34 (m, 4H, CH_2CO), 4.04 (q, J = 7.0 Hz, 1H, CH_3C*H*), 4.78 – 4.96 (m, 2H, CH=CH_2), 5.62 – 5.75 (m, 1H, C*H*=CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 19.8, 21.3, 22.7, 33.0, 35.2, 41.8, 42.2, 70.8, 115.1, 137.9, 170.6, 210.4; MS (CI) *m/z* 227 $[M+H]^+$, 244 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{13}H_{23}O_3$ $[M+H]^+$: 227.1647, found: 227.1647; Anal. calculated for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80; found: C, 68.89; H, 9.68%.

(±)-Acetic acid 1-methyl-4-(2-pent-4-enyl-[1,3]dioxolan-2-yl)butyl ester (99)



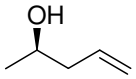
To a solution of (±)-acetic acid 1-methyl-5-oxodec-9-enyl ester (**98**) (5.00 g, 22.1 mmol) in benzene (150 mL) was added ethylene glycol (37.0 mL, 66.4 mmol) in one portion, followed by *p*TSA (556 mg, 2.92 mmol). The reaction mixture was heated to 90 °C under Dean-Stark phase-separating apparatus. After 18 h the reaction mixture was allowed to cool to 23 °C, diluted with EtOAc (100 mL), washed with sat. aq. $NaHCO_3$ (2 × 80 mL) and dried (Na_2SO_4). Concentration *in vacuo* was followed by flash column chromatography (EtOAc : hexanes, 1 : 9) to afford ketal **99** (5.25 g, 88%) as a colourless oil: R_f 0.45 (EtOAc : hexanes, 1 : 9); IR (film) ν_{max} 1732, 1451, 1371, 1245, 1042 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.18 (d, J = 6.0 Hz, 3H, CH_3CH), 1.33 – 1.72 (m, 10H, CH_2), 2.06 (s, 3H, CH_3CO$_2$R) 2.36 – 2.40 (m, 2H, CH_2), 3.90 (s, 4H, O(CH_2)$_2$O), 4.85 – 4.91 (m, 1H, CHCH$_3$), 4.95 – 5.01 (m, 2H, CH=CH_2), 5.67 – 5.86 (m, 1H, CH=CH$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 19.9, 21.4, 23.1, 33.9, 36.5, 36.8, 42.3, 64.9 (2C), 70.8, 111.5, 114.5, 138.6, 170.8; MS (CI) *m/z* 271 $[M+H]^+$, 288 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{15}H_{27}O_4$ $[M+H]^+$: 271.1909, found: 271.1900; Anal. calculated for $C_{15}H_{26}O_4$: C, 66.64; H, 9.69; found: C, 66.53; H, 9.59%.

(±)-5-(2-Pent-4-enyl-[1,3]dioxolan-2-yl)-pentan-2-ol (93)[84]



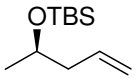
To a solution of (±)-acetic acid 1-methyl-4-(2-pent-4-enyl-[1,3]dioxolan-2-yl)butyl ester (**99**) (915 mg, 3.39 mmol) in MeOH (5 mL) was added aqueous KOH (3 M, 8.00 mL, 24.0 mmol). The mixture was stirred at 23 °C for 3 h after which time the reaction was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (20 mL), washed with H_2O (10 mL), brine (10 mL), then dried (Na_2SO_4). Concentration *in vacuo* was followed by flash column chromatography (EtOAc : hexanes, 1 : 2) to afford (±)-alcohol **93** (816 mg, 98%) as a colourless oil: R_f 0.55 (EtOAc : hexanes, 1 : 3); IR (film) ν_{max} 3422, 1456, 1147, 1044, 911 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.15 (d, *J* = 6.0 Hz, 3H, C*H*$_3$CH), 1.35 – 1.47 (m, 6H, C*H*$_2$), 1.55 – 1.61 (m, 4H, C*H*$_2$), 2.07 (*app.* q, *J* = 7.0 Hz, 2H, C*H*$_2$CHOH), 2.39 (*br.* s, 1H, O*H*), 3.79 – 3.85 (m, 1H, CH_3C*H*), 3.94 (s, 4H, O(C*H*$_2$)$_2$O), 4.97 (dd, *J* = 1.0, 10.0 Hz, 1H, CH=C*H*$_2$), 5.03 (dd, *J* = 1.0, 17.0 Hz, 1H, CH=C*H*$_2$), 5.82 (tdd, *J* = 6.0, 10.0, 17.0 Hz, 1H, C*H*=CH$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.0, 22.8, 23.1, 33.9, 36.6, 37.0, 39.4, 65.0 (2C), 67.9, 111.7, 114.7, 138.7; MS (CI) *m/z* 229 $[M+H]^+$, 246 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{13}H_{28}NO_3$ $[M+NH_4]^+$: 246.2069, found: 246.2068.

(*R*)-Pent-4-en-2-ol (101)[77]



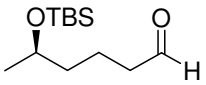
Following the procedure of Kalivretenos *et al.*,[77] to a suspension of CuI (1.64 g, 8.61 mmol) in THF at –30 °C was added a solution of vinylmagnesium bromide (1.0 M in THF, 86.0 mL, 86.0 mmol) dropwise. The resultant dark brown solution was stirred for 10 min before addition of (*R*)-propylene oxide (**100**) (4.0 mL, 57.2 mmol) and allowed to warm slowly to 0 °C. After 18 h the reaction mixture was poured into a slurry of ice (100 g) and sat. aq. NH_4Cl (100 mL) and stirred for 3 h after which time the reaction mixture had turned from brown to blue. The aqueous layer was extracted with Et_2O (3 × 100 mL) and the combined organic extracts washed with sat. aq. NH_4Cl (50 mL), H_2O (50 mL) and dried (Na_2SO_4). Concentration *in vacuo* was followed by distillation to afford alcohol **101** (1.82 g, 37%) as a colourless oil: b.p. 102-8 °C, 760 mmHg [lit.,[185] b.p. 115 °C, 746 mmHg]; R_f 0.30 (EtOAc : hexanes, 1 : 4); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (d, J = 6.0 Hz, 3H, CH_3CH), 2.15 – 2.27 (m, 2H, CH_2), 3.73 – 3.77 (m, 1H, CH_3CH), 5.16 (m, 2H, CH_2=CH), 5.85 – 5.90 (m, 1H, CH=CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.8, 43.7, 68.0, 118.1, 134.8.

(*R*)-4-(*tert*-Butyldimethylsilanyloxy)pent-1-ene (102)[84]



Following the procedure of Kalivretenos *et al.,*[77] to a suspension of (*R*)-pent-4-en-2-ol (**101**) (4.18 g, 48.5 mmol), imidazole (7.93 g, 116 mmol) and DMAP (0.59 g, 4.83 mmol) in DMF (100 mL) at 0 °C, was added TBSCl (8.78 g, 58.2 mmol) portionwise. The reaction was allowed to warm to 23 °C and maintained at this temperature for 18 h then diluted with H_2O (100 mL). The aqueous layer was extracted with Et_2O (3 × 100 mL) and the combined organic extracts washed with 1 M HCl (2 × 25 mL), then dried (Na_2SO_4). Concentration *in vacuo* was followed by flash column chromatography (EtOAc : hexanes, 1 : 30) to afford alkene **102** (5.04 g, 52%) as a colourless oil: R_f 0.75 (EtOAc : hexanes, 1 : 19); $[\alpha]_D$ –6.5 (*c* 1.09, CH_2Cl_2) [lit.,[77] $[\alpha]_D$ –8.4, (*c* 9.46, Et_2O)]; IR (film) ν_{max} 3079, 1472, 1376, 1255, 1131 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 6H, $(CH_3)_2Si$), 0.90 (s, 9H, $C(CH_3)_3$), 1.14 (d, 3H, *J* = 6.0 Hz, CH_3CH), 2.18 – 2.21 (m, 2H, CH_2), 3.84 – 3.86 (m, 1H, CH_3CH), 5.01 (dd, *J* = 15.5 Hz, 2.0 Hz, 2H, CH_2=CH), 5.70 – 5.89 (m, 1H, CH=CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ –4.7, –4.5, 18.2, 23.4, 25.5 (3C), 44.3, 68.4, 116.5, 135.6; MS (CI) *m/z* 201 $[M+H]^+$; HRMS (CI) *m/z* calculated for $C_{11}H_{25}SiO$ $[M+H]^+$: 201.1677, found: 201.1679.

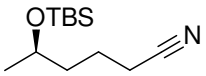
(*R*)-5-(*tert*-Butyldimethylsilanyloxy)hexanal (103)[84]



Following the procedure of Fuerstner *et al.,*[84] a suspension of Schwartz's reagent[186] Cp_2ZrHCl (5.00 g, 19.4 mmol) in CH_2Cl_2 (50 mL) was stirred for 20 min prior to addition of (*R*)-4-(*tert*-butyldimethylsilanyloxy)pent-1-ene (**102**) (1.94 g, 9.70 mmol) in PhMe (30 mL). The resulting yellow suspension was stirred for 18 h at 23 °C in the dark. *tert*-Butyl isocyanate (2.20 mL, 19.4 mmol) was then added dropwise, at which point the reaction mixture turned from yellow to colourless. After 3 h the reaction mixture was cooled to 0 °C and a solution of iodine (2.46 g, 9.70 mmol) in PhMe (20 mL) was added. After 5 min the reaction mixture was quenched by addition of sat. aq. $Na_2S_2O_3$ solution (150 mL). The mixture was filtered, the filtrate diluted with sat. aq. Na_2CO_3 (100 mL), extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic extracts dried (Na_2SO_4). Concentration *in vacuo* was followed by flash column chromatography (EtOAc : hexanes, 1 : 30 → 1 : 20) to afford only aldehyde **103** (469 mg, 21%) as a brown oil: R_f 0.50 (EtOAc : hexanes, 1 : 19); $[\alpha]_D$ –0.9 (*c* 1.32, CH_2Cl_2); IR (film) ν_{max} 1728, 1254, 1140, 1061 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 6H, $(CH_3)_2Si$), 0.89 (s, 9H, $(CH_3)_3C$), 1.14 (d, J = 6.0 Hz, 3H, CH_3CH), 1.41 – 1.45 (m, 2H, CH_2), 1.68 – 1.71 (m, 2H, CH_2), 2.39 – 2.44 (m, 2H, CH_2CHO), 3.79 – 3.81 (m, 1H, CH_3CH), 9.75 (s, 1H, CHO); ^{13}C NMR (75 MHz, $CDCl_3$) δ –4.8 (2C), 18.1, 18.3, 23.7 (3C), 26.3, 38.9, 43.9, 68.2, 202.7; MS (CI) *m/z* 231 $[M+H]^+$, 248 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{12}H_{27}SiO_2$ $[M+H]^+$: 231.1767, found: 231.1770.

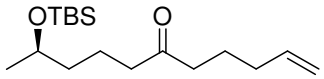
Note : This aldehyde product **103** is obtained from reaction with traces of H_2O in the reaction solvent. Rigorous drying of the PhMe solvent enabled the desired nitrile product **108** to be isolated (see next Experimental).

(*R*)-5-(*tert*-Butyldimethylsilanyloxy)hexanenitrile (108)[84]



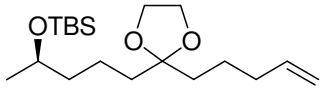
Following the procedure of Fuerstner *et al.,*[84] a suspension of Schwartz's reagent Cp_2ZrHCl (1.94 g, 7.52 mmol) in PhMe (40 mL) was stirred for 20 min prior to addition of (*R*)-4-(*tert*-butyldimethylsilanyloxy)pent-1-ene (**102**) (600 mg, 3.00 mmol). The resulting yellow suspension was stirred for 18 h at 23 °C in the dark. *tert*-Butyl isocyanate (471 μL, 7.52 mmol) was then added slowly and at which point the reaction mixture turned from yellow to colourless. After 3 h the reaction mixture was cooled to 0 °C and a solution of iodine (5.71 g, 11.0 mmol) in PhMe (40 mL) was added. After 5 min the reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with sat. aq. $NaHSO_3$ (50 mL), followed by H_2O (50 mL) and brine (50 mL) and then dried (Na_2SO_4). Concentration *in vacuo* was followed by flash column chromatography (EtOAc : hexanes, 1 : 30 → 1 : 20) to afford nitrile **108** (409 mg, 60%) as a brown oil: R_f 0.55 (EtOAc : hexanes, 1 : 19); $[\alpha]_D$ –16.7 (*c* 1.01, CH_2Cl_2) [lit.,[84] $[\alpha]_D$ –20.6 (*c* 2.46, CH_2Cl_2); IR (film) ν_{max} 2359, 2245, 1254, 1139, 1020 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 6H, $(CH_3)_2Si$), 0.89 (s, 9H, $(CH_3)_3C$), 1.17 (d, *J* = 6.0 Hz, 3H, CH_3CH), 1.70 – 1.74 (m, 2H, CH_2), 1.76 – 1.87 (m, 2H, CH_2), 2.39 (t, *J* = 7.0 Hz, 2H, CH_2CN), 3.85 – 3.90 (m, 1H, CH_3CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ –4.3, –4.8, 17.3, 18.4, 21.7, 23.7, 25.9 (3C), 38.9, 67.6, 119.8; MS (CI) *m/z* 228 $[M+H]^+$, 245 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{12}H_{26}NSiO$ $[M+H]^+$: 228.1770, found: 228.1774.

(*R*)-10-(*tert*-Butyldimethylsilanyloxy)undec-1-en-6-one (109)[84]



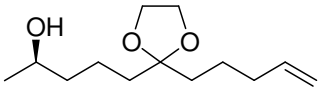
Following the procedure of Fuerstner *et al.,*[84] to a solution of (*R*)-5-(*tert*-butyldimethylsilanyloxy)hexanenitrile (**108**) (405 mg, 1.78 mmol) in Et_2O (5 mL) at 60 °C was added a solution of 4-pentenyl magnesium bromide (**96**) [freshly prepared from 5-bromo-1-pentane (680 μL, 5.73 mmol) and magnesium (147 mg, 6.01 mmol) in Et_2O (25 mL)]. After 4 h the reaction mixture was allowed to cool to 23 °C and quenched by addition of sat. aq. NH_4Cl (30 mL). The aqueous layer was extracted with Et_2O (3 × 50 mL) and the combined organic extracts dried (Na_2SO_4). Concentration *in vacuo* was followed by flash column chromatography (EtOAc : hexanes, 1 : 30) to afford ketone **109** (392 mg, 74%) as a colourless oil: R_f 0.65 (EtOAc : hexanes, 1 : 9); $[\alpha]_D$ –9.5 (*c* 1.09, CH_2Cl_2) [lit.,[84] $[\alpha]_D$ –10.9 (*c* 1.54, CH_2Cl_2); IR (film) ν_{max} 3077, 1713, 1462, 1252, 1002 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 6H, $(CH_3)_2Si$), 0.89 (s, 9H, $C(CH_3)_3$), 1.12 (d, 3H, J = 6.0 Hz, CH_3CH), 1.22 – 1.72 (m, 8H, CH_2), 2.01 – 2.09 (m, 2H, CH_2), 2.36 – 2.43 (m, 2H, CH_2), 3.74 – 3.86 (m, 1H, CH_3CH), 4.95 – 5.05 (m, 2H, CH_2=CH), 5.76 (ddt, J = 17.0, 10.0, 7.0 Hz, 1H, CH=CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ –4.8, –4.4, 14.1, 20.2, 23.7, 25.9 (3C), 31.6, 33.1, 39.1, 41.8, 42.9, 68.3, 115.1, 138.0, 210.9; MS (CI) *m/z* 299 $[M+H]^+$, 316 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{17}H_{35}SiO_2$ $[M+H]^+$: 299.2406, found: 299.2418.

(*R*)-5-[2-(4-*tert*-Butyldimethylsilanyloxypentyl)
-[1,3]dioxolan-2-yl]pent-1-ene (110)[84]



Following the procedure of Fuerstner *et al.,*[84] to a solution of (*R*)-10-(*tert*-butyldimethylsilanyloxy)undec-1-en-6-one (**109**) (319 mg, 1.06 mmol) in PhMe (50 mL) was added ethylene glycol (2.30 mL, 4.10 mmol), followed by *p*TSA (13.1 mg, 0.05 mmol). The reaction mixture was heated to 120 °C under Dean-Stark phase-separating apparatus. After 18 h the reaction mixture was allowed to cool to 23 °C, diluted with EtOAc (50 mL), washed with sat. aq. $NaHCO_3$ (2 × 30 mL) and dried (Na_2SO_4). Concentration *in vacuo* was followed by flash column chromatography (EtOAc : hexanes, 1 : 30) to afford ketal **110** (102 mg, 28%) as a colourless oil: R_f 0.70 (EtOAc : hexanes, 1 : 9); $[\alpha]_D$ −9.3 (*c* 1.10, CH_2Cl_2)) [lit.,[84] $[\alpha]_D$ −10.3 (*c* 1.12, CH_2Cl_2); IR (film) ν_{max} 3077, 1462, 1254, 1002, 835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 6H, $(CH_3)_2Si$), 0.90 (s, 9H, $(CH_3)_3C$), 1.13 (d, *J* = 6.0 Hz, 3H, CH_3CH), 1.26 – 1.71 (m, 10H, CH_2), 2.05 – 2.07 (m, 2H, CH_2), 3.74 – 3.81 (m, 1H, $CHCH_3$), 3.94 (s, 4H, $O(CH_2)_2O$), 4.98 (dd, *J* = 1.5, 10.0 Hz, 1H, $CH=CH_2$), 5.03 (dd, *J* = 1.5, 17.0 Hz, 1H, $CH=CH_2$), 5.82 (tdd, *J* = 7.0, 10.0, 17.0 Hz, 1H, $CH=CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ –4.7, –4.3, 18.2, 20.2, 23.2, 23.9, 25.9 (3C), 34.0, 36.7, 37.3, 40.0, 65.0 (2C), 68.6, 111.7, 114.7, 138.7; MS (CI) *m/z* 343 $[M+H]^+$; HRMS (CI) *m/z* calculated for $C_{19}H_{39}SiO_3$ $[M+H]^+$: 343.2668, found: 343.2663.

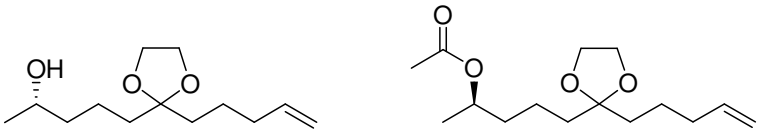
(*R*)-5-(2-Pent-4-enyl-[1,3]dioxolan-2-yl)pentan-2-ol (93)[84]



Following the procedure of Fuerstner *et al.,*[84] to a solution of (*R*)-5-[2-(4-*tert*-butyldimethylsilanyloxypentyl)-[1,3]dioxolan-2-yl]pent-1-ene (**110**) (91 mg, 0.27 mmol) in THF (5 mL) was added TBAF (1.0 M in THF, 0.53 mL, 0.53 mmol). After 24 h the reaction mixture was concentrated *in vacuo*, the residue taken up in brine (10 mL) and extracted with Et_2O (3 x 20 mL), then the combined organic extracts were dried (Na_2SO_4). Concentration *in vacuo* was followed by flash column chromatography (EtOAc : hexanes, 1 : 2) to afford (*R*)-alcohol **93** (42 mg, 68%) as a colourless oil: R_f 0.55 (EtOAc : hexanes, 1 : 3); $[\alpha]_D$ –6.7 (*c* 1.22, CH_2Cl_2) [lit.,[84] $[\alpha]_D$ –6.8 (*c* 1.02, CH_2Cl_2); IR (film) ν_{max} 3422, 1456, 1147, 1044, 911 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.15 (d, *J* = 6.0 Hz, 3H, C*H*$_3$CH), 1.35 – 1.47 (m, 6H, C*H*$_2$), 1.55 – 1.61 (m, 4H, C*H*$_2$), 2.07 (q, *J* =7.0 Hz, 2H, C*H*$_2$CHOH), 2.39 (*br*. s, 1H, O*H*), 3.79 – 3.85 (m, 1H, CH_3C*H*), 3.94 (s, 4H, O(C*H*$_2$)$_2$O), 4.97 (dd, *J* = 1.0, 10.0 Hz, 1H, CH=C*H*$_2$), 5.03 (dd, *J* = 1.0, 17.0 Hz, 1H, CH=C*H*$_2$), 5.82 (tdd, *J* = 6.0, 10.0, 17.0 Hz, 1H, C*H*=CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.0, 22.8, 23.1, 33.9, 36.6, 37.0, 39.4, 65.0 (2C), 67.9, 111.7, 114.7, 138.7; MS (CI) *m/z* 229 $[M+H]^+$, 246 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{13}H_{28}NO_3$ $[M+NH_4]^+$: 246.2069, found: 246.2068.

(*S*)-5-(2-Pent-4-enyl-[1,3]dioxolan-2-yl)pentan-2-ol (93) and

***(R)*- 5-[2-(4-Acetoxypentyl)-[1,3]dioxolan-2-yl]pent-1-ene (99)**

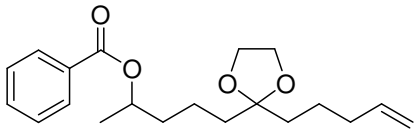


To a solution of (±)-5-(2-pent-4-enyl-[1,3]dioxolan-2-yl)-pentan-2-ol (**93**) (2.40 g, 10.5 mmol) and vinyl acetate (1.95 mL, 31.6 mmol) in hexane (50 mL) was added CAL-B (105 mg, 10 mol%) and the resultant mixture stirred under air at 35 °C for 65 min. After this time the reaction was filtered, concentrated *in vacuo* and purified by flash column chromatography (EtOAc : hexanes, 1 : 8 → 1 : 2) to afford (*S*)-enriched alcohol **93** (1.30 g) and (*R*)-acetate **99** (1.30 g, 46%) as colourless oils. (*S*)-enriched alcohol **93** (1.30 g) was re-subjected to the reaction conditions for a further 3 h. After this time the reaction was filtered, concentrated *in vacuo* and purified by flash column chromatography (EtOAc : hexanes, 1 : 8 → 1 : 2) to afford (*S*)-alcohol **93** (989 mg, 41%) as a colourless oil.

(*R*)-Acetate **99** : R_f 0.45 (EtOAc : hexanes, 1 : 9); $[\alpha]_D$ –1.1 (*c* 1.05, CH_2Cl_2); IR (film) ν_{max} 1732, 1451, 1371, 1245, 1042 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.18 (d, *J* = 6.0 Hz, 3H, C*H*$_3$CH), 1.33 – 1.72 (m, 10H, C*H*$_2$), 2.06 (s, 3H, C*H*$_3$CO) 2.36 – 2.40 (m, 2H, C*H*$_2$), 3.90 (s, 4H, O(C*H*$_2$)$_2$O), 4.85 – 4.91 (m, 1H, CH$_3$C*H*), 4.95 – 5.01 (m, 2H, CH=C*H*$_2$), 5.67 – 5.86 (m, 1H, C*H*=CH$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 19.9, 21.4, 23.1, 33.9, 36.5, 36.8, 42.3, 64.9 (2C), 70.8, 111.5, 114.5, 138.6, 170.8; MS (CI) *m/z* 271 $[M+H]^+$, 288 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{15}H_{27}O_4$ $[M+H]^+$: 271.1909, found: 271.1900; Anal. calculated for $C_{15}H_{26}O_4$: C, 66.64; H, 9.69; found: C, 66.53; H, 9.59%.

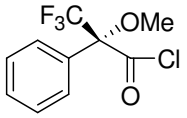
(*S*)-Alcohol **93** is spectroscopically identical to (±)-alcohol **93** except: $[\alpha]_D$ +6.9 (*c* 1.19, CH_2Cl_2).

Benzoic acid 1-methyl-4-(2-pent-4-enyl-[1,3]dioxolan-2-yl)butyl ester (126)



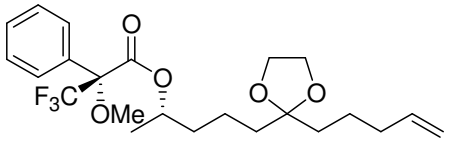
A mixture of (±)-5-(2-pent-4-enyl-[1,3]dioxolan-2-yl)pentan-2-ol (**93**) (86 mg, 0.38 mmol), benzoyl chloride (131 μL, 1.13 mmol) and dry pyridine (2.0 mL) were stirred together at 23 °C. After 4 h MeOH (2.0 mL) was added dropwise and the reaction mixture concentrated *in vacuo*. The residue was redissolved in CH_2Cl_2 (10 mL), washed with H_2O (5 mL) then brine (5 mL) and dried (Na_2SO_4). Concentration *in vacuo* was followed by flash column chromatography (EtOAc : hexanes, 6 : 94) to afford benzoyl ester **126** (115 mg, 92%) as a colourless oil: R_f 0.80 (EtOAc : hexanes, 1 : 3); IR (film) ν_{max} 3072, 1715, 1451, 1275, 1111, 1070, 712 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.36 (d, *J* = 6.0 Hz, 3H, C*H*$_3$CH), 1.40 – 1.56 (m, 4H, C*H*$_2$), 1.58 – 1.70 (m, 4H, C*H*$_2$), 1.71 – 1.83 (m, 2H, C*H*$_2$), 2.04 (*app.* q, *J* = 6.5 Hz, 2H, C*H*$_2$CH=CH$_2$), 3.91 (s, 4H, O(C*H*$_2$)$_2$O), 4.92 – 5.04 (m, 2H, CH=*CH*$_2$), 5.14 – 5.22 (m, 1H, CH$_3$C*H*), 5.79 (tdd, *J* = 6.5, 10.0, 17.0 Hz, 1H, C*H*=CH$_2$), 7.43 – 7.48 (m, 2H, *m*-Ar*H*), 7.54 – 7.59 (m, 1H, *p*-Ar*H*), 8.04 – 8.08 (m, 2H, *o*-Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 20.1, 23.1, 33.9, 36.2, 36.5, 36.9, 65.0 (2C), 71.5, 83.9, 111.5, 114.7, 128.3 (2C), 129.7 (2C), 132.7, 138.6, 166.2; MS (CI) *m/z* 333 $[M+H]^+$, 350 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{20}H_{32}NO_4$ $[M+NH_4]^+$: 350.2318, found: 350.2316.

(*R*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropionyl chloride (129)[89]



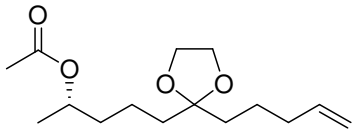
Following the procedure of Mosher *et al.*,[89] to a solution of (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropionic acid (**128**) (500 mg, 2.14 mmol) in thionyl chloride (5 mL) was added NaCl (50 mg) and the resultant mixture stirred at 80 °C for 46 h. Concentration *in vacuo* afforded acid chloride **129** (540 mg, 100% by mass) which was used crude without further purification: IR (film) ν_{max} 1790, 1496, 1451, 1262, 1173, 804 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H, C*H*$_3$O), 7.47 – 7.52 (m, 3H, Ar*H*), 7.58 – 7.62, 2H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.7, 89.1, 121.2, 124.1, 126.9, 128.8 (2C), 130.6 (2C), 171.0.

(*R,S*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropionic acid 1-methyl-4-(2-pent-4-enyl-[1,3]dioxolan-2-yl)butyl ester (130)



To a solution of (*S*)-5-(2-pent-4-enyl-[1,3]dioxolan-2-yl)pentan-2-ol (**93**) (20 mg, 0.09 mmol) in pyridine (1 mL) was added (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropionyl chloride (**129**) (67 mg, 0.26 mmol). After 18 h, GC analysis indicated complete alcohol consumption. The reaction mixture was concentrated *in vacuo* and crude analysis performed. A small sample was purified by flash column chromatography (EtOAc : hexanes, 1 : 9) to afford ester **130** as a colourless oil: R_f 0.70 (EtOAc : hexanes, 1 : 3); IR (film) ν_{max} 3433, 2953, 2874, 1742. 1452, 1271, 1169, 1123, 1019 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.36 (d, J = 6.0 Hz, 3H, CH_3CH), 1.40 – 1.70 (m, 10H, CH_2), 2.05 (*app.* q, J = 7.0 Hz, 2H, CH_2CHCH$_3$), 3.58 (s, 3H, CH_3O), 3.87 – 3.92 (m, 4H, O(CH_2)$_2$O), 4.97 (dd, J = 2.0, 10.0 Hz, 1H, CH=CH_2), 5.02 (dd, J = 2.0, 17.0 Hz, 1H, CH=CH_2), 5.18 (qd, J = 6.0, 12.5 Hz, 1H, CH$_3$CH), 5.80 (tdd, J = 6.7, 10.0, 17.0 Hz, 1H, CH=CH$_2$), 7.39 – 7.44 (m, 3H, ArH), 7.54 – 7.57 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5, 19.8, 23.1, 33.9, 35.7, 36.6, 36.7, 55.4, 64.9 (2C), 73.9, 111.4, 114.7, 122.0, 124.8, 127.3 (2C), 128.4 (2C), 129.5, 132.6, 138.6, 166.1; MS (CI) *m/z* 444 $[M+H]^+$, 464 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{23}H_{35}F_3NO_5$ $[M+NH_4]^+$: 462.2454, found: 462.2454.

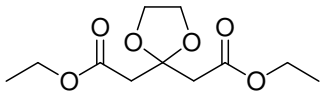
(*S*)-5-[2-(4-Acetoxypentyl)-[1,3]dioxolan-2-yl]pent-1-ene (99)



To a solution of (*R*)-5-(2-pent-4-enyl-[1,3]dioxolan-2-yl)pentan-2-ol (**93**) (270 mg, 1.18 mmol) and triphenylphosphine (787 mg, 3.0 mmol) in PhMe (10 mL) at –15 °C was added acetic acid (169 µl, 3.0 mmol), followed by DIAD (503 µL, 3.0 mmol) dropwise. The resultant mixture was allowed to warm slowly to 23 °C and stirred for 72 h. Concentration *in vacuo* was followed by flash column chromatography (EtOAc : hexanes, 1 : 9) to afford (*S*)-acetate **99** (292 mg, 91%) as a colourless oil:

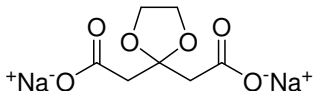
(*S*)-Acetate **99** is spectroscopically identical to (*R*)-acetate **99** except: $[\alpha]_D$ +1.1 (*c* 1.12, CH_2Cl_2)

(2-Ethoxycarbonylmethyl-[1,3]dioxolan-2-yl)acetic acid ethyl ester (139)[187]



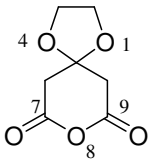
To a solution of diethyl 1,3-acetonedicarboxylate (**92**) (100 g, 494 mmol) and ethylene glycol (55.0 mL, 989 mmol) in PhMe (1 L) was added $BF_3 \cdot OEt_2$ (3.60 mL, 29.3 mmol). The reaction mixture was heated to 120 °C under Dean-Stark phase-separating apparatus. After 18 h the reaction mixture was allowed to cool to 23 °C and quenched by addition of sat. aq. $NaHCO_3$ (100 mL). The aqueous layer was extracted with Et_2O (3 × 500 mL) and the combined organic extracts dried (Na_2SO_4). Concentration *in vacuo* afforded diester **139** (79.0 g, 65% by mass) as a colourless oil which was used crude without further purification: R_f 0.30 (EtOAc : hexanes, 1 : 3); IR (film) ν_{max} 1736, 1372, 1185 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, J = 7.0 Hz, 6H, CH_3CH_2), 2.96 (s, 4H, CH_2), 4.03 (s, 4H, $O(CH_2)_2O$), 4.17 (q, J = 7.0 Hz, 4H, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1 (2C), 42.2 (2C), 60.6 (2C), 65.2 (2C), 106.8, 169.4 (2C); MS (CI) *m/z* 247 $[M+H]^+$, 264 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{11}H_{19}O_6$ $[M+H]^+$: 247.1182, found: 247.1174.

Disodium-(2-carboxymethyl-[1,3]dioxolan-2-yl)acetate (143)[95]



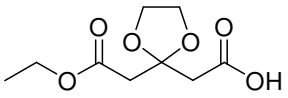
To a solution of the crude (2-ethoxycarbonylmethyl-[1,3]dioxolan-2-yl)acetic acid ethyl ester (**139**) (72.6 g, 295 mmol) in absolute EtOH (300 mL) at 80 °C was added a solution of sodium hydroxide (19.5 g, 487 mmol) in hot absolute EtOH (200 mL) over a 2 h period. The mixture was refluxed at 80 ^{o}C for 1 h, filtered hot through a glass sinter funnel and the precipitate washed with hot absolute EtOH (100 mL). The crude white powder was recrystallised from H_2O/EtOH to afford disodium salt **143** (25.0 g, 62% over 2 steps) as colourless blades: m.p. >250 ^{o}C; IR (nujol) ν_{max} 3431, 3385, 1562, 1405, 1041, 920 cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 2.53 (s, 4H, CH_2), 3.86 (s, 4H, O(CH_2)$_2$O); ^{13}C NMR (75 MHz, D_2O) δ 46.1 (2C), 64.6 (2C), 108.3, 177.8 (2C).

1,4,8-Trioxa-spiro[4.5]decane-7,9-dione (140)[95]



Following the procedure of Bruchter *et al.,*[95] to a solution of disodium-(2-carboxymethyl-[1,3]dioxolan-2-yl)acetate (**143**) (23.0 g, 100 mmol) in CH_2Cl_2 (500 mL) was added a solution of oxalyl chloride (17.0 mL, 200 mmol) in CH_2Cl_2 (100 mL) portionwise over 30 min. The resulting suspension was refluxed at 50 °C for 2 h and filtered hot through a glass sinter funnel. The filtrate was concentrated *in vacuo* to one third of its volume and the resultant bright yellow solution heated to boiling, followed by saturation with petroleum ether and chilling. Anhydride **140** was obtained upon filtration and recrystallisation from CH_2Cl_2/petroleum ether gave colourless blades (11.7 g, 68%): m.p. 111−112 °C (CH_2Cl_2/petroleum ether) [lit.,[95] 112−113 °C ($CHCl_3$/petroleum ether)]; IR (nujol) ν_{max} 1821, 1776, 1266, 1056, 950 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.99 (s, 4H, CH_2), 4.05 (s, 4H, O(CH_2)$_2$O); ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.9 (2C), 65.6 (2C), 103.5, 163.8 (2C); MS (CI) *m/z* 190 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_7H_{12}NO_5$ $[M+NH_4]^+$: 190.0715, found: 190.0710.

(2-Ethoxycarbonylmethyl-[1,3]dioxolan-2-yl)-acetic acid (141)[95]



Method A

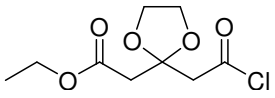
Following the procedure of Bruchter *et al.,*[95] solid 1,4,8-trioxa-spiro[4.5]decane-7,9-dione (**140**) (9.88 g, 57.4 mmol) and absolute EtOH (6.70 mL, 11.5 mmol) were heated to 80 °C at which time all solids had dissolved. The resulting solution was gently refluxed at that temperature for 18 h. Concentration *in vacuo* was followed by flash column chromatography (EtOAc : hexanes, 2 : 3) to afford carboxylic acid **141** (12.4 g, 99%) as a colourless viscous oil.

Method B

To a solution of (2-ethoxycarbonylmethyl-[1,3]dioxolan-2-yl)acetic acid ethyl ester (**139**) (2.00 g, 8.12 mmol) in EtOH (10 mL) at 0 °C was added a solution of potassium hydroxide (456 mg, 8.12 mmol) in H_2O (20 mL) dropwise. The resultant yellow solution was allowed to warm to 23 °C. After 72 h the reaction mixture was concentrated *in vacuo* to one third of its volume, diluted with H_2O (50 mL) and extracted with Et_2O (3 × 15 mL). The aqueous layer was cooled to 0 ^oC and carefully acidified to pH 4.5 with 1 M HCl, then extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine (20 mL) and dried (Na_2SO_4). Concentration *in vacuo* afforded carboxylic acid **141** (991 mg, 56%), which was spectroscopically identical to that prepared by Method A: R_f 0.40 (EtOAc : hexanes, 1 : 1); IR (film) ν_{max} 3472, 1734, 1373, 1190, 1034, 952 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.17 (t, J = 7.0 Hz, 3H, CH_3CH_2), 2.84 (s, 2H, CH_2CO_2Et), 2.88 (s, 2H, CH_2CO_2H), 3.94 (s, 4H, $O(CH_2)_2O$) 4.03 (q, J = 7.0 Hz, 2H, CH_2CH_3), 8.76 (*br.* s, 1H, CO_2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 42.1, 42.2, 61.4, 65.1 (2C), 106.8, 169.4, 173.9; MS (CI) *m/z* 219 $[M+H]^+$, 236 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_9H_{18}NO_6$ $[M+NH_4]^+$: 236.1134, found: 236.1136.

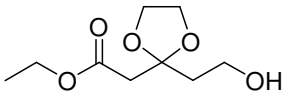
Note : 32% of starting diester **139** was also obtained from the hydrolysis (Method B), therefore the yield based on starting material recovery is 88% .

(2-Chlorocarbonylmethyl-[1,3]dioxolan-2-yl)acetic acid ethyl ester (144)[95]



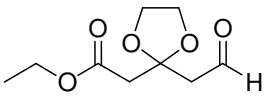
To a solution of (2-ethoxycarbonylmethyl-[1,3]dioxolan-2-yl)acetic acid (**141**) (1.00 g, 4.59 mmol) in PhMe (15 mL) at 0 °C was added oxalyl chloride (1.20 mL, 13.7 mmol) dropwise. The resulting solution was allowed to warm to 23 °C over 3 h. Concentration *in vacuo* afforded acid chloride **144** (1.04 g, >100% by mass) as a pale yellow oil which was used crude without further purification: R_f 0.25 (EtOAc : hexanes, 1 : 4); IR (film) ν_{max} 1808, 1736, 1033, 951 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (t, J = 7.0 Hz, 3H, CH_3CH_2), 2.78 (s, 2H, CH_2CO_2Et), 3.55 (s, 2H, CH_2CO_2Cl), 4.00 (s, 4H, $O(CH_2)_2O$), 4.12 (q, J = 7.0 Hz, 2H, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 42.2, 42.9, 60.9, 65.4 (2C), 105.9, 168.9, 169.4; MS (CI) *m/z* 236 $[M(^{35}Cl)]^+$, 238 $[M(^{37}Cl)]^+$, 254 $[M(^{35}Cl)+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_9H_{13}{}^{35}ClO_5$ $[M]^+$: 236.1121, found: 236.1116.

[2-(2-Hydroxyethyl)-[1,3]dioxolan-2-yl]acetic acid ethyl ester (145)



To a solution of (2-ethoxycarbonylmethyl-[1,3]dioxolan-2-yl)acetic acid (**141**) (1.29 g, 5.90 mmol) in THF (10 mL) at 0 °C was added BH_3·THF (1.0 M in THF, 11.8 mL, 11.8 mmol) and the resultant solution stirred at 0 °C for a further 3 h. MeOH (20 mL) was added and the reaction allowed to warm to 23 °C and maintained for 2 h. Concentration *in vacuo* afforded alcohol **145** (1.18 g, 98% by mass) as a colourless oil which was used without further purification: R_f 0.25 (EtOAc : hexanes, 1 : 1); IR (film) ν_{max} 3454, 2980, 1732, 1372, 1213, 1113, 1039, 950 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, J = 7.0 Hz, 3H, CH_3CH_2), 2.05 – 2.08 (m, 2H, CH_2CH_2OH), 2.78 (s, 2H, CH_2CO_2Et), 3.70 – 3.80 (m, 4H, $O(CH_2)_2O$), 4.00 – 4.03 (m, 2H, CH_2CH_2OH), 4.17 (q, J = 7.0 Hz, 2H, CH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 39.0, 42.7, 58.6, 60.8, 64.8 (2C), 109.6, 169.3; MS (CI) *m/z* 205 $[M+H]^+$, 222 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_9H_{17}O_5$ $[M+H]^+$: 205.1076, found: 205.1078.

[2-(2-Oxoethyl)-[1,3]dioxolan-2-yl]acetic acid ethyl ester (91)[95]



Method A

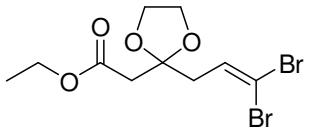
Following the procedure of Fleet *et al.,*[49] to a solution of triphenylphosphine (21.6 g, 82.4 mmol) in CH_2Cl_2 (150 mL) was added finely powdered copper (I) chloride (4.00 g, 40.4 mmol). The resulting suspension was stirred for 15 min until the copper had dissolved, after which time a suspension of sodium borohydride (1.52 g, 40.4 mmol) in EtOH (15 mL) was added. After 30 min the organic layer was separated, washed with H_2O (3 × 50 mL) and dried (Na_2SO_4). Saturation with Et_2O (200 mL) afforded colourless needles which were collected by filtration to afford *bis*(triphenylphosphine)copper (I) borohydride (18.3 g, 76%) which was used crude without further purification: m.p. 171−173 °C (CH_2Cl_2/Et_2O) [lit.,[49] 172−174 °C].

To a suspension of freshly prepared *bis*(triphenylphosphine)copper(I) borohydride (2.57 g, 4.26 mmol) and triphenylphosphine (2.23 g, 8.52 mmol) in acetone (20 mL) was added crude (2-chlorocarbonylmethyl-[1,3]dioxolan-2-yl)acetic acid ethyl ester (**144**) (1.00 g, 4.26 mmol) in acetone (10 mL) at 23 °C. After 30 min the reaction mixture was filtered through a sinter funnel and the filtrate concentrated *in vacuo.* The crude product was triturated with cold Et_2O to remove Ph_3PO. Concentration of the filtrate *in vacuo* was followed by flash column chromatography (Et_2O : PhMe, 1 : 9) to afford aldehyde **91** (816 mg, 88% over two steps) as a colourless oil.

Method B

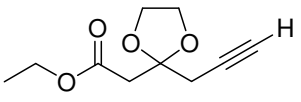
To a solution of oxalyl chloride (131 μL, 1.5 mmol) in CH_2Cl_2 (3 mL) at –78 °C was added DMSO (250 μL, 3.5 mmol) and the reaction stirred for 15 min before addition of [2-(2-hydroxyethyl)-[1,3]dioxolan-2-yl]acetic acid ethyl ester (**145**) (212 mg, 1.04 mmol) in CH_2Cl_2 (1 mL). After 1 h at –78 °C, Et_3N (832 μL, 6.0 mmol) was added, the solution allowed to warm to 23 °C over 1 h and then quenched by the addition of H_2O (3 mL) and EtOAc (5 mL). The organic layer was separated and the aqueous phase back-extracted with EtOAc (3 × 5 mL). The combined organic extracts were then washed with brine (5 mL) and dried (Na_2SO_4). Concentration *in vacuo* was followed immediately by flash column chromatography (Et_2O : PhMe, 1 : 9) to afford aldehyde **91** as a colourless oil (181 mg, 84% over two steps) which was spectroscopically identical to that prepared by Method A: R_f 0.55 (EtOAc : hexanes, 1 : 1); IR (film) ν_{max} 1731, 1372, 1190, 1034, 949 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, J = 7.0 Hz, 3H, CH_3CH$_2$), 2.71 (s, 2H, CH_2CO$_2$Et), 2.96 (s, 2H, CH_2CHO), 3.94 – 3.97 (m, 4H, O(CH_2)$_2$O), 4.12 (q, J = 7.0 Hz, 2H, CH_2CH$_3$), 9.72 (s, 1H, C*H*O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 42.1, 50.3, 60.7, 65.1 (2C), 106.8, 169.3, 199.6; MS (CI) *m/z* 203 $[M+H]^+$, 220 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_9H_{15}O_5$ $[M+H]^+$: 203.0919, found: 203.0914.

[2-(3,3-Dibromoallyl)-[1,3]dioxolan-2-yl]acetic acid ethyl ester (156)



To a suspension of triphenylphosphine (1.10 g, 4.21 mmol) in CH_2Cl_2 (6 mL) at 0 °C was added carbon tetrabromide (700 mg, 2.10 mmol). The mixture was stirred for 30 min before the dropwise addition of [2-(2-oxo-ethyl)-[1,3]dioxolan-2-yl]acetic acid ethyl ester (**91**) (210 mg, 1.05 mmol) in CH_2Cl_2 (2 mL) and the resulting suspension was stirred for a further 48 h in the dark. Concentration *in vacuo* was followed by flash column chromatography (EtOAc : hexanes, 1 : 1) to afford dibromide **156** (285 mg, 77%) as a colourless oil: R_f 0.55 (EtOAc : hexanes, 1 : 1); IR (film) ν_{max} 1737, 1371, 1242, 1037, 950 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, J = 7.0 Hz, 3H, CH_3CH_2), 2.61 – 2.63 (m, 2H, $CH_2CH{=}CBr_2$), 2.64 (s, 2H, CH_2CO_2Et), 3.96 – 3.99 (m, 4H, $O(CH_2)_2O$), 4.11 (q, J = 7.0 Hz, 2H, CH_2CH_3), 6.44 (t, J = 7.0 Hz, 1H, $CH{=}CBr_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 41.4, 42.7, 60.7, 65.2 (2C), 91.4, 107.8, 133.1, 168.9; MS (CI) *m/z* 357 $[M(^{79}Br)(^{79}Br)+H]^+$, 359 $[M(^{79}Br)(^{81}Br)+H]^+$, 361 $[M(^{81}Br)(^{81}Br)+H]^+$, 374 $[M(^{79}Br)(^{79}Br)+NH_4]^+$, 376 $[M(^{79}Br)(^{81}Br)+NH_4]^+$, 378 $[M(^{81}Br)(^{81}Br)+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{10}H_{18}{}^{79}Br^{79}BrNO_4$ $[M+NH_4]^+$: 373.9597, found: 373.9591; calculated for $C_{10}H_{18}{}^{79}Br^{81}BrNO_4$ $[M+NH_4]^+$: 375.9577, found: 375.9576; calculated for $C_{10}H_{18}{}^{81}Br^{81}BrNO_4$ $[M+NH_4]^+$: 377.9555, found: 377.9557; Anal. calculated for $C_{10}H_{14}BrO_4$: C, 33.55; H, 3.94; found: C, 33.47; H, 3.87%.

(2- Prop-2-ynyl-[1,3]dioxolan-2-yl)acetic acid ethyl ester (90)



Method A

To a suspension of magnesium (320 mg, 13.2 mmol) in THF (10 mL) was added 1,2-dibromoethane (0.25 mL, 2.90 mmol) and the reaction mixture was heated to 70 °C at which point the reaction mixture turned from brown to colourless. [2-(3,3-dibromoallyl)-[1,3]dioxolan-2-yl]acetic acid ethyl ester (**156**) (2.30 g, 6.42 mmol) in THF (15 mL) was added dropwise and the temperature maintained at 70 °C for a further 1 h before cooling to 23 °C and quenching by the addition of sat. aq. NH_4Cl (5 mL) and H_2O (25 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts dried (Na_2SO_4). Concentration *in vacuo* was followed by flash column chromatography (EtOAc : hexanes, 1 : 9 → 1 : 3) to afford alkyne **90** (826 mg, 65%) as a colourless oil:

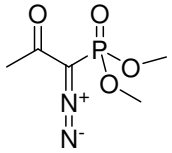
Method B

To a solution of (1-diazo-2-oxo-propyl)phosphonic acid diethyl ester (**158**) (268 mg, 1.22 mmol and [2-(2-oxo-ethyl)-[1,3]dioxolan-2-yl]acetic acid ethyl ester (**91**) (100 mg, 0.49 mmol) in THF (5 mL) at –78 °C was added sodium methoxide (2.45 mL, 0.5 M in THF, 1.22 mmol) and the reaction mixture was allowed to warm slowly to 23 °C. After 2 h, the reaction mixture was quenched by the addition of sat. aq. NH_4Cl (2 mL) and diluted with H_2O (20 mL). The aqueous layer was extracted with EtOAc (3 × 15 mL) and the combined organic extracts dried (Na_2SO_4). Concentration *in vacuo* was followed by flash column chromatography (EtOAc : hexanes, 1 : 9) to afford alkyne **90** (38 mg, 33%) as a colourless oil which was spectroscopically identical to that prepared by Method A.

Method C

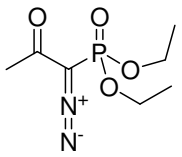
To a solution of TMS-diazomethane (**181**) (345 μL, 0.69 mmol) in THF (3 mL) at –78 °C was added dropwise *n*-BuLi (239 μL, 2.5 M in hexanes, 0.60 mmol). After 30 min, [2-(2-oxo-ethyl)-[1,3]dioxolan-2-yl]acetic acid ethyl ester (**91**) (93 mg, 0.46 mmol) in THF (0.5 mL) was added and the resultant solution stirred at –78 °C for 1 h, then 0 °C for 1 h. Concentration *in vacuo* was followed by flash column chromatography (EtOAc : hexanes, 1 : 4) to afford alkyne **90** (36 mg, 39%) as a colourless oil which was spectroscopically identical to that prepared by Method A: R_f 0.40 (EtOAc : hexanes, 1 : 1); IR (film) ν_{max} 3283, 1455, 1129, 1082, 911 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.0 Hz, 3H, CH_3CH_2), 2.07 (t, *J* = 2.5 Hz, 1H, C≡C*H*), 2.79 (d, *J* = 2.5 Hz, 2H, $CH_2C{\equiv}CH$), 2.85 (s, 2H, CH_2CO_2Et), 4.04 – 4.10 (m, 4H, $O(CH_2)_2O$), 4.17 (q, *J* = 7.0 Hz, 2H, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 28.7, 41.8, 60.7, 65.6 (2C), 70.5, 79.5, 107.7, 169.1; MS (CI) *m/z* 199 $[M+H]^+$, 216 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{10}H_{18}NO_4$ $[M+NH_4]^+$: 216.1236, found: 216.1235; Anal. calculated for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12; found: C, 60.49; H, 7.12%.

(1-Diazo-2-oxo-propyl)phosphonic acid dimethyl ester (158)[100]



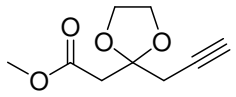
To a suspension of NaH (60% dispersion in mineral oil, 168 mg, 4.20 mmol) in PhMe (8 mL) and THF (2 mL) at 0 °C was added dimethyl (2-oxopropyl)phosphonate (**165**) (552 μL, 3.99 mmol) in PhMe (4 mL). After 1 h at 0–5°C, tosyl azide (**177**) [freshly prepared from tosyl chloride (828 mg, 4.20 mmol) and sodium azide (273 mg, 4.20 mmol][104] in PhMe (4 mL) was added dropwise and the reaction mixture allowed to warm slowly to 23 °C. After 2 h, the reaction mixture was filtered through celite, concentrated *in vacuo* and purified by flash column chromatography (EtOAc : hexanes, 3 : 1) to afford azide **158** (737 mg, 96%) as a yellow oil: R_f 0.20 (EtOAc); IR (film) ν_{max} 2123, 1659, 1273, 1180, 1024 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.10 (s, 3H, $COCH_3$), 3.69 (d, J = 12.0 Hz, 6H, $P(OCH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.0, 53.5 (2C), 189.7; MS (CI) *m/z* 193 $[M+H]^+$, 210 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_5H_{13}N_3PO_4$ $[M+NH_4]^+$: 210.0641, found: 210.0641.

(1-Diazo-2-oxo-propyl)phosphonic acid diethyl ester (179)[188]



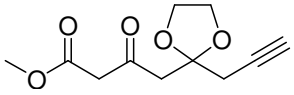
To a suspension of NaH (60% dispersion in oil, 168 mg, 4.20 mmol) in PhMe (8 mL) and THF (2 mL) at 0 °C was added diethyl (2-oxopropyl)phosphonate (**178**) (781 µL, 4.00 mmol) in PhMe (4 mL). After 1 h at 0–5 °C, tosyl azide (**177**) [freshly prepared from tosyl chloride (828 mg, 4.20 mmol) and sodium azide (273 mg, 4.20 mmol][104] in PhMe (4 mL) was added dropwise and the reaction mixture allowed to warm slowly to 23 °C. After 2 h the reaction mixture was filtered through celite, concentrated *in vacuo* and purified by flash column chromatography (EtOAc : hexanes, 3 : 1) to afford azide **179** (792 mg, 90%) as a yellow oil: R_f 0.25 (EtOAc); IR (film) ν_{max} 2122, 1659, 1268, 1171, 1018 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (t, J = 7.5 Hz, 6H, CH_2CH_3), 2.22 (s, 3H, $COCH_3$), 4.15 (q, J = 7.5 Hz, 4H, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.1, 27.2, 63.4 (2C), 190.2; MS (CI) *m/z* 221 $[M+H]^+$, 238 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_7H_{17}N_3PO_4$ $[M+NH_4]^+$: 238.0957, found: 238.0961.

(2-Prop-2-ynyl-[1,3]dioxolan-2-yl)acetic acid methyl ester (180)



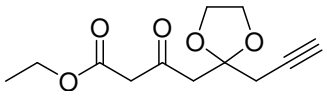
To a solution of [2-(2-oxo-ethyl)-[1,3]dioxolan-2-yl]acetic acid ethyl ester (**91**) (600 mg, 2.97 mmol) and K_2CO_3 (1.23 g, 8.91 mmol) in MeOH (50 mL) was added (1-diazo-2-oxo-propyl)-phosphonic acid dimethyl ester (**158**) (585 mg, 3.05 mmol). After 18 h the reaction mixture was diluted with Et_2O (50 mL), washed with sat. aq. $NaHCO_3$ (2 × 10 mL) and the organic layer dried (Na_2SO_4). Concentration *in vacuo* was followed by flash column chromatography (EtOAc : hexanes, 1 : 9) to afford alkyne **180** (311 mg, 57%) as a colourless oil: R_f 0.30 (EtOAc : hexanes, 1 : 1); IR (film) ν_{max} 3279, 1737, 1436, 1208, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.04 (t, *J* = 2.5 Hz, 1H, C≡C*H*), 2.73 (d, *J* = 2.5 Hz, 2H, CH_2C≡CH), 2.82 (s, 2H, C$H_2$$CO_2$Me), 3.67 (s, 3H, CO_2CH_3), 3.98 – 4.04 (m, 4H, O(CH_2)$_2$O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.6, 41.6, 51.8, 65.6 (2C), 71.9, 79.5, 107.6, 169.5; MS (CI) *m/z* 185 $[M+H]^+$, 202 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_9H_{16}NO_4$ $[M+NH_4]^+$: 202.1079, found: 202.1077; Anal. calculated for $C_{19}H_{12}O_4$: C, 58.69; H, 6.57; found: C, 58.49; H, 6.48%.

3-Oxo-4-(2-prop-2-ynyl-[1,3]dioxolan-2-yl)butyric acid methyl ester (186)



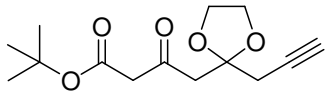
To a solution of MeOAc (1.00 mL, 12.7 mmol) in THF (20 mL) at –78 °C was added LDA (6.33 mL, 2.0 M in THF/heptane/ethyl benzene, 12.7 mmol) dropwise and the resultant solution stirred for 15 min before addition of (2-prop-2-ynyl-[1,3]dioxolan-2-yl)acetic acid methyl ester (**180**) (776 mg, 4.22 mmol) in THF (10 mL). The reaction mixture was allowed to warm slowly to 23 °C over 4 h, then quenched with pH 7.0 buffer (30 mL), extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were washed with sat. aq. NH_4Cl (10 mL), then dried (Na_2SO_4). Concentration *in vacuo* was followed by flash column chromatography (EtOAc : hexanes, 1 : 2) to afford alkyne **186** (277 mg, 29%) as a pale yellow oil: R_f 0.30 (EtOAc : hexanes, 1 : 1); IR (film) ν_{max} 3280, 1744, 1719, 1439, 1327, 1029 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.05 (t, *J* = 2.5 Hz, 1H, C≡C*H*), 2.65 (d, *J* = 2.5 Hz, 2H, CH_2C≡CH), 3.06 (s, 2H, CH_2CO(CH_2)$_2$O), 3.53 (s, 2H, C(O)CH_2C(O)), 3.69 (s, 3H, CO_2CH_3), 3.96 – 4.03 (m, 4H, O(CH_2)$_2$O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.8, 49.0, 50.4, 52.3, 65.4 (2C), 70.9, 79.2, 107.9, 167.4, 199.3; MS (CI) *m/z* 227 $[M+H]^+$, 244 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{11}H_{18}NO_5$ $[M+NH_4]^+$: 244.1185, found: 244.1182; Anal. calculated for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24; found: C, 58.48; H, 6.24%.

3-Oxo-4-(2-prop-2-ynyl-[1,3]dioxolan-2-yl)butyric acid ethyl ester (89)



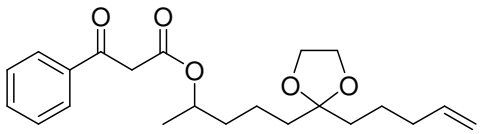
To a solution of *N,N*-di*iso*propylamine (3.58 mL, 25.3 mmol) in THF (10 mL) at –78 °C was added *n*-BuLi (2.5 M in hexanes, 10.1 mL, 25.3 mmol) and the resultant solution warmed to 23 °C for 15 min, recooled to –78 °C and MeOAc (2.01 mL, 25.3 mmol) added. After 30 min, (2-prop-2-ynyl-[1,3]dioxolan-2-yl)acetic acid ethyl ester (**90**) (776 mg, 4.22 mmol) was added and the reaction allowed to warm to 23 °C slowly over 4 h. After this time, the reaction was quenched with pH 7.0 buffer (10 mL), extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts washed with sat. aq. NH_4Cl (10 mL), then dried (Na_2SO_4). Concentration *in vacuo* was followed by flash column chromatography (EtOAc : hexanes, 1 : 2) to afford alkyne **89** (86 mg, 86%) as a yellow oil: R_f 0.30 (EtOAc : hexanes, 1 : 1); IR (film) ν_{max} 3281, 1724, 1327, 1152, 1030, 951 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.0 Hz, 3H, CH_2CH_3), 2.05 (t, *J* = 2.5 Hz, 1H, C≡C*H*), 2.62, (d, *J* = 2.5 Hz, 2H, $CH_2C{\equiv}CH$), 3.04 (s, 2H, $CH_2CO(CH_2)_2O$), 3.52 (s, 2H, $C(O)CH_2C(O)$), 3.95 – 4.05 (m, 4H, $O(CH_2)_2O$), 4.15 (q, *J* = 7.0 Hz, 2H, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 28.8, 49.0, 50.6, 61.3, 65.4, 65.6, 70.9, 79.2, 107.9, 171.7, 199.5; MS (CI) *m/z* 241 $[M+H]^+$, 258 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{12}H_{17}O_5$ $[M+H]^+$: 241.1076, found: 241.1074.

3-Oxo-4-(2-prop-2-ynyl-[1,3]dioxolan-2-yl)butyric acid *tert*-butyl ester (187)



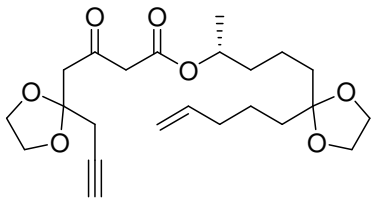
To a solution of *t*-BuOAc (2.13 mL, 16.3 mmol) in THF (40 mL) at –78 °C was added LDA (8.15 mL, 2.0 M in THF/heptane/ethyl benzene, 16.3 mmol) dropwise and the resultant solution stirred for 15 min before addition of (2-prop-2-ynyl-[1,3]dioxolan-2-yl)acetic acid ethyl ester (**90**) (1.00 g, 5.43 mmol) in THF (10 mL). The reaction mixture was allowed to warm slowly to 23 °C over 4 h, then quenched with pH 7.0 buffer (50 mL), extracted with CH_2Cl_2 (3 × 25 mL). The combined organics were washed with sat. aq. NH_4Cl (50 mL), then dried (Na_2SO_4). Concentration *in vacuo* was followed by flash column chromatography (EtOAc : hexanes, 1 : 3) to afford alkyne **187** (1.00 g, 69%) as an orange oil: R_f 0.30 (EtOAc : hexanes, 1 : 1); IR (film) ν_{max} 3281, 1716, 1414, 1325, 1150, 1029 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9H, $C(CH_3)_3$) 2.05 (t, J = 2.5 Hz, 1H, C≡C*H*), 2.65 (d, J = 2.5 Hz, 2H, $CH_2C{\equiv}CH$), 3.04 (s, 2H, $CH_2CO(CH_2)_2O$), 3.44 (s, 2H, $C(O)CH_2C(O)$), 3.99 – 4.06 (m, 4H, $O(CH_2)_2O$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.0 (3C), 28.8, 48.9, 51.9, 65.5 (2C), 70.8, 79.3, 81.9, 107.0, 166.2, 199.8; MS (CI) *m/z* 269 $[M+H]^+$, 286 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{14}H_{24}NO_5$ $[M+NH_4]^+$: 286.1654, found: 286.1654.

3-Oxo-3-phenylpropionic acid 1-methyl-4-(2-pent-4-enyl-[1,3]dioxolan-2-yl)butyl ester (193)



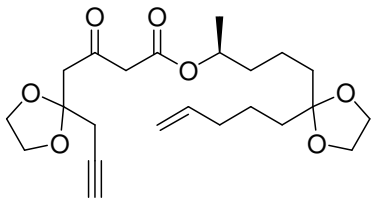
Following the procedure of Bandgar and Uppalla,[111] to a solution of (±)-5-(2-pent-4-enyl-[1,3]dioxolan-2-yl)pentan-2-ol (**93**) (103 mg, 0.70 mmol) and ethyl benzoylacetate (**192**) (78 μL, 0.70 mmol) in PhMe (3 mL) was added Zn dust (20 mg) and the resulting suspension heated to 110 °C under a distillation condenser for 72 h. After this time, the reaction was cooled, filtered, concentrated *in vacuo* and purified by flash column chromatography (EtOAc : hexanes, 1 : 2) to afford β-ketoester **193** (140 mg, 64%) as a pale yellow oil: R_f 0.80 (EtOAc : hexanes, 1 : 3); IR (film) ν_{max} 3070, 1736, 1687, 1634, 1451, 1266, 1021 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.21 (d, *J* = 6.5 Hz, 3H, C*H*$_3$CH), 1.30 – 1.61 (m, 10H, C*H*$_2$), 2.09 (*app.* q, *J* = 7.0 Hz, 2H, C*H*$_2$CH=CH$_2$), 3.91 (s, 4H, O(C*H*$_2$)$_2$O), 3.97 (s, 2H, C(O)C*H*$_2$C(O)), 4.93 – 5.04 (m, 3H, CH=C*H*$_2$ and CH$_3$C*H*), 5.80 (tdd, *J* = 6.5, 10.0, 17.0 Hz, 1H, C*H*=CH$_2$), 7.48 (t, *J* = 8.0 Hz, 2H, *m*-Ar*H*), 7.59 (t, *J* = 8.0 Hz, 1H, *p*-Ar*H*), 7.94 (d, *J* = 8.0 Hz, 2H, *o*-Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.6, 19.8, 23.1, 33.9, 35.9, 36.6, 36.8, 46.3, 64.9 (2C), 72.2, 111.5, 114.6, 128.5 (2C), 128.7 (2C), 133.6, 136.1, 138.7, 167.2, 192.5; MS (CI) *m/z* 375 $[M+H]^+$, 392 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{22}H_{34}NO_5$ $[M+NH_4]^+$: 392.2437, found: 392.2445.

(*R*)-3-Oxo-4-(2-prop-2-ynyl-[1,3]dioxolan-2-yl)butyric acid 1-methyl-4-(2-pent-4-enyl-[1,3]dioxolan-2-yl)butyl ester (88)



A mixture of 3-oxo-4-(2-prop-2-ynyl-[1,3]dioxolan-2-yl)butyric acid ethyl ester (**89**) (200 mg, 0.88 mmol), (±)-5-(2-pent-4-enyl-[1,3]dioxolan-2-yl)pentan-2-ol (**93**) (500 mg, 2.2 mmol) and CAL-B (140 mg, 20% w/w) were heated together neat at 45 °C for 5 days. After this time the reaction mixture was diluted with CH_2Cl_2 (10 mL) and filtered through a sinter funnel. Concentration of the filtrate *in vacuo* was followed by flash column chromatography (Et_2O : CH_2Cl_2 : petroleum ether, 5 : 5 : 1) to afford (*R*)-enriched enyne **88** (200 mg, 54%) as a pale yellow oil: R_f 0.55 (EtOAc : hexanes, 1 : 1); $[\alpha]_D$ –1.7 (*c* 1.25, CH_2Cl_2); IR (film) ν_{max} 3279, 2952, 2893, 1738, 1715, 1640, 1033 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (d, *J* = 6.0 Hz, 3H, C*H*$_3$CH), 1.32 – 1.70 (m, 10H, C*H*$_2$), 2.02 – 2.08 (m, 2H, C*H*$_2$CH=CH$_2$), 2.20 – 2.25 (m, 1H, C≡C*H*), 2.66 (d, *J* = 2.5 Hz, 2H, C*H*$_2$C≡CH), 3.06 (s, 2H, C*H*$_2$COR), 3.53 (s, 2H, C*H*$_2$(CO)$_2$), 3.92 (s, 4H, O(C*H*$_2$)$_2$O), 4.00 – 4.07 (m, 4H, O(C*H*$_2$)$_2$O), 4.93 – 5.11 (m, 3H, CH=C*H*$_2$ and CH$_3$C*H*), 5.67 – 5.86 (m, 1H, C*H*=CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4, 19.6, 23.1, 28.9, 35.1, 35.9, 36.6, 36.9, 49.0, 50.9, 65.0 (2C), 65.6 (2C), 70.9, 72.2, 79.3, 107.9, 111.4, 114.7, 138.7, 166.7, 199.4; MS (CI) *m/z* 423 $[M+H]^+$, 440 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{23}H_{38}NO_7$ $[M+NH_4]^+$: 440.2648, found: 440.2648; Anal. calculated for $C_{23}H_{34}O_7$: C, 65.38; H, 8.11; found: C, 65.29; H, 7.99%.

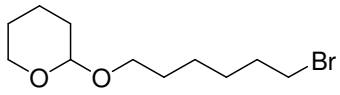
(*S*)-3-Oxo-4-(2-prop-2-ynyl-[1,3]dioxolan-2-yl)butyric acid 1-methyl-4-(2-pent-4-enyl-[1,3]dioxolan-2-yl)butyl ester (88)



To a solution of (*S*)-5-(2-pent-4-enyl-[1,3]dioxolan-2-yl)pentan-2-ol (**93**) (1.28 g, 5.60 mmol) and 3-oxo-4-(2-prop-2-ynyl-[1,3]dioxolan-2-yl)butyric acid ethyl ester (**89**) (450 mg, 1.88 mmol) in PhMe (20 mL) was added Zn dust (25 mg, 0.38 mmol) and the resulting suspension heated to 110 °C under a distillation condenser for 72 h. After this time the reaction was cooled, filtered, concentrated *in vacuo* and purified by flash column chromatography (Et_2O : CH_2Cl_2 : petroleum ether, 5 : 5 : 1) to afford (*S*)-enyne **88** (537 mg, 68%).

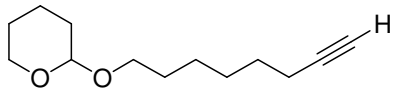
(*S*)-Enyne **88** is spectroscopically identical to (*R*)-enriched enyne **88** except: $[\alpha]_D$ +3.40 (*c* 1.00, CH_2Cl_2)

2-(6-Bromo-hexyloxy)tetrahydropyran (225)[128]



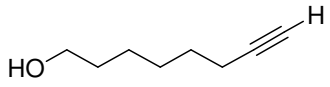
Following the procedure of Morimoto *et al.,*[128] to a solution of 6-bromo-1-hexanol (**224**) (9.60 g, 53.0 mmol) and 3,4-dihydropyran (9.67 mL, 106 mmol) in CH_2Cl_2 (40 mL) was added PPTS (1.33 g, 5.29 mmol). After 18 h, the reaction mixture was diluted with EtOAc (100 mL), washed with H_2O (3 × 50 mL) and the organic layer dried (Na_2SO_4). Concentration *in vacuo* was followed by flash column chromatography (EtOAc : hexanes, 3 : 97) to afford bromide **225** (13.9 g, 99%) as a colourless oil: R_f 0.60 (EtOAc : hexanes, 1 : 9); IR (film) ν_{max} 1451, 1351, 1127, 1029, 980, 868 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.39 – 1.90 (m, 14H, CH_2), 3.36 – 3.45 (m, 3H, CH_2), 3.46 – 3.55 (m, 1H, CH_2), 3.75 (dt, J = 9.5, 6.5 Hz, 1H CH_2), 3.84 – 3.91 (m, 1H, CH_2), 4.57 – 4.60 (m, 1H, CH(OR)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.7, 25.4 (2C), 28.0, 29.6, 30.8, 32.8, 34.0, 62.4, 67.4, 98.9; MS (CI) *m/z* 263 [M(^{79}Br)+H]$^+$, 265 [M(^{81}Br)+H]$^+$, 282 [M(^{79}Br)+NH_4]$^+$, 284 [M(^{81}Br)+NH_4]$^+$; HRMS (CI) *m/z* calculated for $C_{11}H_{25}{}^{79}BrNO_2$ [M+NH_4]$^+$: 282.1055, found: 282.1059; calculated for $C_{11}H_{25}{}^{81}BrNO_2$ [M+NH_4]$^+$: 284.1035, found: 284.1036.

2-Oct-7-ynyloxytetrahydropyran (226) [128]



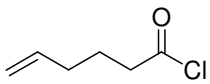
Following the procedure of Morimoto *et al.*,[128] to a suspension of sodium iodide (22.3 g, 149 mmol) in DMSO (150 mL) at 23 °C was added lithium acetylide ethylene diamine complex (5.48 g, 59.5 mmol) portionwise. After 15 min, 2-(6-bromo-hexyloxy)tetrahydropyran (**225**) (13.1 g, 49.6 mmol) in DMSO (50 mL) was added dropwise and the resulting dark brown suspension was stirred for a further 4 h before cooling to 0 °C and quenching by the addition of H_2O (500 mL). The reaction was extracted with EtOAc : hexanes, 1 : 3 (3 × 150 mL) and the combined organic extracts were washed with brine (3 × 100 mL), then dried (Na_2SO_4). Concentration *in vacuo* was followed by flash column chromatography (EtOAc : hexanes, 2 : 98) to afford alkyne **226** (8.33 g, 80%) as a colourless oil: R_f 0.70 (EtOAc : hexanes, 1 : 9); IR (film) ν_{max} 3299, 1454, 1352, 1128, 1073, 1030, 868 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 – 1.85 (m, 14H, CH_2), 1.96 (t, J = 2.5 Hz, 1H, C≡CH), 2.20 (td, J = 7.0, 2.5 Hz, 2H, CH_2C≡CH), 3.36 – 3.44 (m, 1H, CH_2), 3.47 – 3.55 (m, 1H, CH_2), 3.70 – 3.79 (m, 1H CH_2), 3.84 – 3.93 (m, 1H, CH_2), 4.57 – 4.61 (m, 1H, CH(OR)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.3, 19.6, 25.5, 25.8, 28.4, 28.5, 29.6, 30.7, 62.2, 67.4, 68.2, 84.5, 98.8; MS (CI) *m/z* 228 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{13}H_{26}NO_2$ $[M+NH_4]^+$: 228.1964, found: 228.1970.

Oct-7-yn-1-ol (227)[189]



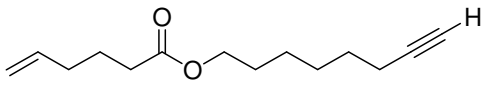
To a solution of 2-oct-7-ynyloxytetrahydropyran (**226**) (8.28 g, 39.4 mmol) in EtOH (200 mL) was added *p*TSA (15.0 g, 78.8 mmol) portionwise. The resulting solution was stirred at 23 °C for 45 min and then concentrated *in vacuo*. The residue was dissolved in sat. aq. $NaHCO_3$ (100 mL), extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic extracts dried (Na_2SO_4). Concentration *in vacuo* was followed by flash column chromatography (EtOAc : hexanes, 15 : 85) to afford alcohol **227** (4.91 g, 99%) as a colourless oil: R_f 0.45 (EtOAc : hexanes, 1 : 3); IR (film) ν_{max} 3300, 1462, 1433, 1055, 631 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 – 1.48 (m, 5H, C*H*$_2$ + O*H*), 1.50 – 1.65 (m, 4H, C*H*$_2$), 1.97 (t, *J* = 2.5 Hz, 1H, C≡C*H*), 2.10 (td, *J* = 7.0, 2.5 Hz, 2H, C*H*$_2$C≡CH), 3.67 (t, *J* = 7.0 Hz, 2H, C*H*$_2$OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 25.2, 28.4, 28.5, 32.4, 62.4, 68.3, 84.6; MS (CI) *m/z* 144 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_8H_{18}NO$ $[M+NH_4]^+$: 144.1388, found: 144.1385.

Hex-5-enoyl chloride (229)[190]



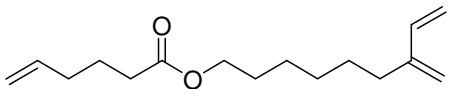
To a solution of 5-hexenoic acid (**228**) (7.73 g, 67.7 mmol) in CH_2Cl_2 (250 mL) was added oxalyl chloride (17.73 mL, 203 mmol) followed by DMF (1 drop). After 2 h the reaction mixture was concentrated *in vacuo* to afford acid chloride **229** (8.94 g, 100% by mass) as a pale yellow oil which was used crude without further purification: R_f 0.20 (EtOAc : hexanes, 1 : 9); IR (film) ν_{max} 3077, 2866, 1799, 1640, 1405, 994, 915 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.73 – 1.89 (m, 2H, CH_2), 2.07 – 2.19 (m, 2H, CH_2CH=CH_2), 2.85 – 2.95 (m, 2H, CH_2CO), 4.97 – 5.11 (m, 2H, CH=CH_2), 5.62 – 5.84 (m, 1H, CH=CH_2); MS (CI) *m/z* 150, 152 $[M+NH_4]^+$.

Hex-5-enoic acid oct-7-ynyl ester (230)



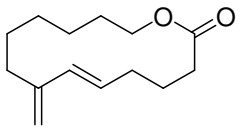
To a solution of hex-5-enoyl chloride (**229**) (0.20 g, 1.51 mmol) and oct-7-yn-1-ol (**227**) (0.159 g, 1.26 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added *N,N*-di*iso*propylethylamine (660 μL, 3.79 mmol) and the resulting reaction mixture was allowed to warm slowly to 23 °C. After 24 h, the reaction mixture was diluted with H_2O (50 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were then washed with brine (2 × 25 mL) and dried ($MgSO_4$). Concentration *in vacuo* was followed by flash column chromatography (EtOAc, hexanes, 1 : 20) to afford ester **230** (305 mg, 92%) as a colourless oil: R_f 0.75 (EtOAc : hexanes, 1 : 9); IR (film) ν_{max} 3299, 1732, 1457, 1169, 913 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 – 1.45 (m, 4H, C*H*$_2$), 1.46 – 1.55 (m, 2H, C*H*$_2$), 1.56 – 1.65 (m, 2H, C*H*$_2$), 1.65 – 1.76 (m, 2H, C*H*$_2$), 1.93 (t, *J* = 2.5 Hz, 1H, C≡C*H*), 2.07 (app. q, *J* = 7.0 Hz, 2H, C*H*$_2$), 2.17 (td, *J* = 7.0, 2.5 Hz, 2H, C*H*$_2$C≡CH), 2.29 (t, *J* = 7.5 Hz, 2H, C*H*$_2$CO$_2$R) 4.05 (t, *J* = 6.5 Hz, 2H, C*H*$_2$OCOR), 4.94 – 5.05 (m, 2H, C*H*$_2$=CH), 5.69 – 5.83 (m, 1H, CH$_2$=C*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.3, 24.1, 25.5, 28.3 (2C), 28.5, 33.1, 33.6, 64.3, 68.3, 84.4, 115.3, 137.7, 173.7; MS (CI) *m/z* 223 $[M+H]^+$, 240 $[M+H]^+$; HRMS (CI) *m/z* calculated for $C_{14}H_{23}O_2$ $[M+H]^+$: 223.1698, found: 223.1703.

Hex-5-enoic acid 7-methylenenon-8-enyl ester (231)



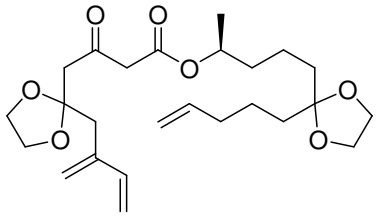
To a solution of hex-5-enoic acid oct-7-ynyl ester (**230**) (35 mg, 158 μmol) in CH_2Cl_2 (50 mL) with a slow stream of ethylene gas bubbled through, was added Grubbs' second generation catalyst (**196**) (13 mg, 10 mol %). After 72 h, the reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (EtOAc : hexanes, 2 : 98) to afford triene **231** (30 mg, 77%) as a colourless oil: R_f 0.85 (EtOAc : hexanes, 1 : 9); IR (film) ν_{max} 3080, 1736, 1594, 1459, 1171 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.38 – 1.40 (m, 4H, $(CH_2)_2$), 1.52 (td, J = 7.5, 14.5 Hz, 2H, CH_2), 1.62 – 1.68 (m, 2H, CH_2), 1.75 (quint, J = 7.5 Hz, 2H, CH_2), 2.11 (dd, J = 7.0, 14.5 Hz, 2H, CH_2), 2.23 (t, J = 6.5 Hz, 2H, $CH_2C(R)=CH_2$), 2.33 (t, J = 7.5 Hz, 2H, CH_2CO_2R), 4.09 (t, J = 7.0 Hz, 2H, CH_2OCOR), 4.99 – 5.04 (m, 4H, $CH_2=CR_2$ and $CH_2=CHR$), 5.07 (dd, J = 2.5, 11.0 Hz, 1H, $CH_2=CR\text{-}CH=CH_2$), 5.24 (dd, J = 2.5, 17.5 Hz, 1H, $CH_2=CR\text{-}CH=CH_2$), 5.80 (tdd, J = 6.5, 10.0, 17.0 Hz, 1H, $CH_2CH=CH_2$), 6.39 (dd, J = 11.0, 17.5 Hz, 1H, $CH_2=CR\text{-}CH=CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.1, 25.8, 28.0, 28.6, 29.2, 31.2, 33.6, 64.4, 113.1, 115.3, 115.3, 115.6, 137.7, 139.0, 146.4, 173.7; MS (CI) *m/z* 251 $[M+H]^+$, 268 $[M+H]^+$; HRMS (CI) *m/z* calculated for $C_{16}H_{27}O_2$ $[M+H]^+$: 251.2011, found: 251.2007; Anal. calculated for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47; found: C, 76.69; H, 10.39%.

8-Methyleneoxacyclotetradec-6-en-2-one (232)



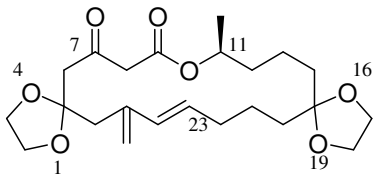
To a solution of hex-5-enoic acid 7-methylenenon-8-enyl ester (**231**) (18 mg, 81 μmol) in CH_2Cl_2 (50 mL) with a slow stream of argon bubbled through at 50 °C, was added Grubbs' second generation catalyst (**196**) (6 mg, 10 mol %). After 72 h at this temperature, the reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (EtOAc : hexanes, 2 : 98) to afford macrocycle **232** (16 mg, 98%) as a colourless oil: R_f 0.75 (EtOAc : hexanes, 1 : 9); IR (film) ν_{max} 2929, 1733, 1454, 1175 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 – 1.35 (m, 2H, CH_2), 1.38 – 1.46 (m, 2H, CH_2), 1.53 (quint, J = 7.0 Hz, 2H, CH_2), 1.60 – 1.76 (m, 2H, CH_2), 1.87 – 1.94 (m, 2H, CH_2), 2.20 – 2.27 (m, 4H, CH_2), 2.34 – 2.39 (m, 2H, CH_2), 4.16 (t, J = 5.0 Hz, 2H, CH_2OCOR), 4.87 (d, J = 2.0 Hz, 1H, C=CH_2), 4.97 (d, J = 2.0 Hz, 1H, C=CH_2), 5.71 (td, J = 7.5, 15.5 Hz, 1H, C(=CH_2)-CH=CHR); 6.07 (d, J = 15.5 Hz, 1H, C(=CH_2)-CH=CHR); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8, 24.7, 26.4, 28.0, 28.3, 30.5, 33.2, 63.7 (2C), 114.1, 128.3, 133.8, 146.4, 174.1; MS (CI) *m/z* 223 $[M+H]^+$, 240 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{14}H_{23}O_2$ $[M+H]^+$: 223.1698, found: 223.1700.

(*S*)-4-[2-(2-Methylenebut-3-enyl)-[1,3]dioxolan-2-yl]-3-oxobutyric acid 1-methyl-4-(2-pent-4-enyl-[1,3]dioxolan-2-yl)butyl ester (233)



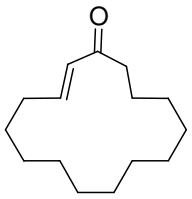
To a solution of (*S*)-3-oxo-4-(2-prop-2-ynyl-[1,3]dioxolan-2-yl)butyric acid 1-methyl-4-(2-pent-4-enyl-[1,3]dioxolan-2-yl)butyl ester (**88**) (255 mg, 0.60 mmol) in CH_2Cl_2 (1 L) with a slow stream of ethylene gas bubbled through, was added Grubbs' second generation catalyst (51 mg, 10 mol %) in CH_2Cl_2 (5 mL), *via* syringe pump over 6 h. After a further 72 h the reaction was concentrated *in vacuo* and purified by flash column chromatography (EtOAc : hexanes, 1 : 9) to afford triene **233** (196 mg, 72%) as a colourless oil: R_f 0.65 (EtOAc : hexanes, 1 : 1); $[\alpha]_D$ +2.9 (*c* 1.10, CH_2Cl_2); IR (film) ν_{max} 3082, 1739, 1714, 1633, 1469, 1240, 1035, 908 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (d, J = 6.0 Hz, 3H, CH_3CH), 1.31 – 1.73 (m, 10H, CH_2), 2.06 (*app.* q, J = 6.5 Hz, 2H, CH_2CH=CH$_2$), 2.65 (s, 2H, CH_2CR=CH$_2$), 2.92 (s, 2H, CH_2CO(CH$_2$)$_2$O), 3.53 (s, 2H, C(O)CH_2C(O)), 3.93 (s, 4H, O(CH_2)$_2$O), 3.96 (s, 4H, O(CH_2)$_2$O), 4.91 – 5.12 (m, 3H, CH=CH_2 and CH$_3$CH), 5.04 – 5.13 (m, 2H, CH=CH_2), 5.23 (d, J = 11.0 Hz, 1H, CH$_2$=CR-CH=CH_2); 5.34 (d, J = 17.5 Hz, 1H, CH$_2$=CR-CH=CH_2); 5.69 – 5.88 (m, 1H, CH$_2$CH=CH$_2$), 6.41 (dd, J = 17.5, 11.0 Hz, 1H, CH$_2$=CR-CH=CH$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 22.8, 23.1, 33.9, 36.6, 36.9, 39.4, 41.9, 50.1, 50.9, 65.0 (2C), 65.1 (2C), 72.1, 109.4, 111.5, 114.4, 114.7, 120.5, 138.7, 139.1, 141.0, 166.9, 200.2; MS (CI) *m/z* 451 $[M+H]^+$, 468 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{25}H_{42}NO_7$ $[M+NH_4]^+$: 468.2948, found: 468.2950; Anal. calculated for $C_{25}H_{38}O_7$: C, 66.64; H, 8.50; found: C, 66.64; H, 8.44%.

(S)-11-Methyl-25-methylene-1,4,10,16,19-pentaoxadispiro [4.9.4.7]hexacos-23-ene-7,9-dione (87)



To PhMe (150 mL) at 80 °C with a slow stream of argon bubbled through, were added both (*S*)-4-[2-(2-Methylenebut-3-enyl)-[1,3]dioxolan-2-yl]-3-oxobutyric acid 1-methyl-4-(2-pent-4-enyl-[1,3]dioxolan-2-yl)butyl ester (**233**) (677 mg, 1.61 mmol) in PhMe (15 mL) and Grubbs' second generation catalyst (**196**) (136 mg, 10 mol%) in PhMe (15 mL), *via* two separate syringe pumps over 10 h. After a further 72 h at this temperature, the reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (EtOAc : hexanes, 1 : 9) to afford macrocycle **87** (578 mg, 85%) as a colourless oil: R_f 0.55 (EtOAc : hexanes, 1 : 1); $[\alpha]_D$ +15.5 (*c* 1.13, CH_2Cl_2); IR (film) ν_{max} 2929, 1733, 1715, 1454, 1125, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (d, *J* = 6.5 Hz, 3H, C*H*$_3$CH), 1.28 – 1.70 (m, 10H, C*H*$_2$), 2.08 – 2.30 (m, 2H), 2.61 (AB q, *J* = 14.0 Hz, 1H, C*H*$_2$CR=CH$_2$), 2.74 (AB q, *J* = 14.0 Hz, 1H, C*H*$_2$CR=CH$_2$), 2.80 (AB q, *J* = 14.0 Hz, 1H, C*H*$_2$CO(CH$_2$)$_2$O), 3.14 (AB q, *J* = 14.0 Hz, 1H, C*H*$_2$CO(CH$_2$)$_2$O), 3.44 (AB q, *J* = 15.5 Hz, 1H, C(O)C*H*$_2$C(O)), 3.57 (AB q, *J* = 15.5 Hz, 1H, C(O)C*H*$_2$C(O)), 3.87 – 3.92 (m, 8H, O(C*H*$_2$)$_2$O × 2), 4.82 – 4.92 (m, 1H, CH$_3$C*H*), 5.01 (d, *J* = 1.5 Hz, 1H, C=C*H*$_2$), 5.09 (d, *J* = 1.5 Hz, 1H, C=C*H*$_2$), 5.71 (td, *J* = 7.5, 15.5 Hz, 1H, C(=CH$_2$)-CH=C*H*R), 6.08 (d, *J* = 15.5 Hz, 1H, C(=CH$_2$)-C*H*=CHR); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 20.8, 23.1, 32.6, 34.8, 36.3, 36.6, 39.7, 50.1, 50.8, 64.6 (2C), 65.0 (2C), 65.2, 109.3, 111.8, 118.7, 131.2, 133.2, 140.5, 167.0, 200.4; MS (CI) *m/z* 423 $[M+H]^+$, 440 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{23}H_{38}NO_7$ $[M+NH_4]^+$: 423.2383, found: 423.2387; Anal. calculated for $C_{25}H_{34}O_7$: C, 65.38; H, 8.11; found: C, 65.41; H, 8.05%.

Cyclopentadec-2-enone (240)[191]



Method A

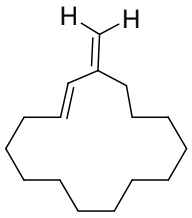
To a solution of cyclopentadecanone (**239**) (1.0 g, 4.46 mmol) in DMSO : fluorobenzene, 7 : 1 (20 mL) was added IBX (2.12 g, 8.03 mmol) and the resulting beige suspension was heated at 60 °C for 24 h. After this time, the reaction mixture was cooled to 23 °C and diluted with Et_2O (50 mL). The organic layer was separated and washed with 5% aq. $NaHCO_3$ (3 × 50 mL), then H_2O (2 × 50 mL) and dried ($MgSO_4$). Concentration *in vacuo* was followed by flash column chromatography (EtOAc : hexanes, 2.5 : 97.5) to afford enone **240** (505 mg, 51 %) as a colourless oil:

Method B

To a solution of 3-methylenecyclopentadecene (**241**) (359 mg, 1.63 mmol) in CH_3CN (7.0 mL) was added aqueous Na_2·EDTA solution (4×10^{-4} M, 5.0 mL), $NaHCO_3$ (685 mg, 8.16 mmol) and the resulting homogeneous solution was cooled to 0 °C and a –78 °C dry-ice condenser affixed. 1,1,1-Trifluoroacetone (**234**) (73 µL, 0.81 mmol) was added *via* precooled syringe, followed by Oxone® (500 mg, 0.81 mmol). The resulting solution was stirred for 1 h at 0 °C, then further 1,1,1-trifluoroacetone (73 µL, 0.81 mmol) and Oxone® (500 mg, 0.81 mmol) were added. After 4 h at 0 °C the reaction was poured into H_2O (50 mL), extracted with CH_2Cl_2 (3 × 20 mL), dried ($MgSO_4$) and concentrated *in vacuo.* The residue was dissolved in *t*-BuOH / H_2O / THF (45 : 45 : 10, 4 mL) and $NaIO_4$ (384 mg, 1.80 mmol) added, followed by HIO_4 (37 mg, 0.16 mmol). The resulting reaction mixture was stirred at 23 °C for 18 h, then H_2O (10 mL) was added and the aqueous layer extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed with H_2O (5 mL) and dried ($MgSO_4$).

Concentration *in vacuo* was followed by flash column chromatography (EtOAc : hexanes, 2.5 : 97.5) to afford enone **240** (292 mg, 83%) as a colourless oil which was spectroscopically identical to the product of Method A: R_f 0.50 (EtOAc : hexanes, 1 : 9); IR (film) ν_{max} 1690, 1664, 1622, 1457, 979 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.20 – 1.37 (m, 16H, CH_2), 1.50 – 1.60 (m, 2H, CH_2), 1.64 – 1.74 (m, 2H, CH_2), 2.23 – 2.31 (m, 2H, CH_2), 2.46 – 2.54 (m, 2H, CH_2), 6.21 (d, J = 15.5 Hz, 1H, CH=C*H*-C=O), 6.83 (dt, J = 15.5, 7.5 Hz, 1H, C*H*=CH-C=O); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.4, 25.3, 26.0, 26.2, 26.5, 26.7 (2C), 26.9 (2C), 27.0, 31.7, 40.1, 130.7, 148.2, 201.9; MS (CI) *m/z* 223 $[M+H]^+$, 240 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{15}H_{27}O$ $[M+H]^+$: 223.1984, found: 223.1983.

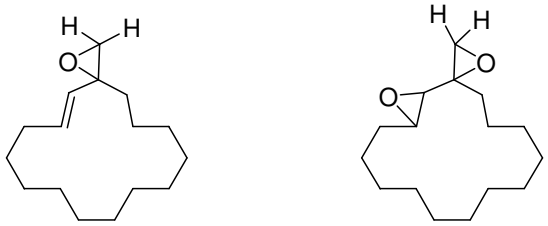
3-Methylenecyclopentadecene (241)



Following the procedure of Payack *et al.,*[134] to a suspension of titanocene dichloride (10.0 g, 40.0 mmol) in PhMe (80 mL) at –5 °C was added MeLi (1.6 M in Et_2O, 58 mL, 92.4 mmol) dropwise. After 1 h, the reaction mixture was warmed to 0 °C and quenched carefully with ice-cold 6% aq. NH_4Cl (25 mL). The organic layer was separated, washed with H_2O (2 × 25 mL), brine (2 × 25 mL) and dried ($MgSO_4$). The resulting red solution was concentrated to one third volume *in vacuo*. ^{1}H NMR assay indicated 7.8 g (94%) of dimethyltitanocene, which was stored in the freezer and used as a 0.33 M solution in PhMe.

To a solution of cyclopentadec-2-enone (**240**) (3.29 g, 14.8 mmol) in PhMe (2.0 mL) was added dimethyltitanocene (0.33 M in PhMe, 18.0 mL, 6.00 mmol) and the resulting solution was stirred at 75 °C for 24 h in the dark. After this time, the cooled reaction mixture was filtered through a long silica column, the filtrate concentrated *in vacuo* and purified by flash column chromatography (hexanes) to afford diene **241** (2.41 g, 74%) as a colourless oil: R_f 1.00 (hexanes); IR (film) ν_{max} 3076, 1603, 1459, 966, 833 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 – 1.38 (m, 16H, CH_2), 1.43 – 1.52 (m, 4H, CH_2), 2.15 – 2.29 (m, 4H, CH_2), 4.85 (*app*. d, *J* = 14.5 Hz, 2H, =CH_2), 5.73 (d, *J* = 15.5 Hz, 1H, CH=C*H*-C=O), 6.05 (dt, *J* = 15.5, 7.5 Hz, 1H, C*H*=CH-C=O); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.3, 26.5, 26.7, 26.8, 27.0, 27.1, 27.2, 28.0, 29.8, 31.9, 32.2, 33.1, 113.4, 130.9, 132.2, 146.8; MS (CI) *m/z* 221 $[M+H]^+$, 238 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{16}H_{29}$ $[M+H]^+$: 221.2269, found: 221.2271.

1-Oxa-spiro[2.14]heptadec-4-ene (243) and
1,5-dioxa-dispiro[2.1.12]octadecane (244)



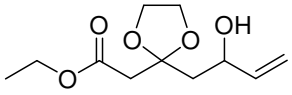
To a solution of 3-methylenecyclopentadecene (**241**) (600 mg, 2.72 mmol) in MeCN (19 mL) was added aqueous Na_2·EDTA solution (4×10^{-4} M, 13.5 mL), $NaHCO_3$ (1.14 g, 13.6 mmol) and the resulting homogeneous solution was cooled to 0 °C and a –78 °C dry-ice condenser affixed. 1,1,1-Trifluoroacetone (127 μL, 1.42 mmol) was added *via* precooled syringe, followed by Oxone® (838 mg, 1.42 mmol). The resulting solution was stirred for 1 h at 0 °C, then further 1,1,1-trifluoroacetone (127 μL, 1.42 mmol) and Oxone® (838 mg, 1.42 mmol) were added. After 4 h at 0 °C, the reaction was poured into H_2O (100 mL), extracted with CH_2Cl_2 (3×50 mL) and dried ($MgSO_4$). Concentration *in vacuo* was followed by flash column chromatography (EtOAc : hexanes, 97 : 3) to afford epoxide **243** (94 mg, 15%) and diepoxide **244** (27 mg, 4%) as colourless oils:

Monoepoxide **243**: R_f 0.45 (EtOAc : hexanes, 1 : 19); IR (film) ν_{max} 3077, 1725, 1692, 1667, 1624, 1459, 1346, 1286, 980 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.15 – 1.77 (m, 20H, CH_2), 2.04 – 2.17 (m, 2H, CH_2), 2.17 – 2.30 (m, 2H, CH_2), 2.57 (s, 2H, CH_2OCR$_2$), 5.23 – 5.32 (m, 1H, CH=C*H*CH_2O), 5.53 – 5.63 (m, 1H, C*H*=CHCH_2O); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.1, 25.3, 25.7, 26.5, 26.8 (2C), 27.0, 28.1, 28.3, 31.4, 34.9, 37.3, 55.7, 69.5, 129.3, 133.7; MS (CI) *m/z* 237 $[M+H]^+$, 254 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{16}H_{29}O$ $[M+H]^+$: 237.2218, found: 237.2212.

Diepoxide **244**: R_f 0.30 (EtOAc : hexanes, 1 : 19); IR (film) ν_{max} 1459, 1348, 911, 716 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 – 1.67 (m, 20H, CH_2), 1.70 – 1.82 (m, 2H, CH_2), 1.95 – 2.08 (m, 2H, CH_2), 2.50 (d, J = 5.5 Hz, 1H, CH_2OCR$_2$), 2.58 (d, J = 5.5 Hz, 1H, CH_2OCR$_2$), 2.84 – 2.87 (m, 1H, CH(O)CHCH(O)CH$_2$), 2.90 – 2.97 (m, 2H, CH(O)CHCH(O)CH$_2$ + CH(O)CHCH(O)CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.3, 25.4, 26.1, 26.2, 26.5, 26.8, 26.9, 27.2, 27.3, 31.3, 33.4, 33.6, 49.3, 50.8, 57.0, 57.4; MS (CI) *m/z* 253 $[M+H]^+$, 270 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{16}H_{29}O_2$ $[M+H]^+$: 253.2168, found: 253.2164.

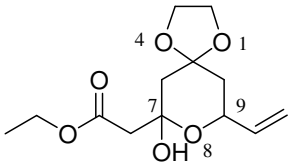
Note : Significant decomposition was observed by TLC analysis upon chromatography.

[2-(2-Hydroxy-but-3-enyl)-[1,3]dioxolan-2-yl]acetic acid ethyl ester (268)



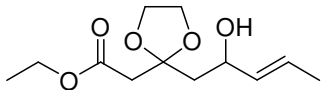
To a solution of [2-(2-oxo-ethyl)-[1,3]dioxolan-2-yl]acetic acid ethyl ester (**91**) (2.02 g, 1.00 mmol) in THF (100 mL) at –78 °C was added vinylmagnesium bromide (1.0 M in THF, 1.00 mL, 1.00 mmol) dropwise. The resultant yellow reaction mixture was stirred for an additional 4 h at –78 °C before quenching by the addition of sat. aq. NH_4Cl (2 mL) and H_2O (10 mL). The reaction mixture was extracted with EtOAc (2 × 50 mL), the combined organic extracts washed with brine (2 × 50 mL) and dried (Na_2SO_4). Concentration *in vacuo* was followed by flash column chromatography (EtOAc : hexanes, 1 : 9) to afford alcohol **268** (900 mg, 39%) as a colourless oil: R_f 0.40 (Et_2O : CH_2Cl_2 : petroleum ether, 1 : 1 : 1); IR (film) ν_{max} 3521, 1734, 1371, 1214, 1033 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.12 (t, *J* = 7.0 Hz, 3H, C*H*$_3$CH$_2$), 1.83 – 2.01 (m, 2H, C*H*$_2$CHOH), 2.59 (s, 2H, C*H*$_2$CO$_2$Et), 3.35 (*br*. s, 1H, O*H*), 3.90 – 3.92 (m, 4H, O(C*H*$_2$)$_2$O), 4.00 (q, *J* = 7.0 Hz, 2H, C*H*$_2$CH$_3$), 4.22 – 4.29 (m, 1H, C*H*OH), 4.92 (dd, *J* = 1.5, 10.5 Hz, 1H, CH=C*H*$_2$), 5.12 (dd, *J* = 1.5, 17.0 Hz, 1H, CH=C*H*$_2$), 5.70 (ddd, *J* = 5.5, 10.5, 17.0 Hz, 1H, C*H*=CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 42.6, 43.3, 60.5, 64.6, 65.0, 68.5, 108.9, 117.4, 140.3, 169.1; MS (CI) *m/z* 231 $[M+H]^+$, 248 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{11}H_{22}NO_5$ $[M+NH_4]^+$: 248.1485, found: 248.1488.

(7-Hydroxy-9-vinyl-1,4,8-trioxaspiro[4,5]dec-7-yl)acetic acid ethyl ester (269)



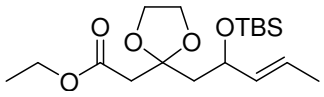
To a solution of freshly distilled EtOAc (0.88 mL, 9.04 mmol) in THF (20 mL) at –78 °C was added LDA (2.0 M in THF/heptane/ethyl benzene, 4.52 mL, 9.04 mmol). After 15 min, [2-(2-hydroxy-but-3-enyl)-[1,3]dioxolan-2-yl]acetic acid ethyl ester (**268**) (520 mg, 2.26 mmol) in THF (2 mL) was added dropwise and the reaction mixture was allowed to warm slowly to 0 °C. After 4 h the reaction was quenched by addition of H_2O (2 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with H_2O (20 mL), then brine (20 mL) and dried (Na_2SO_4). Concentration *in vacuo* was followed by flash column chromatography (EtOAc : hexanes, 1 : 9) to afford hemi-ketal **269** (178 mg, 29%) as a spectroscopically indistinguishable mixture of diastereoisomers: R_f 0.45 (Et_2O : CH_2Cl_2 : hexanes, 1 : 1 : 1); IR (film) ν_{max} 3476, 2980, 2891, 1734, 1210, 1065 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *major diastereoisomer (see Appendix 2a):* δ 1.17 (t, *J* = 7.0 Hz, 3H, C*H*$_3$CH$_2$), 1.45 (*app.* t, *J* = 13.0, Hz, 1H, C*H*$_2$C(H)R), 1.64 – 1.69 (m, 1H, C*H*$_2$C(H)R), 1.84 (AB q, *J* = 13.5 Hz, 1H, C*H*$_2$C(OH)R), 1.99 (AB q, *J* = 13.5 Hz, 1H, C*H*$_2$C(OH)R), 2.51 – 2.69 (m, 2H, C*H*$_2$CO$_2$Et), 3.85 – 3.92 (m, 4H, O(C*H*$_2$)$_2$O), 4.06 (q, *J* = 7.0 Hz, 2H, C*H*$_2$CH$_3$), 4.37 – 4.46 (m, 1H, C*H*OR), 5.00 (dd, *J* = 1.5, 10.5 Hz, 1H, CH=C*H*$_2$), 5.15 (dd, *J* = 1.5, 16.0 Hz, 1H, CH=C*H*$_2$), 5.74 (ddd, *J* = 6.5, 10.5, 16.0 Hz, 1H, C*H*=CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) *both diastereoisomers:* δ 14.1, 38.8, 39.7, 41.9, 45.8, 60.5, 64.0, 64.9, 68.6, 96.1, 105.0, 106.8, 115.1, 135.1, 137.6, 168.8, 170.2; MS (CI) *m/z* 273 $[M+H]^+$, 290 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{13}H_{24}NO_6$ $[M+NH_4]^+$: 290.1604, found: 290.1606.

[2-(2-Hydroxy-pent-3-enyl)-[1,3]dioxolan-2-yl] acetic acid ethyl ester (274)



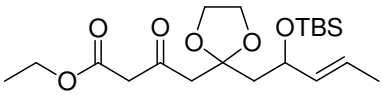
To a solution of [2-(2-oxo-ethyl)-[1,3]dioxolan-2-yl]acetic acid ethyl ester (**91**) (2.15 g, 10.6 mmol) in THF (100 mL) at –78 °C, was added 1-propenylmagnesium bromide (29.8 mL, 0.5 M in THF, 14.9 mmol) dropwise. After 4h at this temperature, the resultant yellow reaction mixture was quenched by the addition of sat. aq. NH_4Cl (2 mL) and H_2O (10 mL). The aqueous layer was extracted with EtOAc (3 × 50 mL), the combined organic extracts washed with brine (3 × 50 mL) and dried (Na_2SO_4). Concentration *in vacuo* was followed by flash column chromatography (EtOAc : hexanes, 1 : 9) to afford alcohol **274** (1.97 g, 76%) as a colourless oil: R_f 0.35 (EtOAc : hexanes, 2 : 3); IR (film) ν_{max} 3518, 1734, 1371, 1033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, *J* = 1.5, 7.0 Hz, 3H, CH_2CH_3), 1.70 (dd, *J* = 1.5, 7.0 Hz, 3H, $CH{=}CHCH_3$), 2.00 – 2.15 (m, 2H, CH_2CHOH), 2.75 (d, *J* = 7.5 Hz, 2H, CH_2CO_2Et), 4.06 – 4.09 (m, 4H, $O(CH_2)_2O$), 4.17 (dq, *J* = 1.5, 7.0 Hz, 2H, CH_2CH_3), 5.41 – 5.58 (m, 2H, $CH{=}CHCH_3$ and $CHOH$), 5.73 (dqd, *J* = 1.0, 6.5, 13.0 Hz, 1H, $CH{=}CHCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 17.7, 42.8, 60.7, 63.9, 64.8, 65.0, 68.7, 109.3, 126.2, 132.7, 169.2; MS (CI) *m/z* 245 $[M+H]^+$, 262 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{12}H_{24}NO_5$ $[M+NH_4]^+$: 262.1654, found: 262.1660.

{2-[2-(*tert*-Butyldimethylsilanyloxy)pent-3-enyl]
-[1,3]dioxolan-2-yl}acetic acid ethyl ester (273)



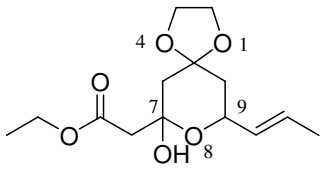
To a solution of [2-(2-hydroxy-pent-3-enyl)-[1,3]dioxolan-2-yl]acetic acid ethyl ester (**274**) (840 mg, 3.44 mmol) in DMF (20 mL) at 0 °C were added imidazole (937 mg, 13.8 mmol) and DMAP (84 mg, 0.69 mmol), followed after 5 min by TBSCl (1.56 g, 10.3 mmol). The resultant suspension was allowed to warm to 23 °C and maintained at that temperature for a further 18 h. After this time, the reaction mixture was diluted with H_2O (50 mL), extracted with EtOAc (3 × 20 mL) and the combined organic extracts dried (Na_2SO_4). Concentration *in vacuo* was followed by flash column chromatography (EtOAc : hexanes, 3 : 97) to afford silyl ether **273** (1.18 g, 96%) as a colourless oil: R_f 0.95 (EtOAc : hexanes, 2 : 3); IR (film) ν_{max} 2957, 1738, 1472, 1252, 1084, 1039, 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (dd, *J* = 4.0, 15.0 Hz, 6H, Si(CH_3)$_2$), 0.88 (s, 9H, C(CH_3)$_3$), 1.27 (t, *J* = 7.0 Hz, 3H, CH_3CH_2), 1.67 (dd, *J* = 4.0, 5.5 Hz, 3H, CH_3C=CH), 1.90 (ddd, *J* = 5.5, 14.5, 26.0 Hz, 1H, CH_2CHOH), 2.17 (ddd, *J* = 7.0, 10.5, 14.5 Hz, 1H, CH_2CHOH), 2.79 (dd, *J* = 4.5, 10.5 Hz, 2H, CH_2CO_2Et), 3.90 – 4.03 (m, 5H, O(CH_2)$_2$O and CHOH), 4.15 (q, *J* = 7.0 Hz, 2H, CH_3CH_2), 5.36 – 5.60 (m, 2H, CH=CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ –4.7, –3.9, 14.2, 18.1, 25.9 (3C) 43.1, 45.2, 60.3, 64.7 (2C), 70.5, 108.2, 122.8, 125.0, 135.2, 169.6; MS (CI) *m/z* 359 $[M+H]^+$, 376 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{18}H_{35}SiO_5$ $[M+H]^+$: 359.2267, found: 359.2264; Anal. calculated for $C_{18}H_{34}SiO_5$: C, 60.30; H, 9.56; found: C, 60.40; H, 9.48%.

4-{2-[2-(*tert*-Butyldimethylsilanyloxy)pent-3-enyl]
-[1,3]dioxolan-2-yl}-3-oxobutyric acid ethyl ester (272)



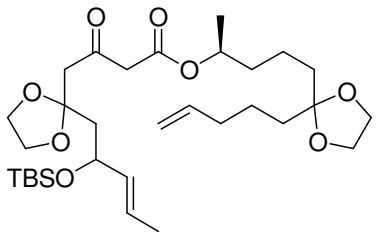
To a solution of *N,N*-di*iso*propylamine (2.37 mL, 16.8 mmol) in THF (20 mL) at –78 °C was added *n*-BuLi (2.5 M in hexanes, 6.70 mL, 16.8 mmol) and the resultant solution warmed to 0 °C for 20 min, then recooled to –78 °C for the addition of EtOAc (1.64 mL, 16.8 mmol). After 30 min {2-[2-(*tert*-butyldimethylsilanyloxy)pent-3-enyl]-[1,3]dioxolan-2-yl}acetic acid ethyl ester (**273**) (1.00 g, 2.79 mmol) was added and the reaction allowed to warm to 23 °C slowly over 4 h. The reaction mixture was quenched with pH 7.0 buffer (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with sat. aq. NH_4Cl (5 mL) and dried (Na_2SO_4). Concentration *in vacuo* was followed by flash column chromatography (EtOAc : hexanes, 3 : 97) to afford β-keto ester **272** (860 mg, 77%) as a pale yellow oil: R_f 0.45 (EtOAc : hexanes, 1 : 4); IR (film) ν_{max} 2957, 1736, 1252, 1033, 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 6H, $Si(CH_3)_2$), 0.89 (s, 9H, $C(CH_3)_3$), 1.29 (dt, *J* = 3.0, 7.0 Hz, 3H, CH_3CH_2), 1.66 – 1.69 (m, 3H, CH_3C=CH), 1.81 (ddd, *J* = 5.0, 14.5, 28.0 Hz, 1H, CH_2CHOH), 2.00 (ddd, *J* = 7.0, 10.0, 14.5 Hz, 1H, CH_2CHOH), 2.63 (AB q, *J* = 15.5 Hz, 1H, CH_2COR), 2.70 (AB q, *J* = 15.5 Hz, 1H, CH_2COR), 3.55 (s, 2H, $CH_2(CO)_2$), 3.90 – 4.00 (m, 4H, $O(CH_2)_2O$), 4.16 – 4.22 (m, 3H, CH_3CH_2 and CHOH), 5.39 – 5.60 (m, 2H, CH=CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ –4.6, –4.0, 14.1, 17.5, 25.9 (3C), 27.3, 44.9, 50.6, 60.4, 61.2, 64.6 (2C), 69.7, 108.6, 125.3, 135.0, 171.9, 200.1; MS (CI) *m/z* 401 $[M+H]^+$, 418 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{20}H_{40}SiNO_6$ $[M+NH_4]^+$: 418.2625, found: 418.2635; Anal. calculated for $C_{20}H_{36}SiO_6$: C, 59.97; H, 9.06; found: C, 59.90; H, 8.97%.

(7-Hydroxy-9-propenyl-1,4,8-trioxa-spiro [4.5]dec-7-yl)acetic acid ethyl ester (275)



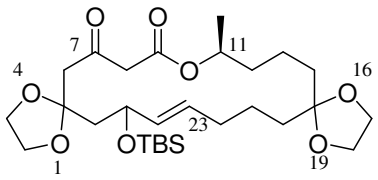
To a solution of 4-{2-[2-(*tert*-butyldimethylsilanyloxy)pent-3-enyl]-[1,3]dioxolan-2-yl}-3-oxobutyric acid ethyl ester (**272**) (66 mg, 0.17 mmol) in THF (1 mL) was added TBAF (1.0 M in THF, 830 μL, 0.83 mmol). After 18 h, the reaction was diluted with brine (10 mL), extracted with CH_2Cl_2 (3 × 6 mL). and the combined organic extracts dried (Na_2SO_4). Concentration *in vacuo* was followed by flash column chromatography to afford hemi-ketal **275** (37 mg, 79%) as an inseparable 2 : 3 mixture of two diastereoisomers: R_f 0.40 (EtOAc : hexanes, 2 : 3); IR (film) ν_{max} 3419, 2962, 1486, 1382, 1151 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *see Appendix 2b*; ^{13}C NMR (100 MHz, $CDCl_3$) *both diastereoisomers:* δ 13.5, 14.1, 17.8, 20.8, 21.1, 22.7, 28.8, 31.6, 40.0, 40.1, 41.9, 53.6, 60.4, 60.7, 64.0, 64.3, 65.0, 68.8, 96.1, 96.2, 106.9, 107.0, 127.7, 129.9, 130.6, 170.4, 170.5; MS (CI) *m/z* 287 $[M+H]^+$, 304 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{14}H_{26}NO_6$ $[M+NH_4]^+$: 304.1760, found: 304.1765.

4-{2-[2-(*tert*-Butyldimethylsilanyloxy)pent-3-enyl]-[1,3]dioxolan-2-yl}-3-oxobutyric acid 1-methyl-4-(2-pent-4-enyl-[1,3]dioxolan-2-yl)butyl ester (277)



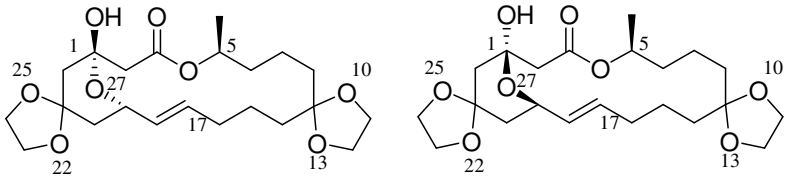
To a solution of (*S*)-5-(2-pent-4-enyl-[1,3]dioxolan-2-yl)pentan-2-ol (**93**) (381 mg, 1.67 mmol) and 4-{2-[2-(*tert*-butyldimethylsilanyloxy)pent-3-enyl]-[1,3]dioxolan-2-yl}-3-oxobutyric acid ethyl ester (**272**) (223 mg, 0.56 mmol) in PhMe (20 mL) was added Zn dust (8 mg, 0.12 mmol) and the resulting suspension heated to 110 °C under a distillation condenser for 72 h. After this time the reaction was cooled, filtered, concentrated *in vacuo* and purified by flash column chromatography (EtOAc : hexanes, 1 : 9) to afford ester **277** (272 mg, 84%) as a ^{1}H NMR spectroscopically indistinguishable mixture of diastereoisomers: R_f 0.70 (EtOAc : hexanes, 1 : 4); IR (film) ν_{max} 1735, 1641, 1251, 1032 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *both diastereoisomers (see Appendix 2c):* δ 0.04 (s, 6H, Si(C*H*$_3$)$_2$), 0.87 (s, 9H, C(C*H*$_3$)$_3$), 1.22 (d, *J* = 6.0 Hz, 3H, C*H*$_3$CH), 1.27 (d, *J* = 7.0 Hz, 3H, C*H*$_3$CH=CH), 2.94 – 2.98 (m, 16H, C*H*$_2$), 3.50 (s, 2H, C(O)C*H*$_2$COR), 3.92 (s, 4H, O(C*H*$_2$)$_2$O), 4.16 (dd, *J* = 7.0, 14.0 Hz, 4H, O(C*H*$_2$)$_2$O), 4.25 – 4.29 (m, 1H, C*H*OTBS), 4.92 – 5.06 (m, 3H, C*H*$_2$=CHR and CH$_3$C*H*), 5.48 – 5.57 (m, 2H, CH$_2$=C*H*R and CH=C*H*CH$_3$), 5.78 (dd, *J* = 7.5, 17.0 Hz, 1H, C*H*=CHMe); ^{13}C NMR (100 MHz, $CDCl_3$) *both diastereoisomers:* δ –4.7, –4.6, –4.2, –4.0, 13.2, 14.2, 17.5, 18.1, 19.6, 19.8, 20.0, 23.1, 25.9, 27.3, 33.9, 35.9, 36.1, 36.9, 44.9, 50.3, 50.5, 50.8, 60.6, 64.5, 64.6, 64.9, 69.7, 70.4, 70.6, 71.9, 108.6, 109.0, 111.4, 114.6, 135.0, 138.6, 167.0, 171.9, 200.1; MS (CI) *m/z* 600 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{31}H_{58}SiNO_8$ $[M+NH_4]^+$: 600.3932, found: 600.3935; Anal. calculated for $C_{31}H_{54}SiO_8$: C, 63.88; H, 9.34; found: C, 63.96; H, 9.26%.

25-(*tert*-Butyldimethylsilanyloxy)-11-methyl-1,4,10,16,19-pentaoxa-dispiro[4.9.4.7]hexacos-23-ene-7,9-dione (278)



To PhMe (150 mL) at 80 °C with a slow stream of argon bubbled through, were added both (*S*)-4-{2-[2-(*tert*-butyldimethylsilanyloxy)pent-3-enyl]-[1,3]dioxolan-2-yl}-3-oxobutyric acid 1-methyl-4-(2-pent-4-enyl-[1,3]dioxolan-2-yl)butyl ester (**277**) (128 mg, 0.22 mmol) in PhMe (15 mL) and Grubbs' second generation catalyst (19 mg, 10 mol %) in PhMe (15 mL), *via* two separate syringe pumps over 10 h. After a further 48 h at this temperature, the reaction mixture was concentrated *in vacuo* and purified by flash column chromatography (EtOAc : hexanes, 1 : 9) to afford macrocyclic diketone **278** (104 mg, 88%) as ^{1}H NMR spectroscopically indistinguishable mixture of diastereoisomers: R_f 0.65 (EtOAc : hexanes, 1 : 4); IR (film) ν_{max} 1736, 1462, 1252, 1121, 1032 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *both diastereoisomers (see Appendix 2d):* δ 0.03 (dd, *J* = 2.0, 11.0 Hz, 6H, Si(C*H*$_3$)$_2$), 0.86 (s, 9H, C(C*H*$_3$)$_3$), 1.22 (d, *J* = 6.2 Hz, 3H, C*H*$_3$CH), 1.16 – 1.60 (m, 10H, C*H*$_2$), 1.98 – 2.03 (m, 4H, C*H*$_2$), 2.71 (AB q, *J* = 13.5 Hz, 1H, C(O)C*H*$_2$CO(C*H*$_2$)$_2$O), 3.11 (AB q, *J* = 13.5 Hz, 1H, C(O)C*H*$_2$CO(C*H*$_2$)$_2$O), 3.38 (AB q, *J* = 16.0 Hz, 1H, C(O)C*H*$_2$CO$_2$R), 3.61 (AB q, *J* = 16.0 Hz, 1H, C(O)C*H*$_2$CO$_2$R), 3.91 (s, 4H, O(C*H*$_2$)$_2$O), 3.95 (s, 4H, O(C*H*$_2$)$_2$O), 4.23 – 4.28 (m, 1H, C*H*OTBS), 4.92 – 5.00 (m, 1H, CH$_3$C*H*), 5.44 – 5.54 (m, 2H, C*H*=C*H*R); ^{13}C NMR (100 MHz, $CDCl_3$) *both diastereoisomers:* δ –4.7, –4.2, 14.2, 18.2, 20.0, 20.5, 20.6, 22.3, 22.4, 25.9 (3C), 27.3, 31.8, 31.9, 35.0, 35.8, 35.9, 36.1, 36.8, 37.0, 44.9, 45.3, 45.5, 49.9, 50.9, 50.6, 51.2, 60.6, 64.4, 64.5, 64.6, 64.8, 69.7, 70.3, 71.9, 108.1, 108.4, 111.6, 130.5, 130.6, 134.4, 134.6, 166.7, 167.3, 171.9, 199.9, 200.3; MS (CI) *m/z* 541 $[M+H]^+$, 558 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{28}H_{49}SiO_8$ $[M+H]^+$: 541.3197, found: 541.3201; Anal. calculated for $C_{28}H_{48}SiO_8$: C, 62.19; H, 8.95; found: C, 62.15; H, 9.03%.

1-Hydroxy-5-methyl-4,10,13,22,25,27-hexaoxa-bicyclo-dispiro[7.4.5.1.4.1.1]heptacos-17-en-3-one (280)



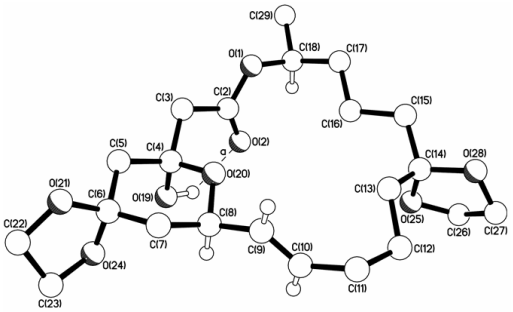
To a solution of 25-(*tert*-butyldimethylsilanyloxy)-11-methyl-1,4,10,16,19-pentaoxa-dispiro[4.9.4.7]hexacos-23-ene-7,9-dione (**278**) (234 mg, 0.43 mmol) in THF (2 mL) was added TBAF (1.0 M in THF, 4.30 mL, 4.30 mmol). After 5 d, the resulting red reaction mixture was quenched by addition of brine (10 mL), extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts dried (Na_2SO_4). Concentration *in vacuo* was followed by flash column chromatography (EtOAc : hexanes, 1 : 2) to afford hemi-ketal **280a** (78 mg, 42%) as a colourless oil and hemi-ketal **280b** (77 mg, 42%) as colourless needles:

Diastereoisomer **280a**:

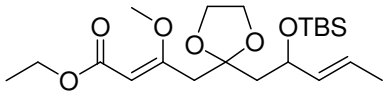
R_f 0.30 (EtOAc : hexanes, 2 : 3); $[\alpha]_D$ +26.5 (*c* = 1.00, CH_2Cl_2); IR (film) ν_{max} 3474, 1725, 1422, 1330, 1065 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.23 (d, *J* = 6.5 Hz, 3H, C*H*$_3$CH), 1.28 – 1.74 (m, 12H, C*H*$_2$), 1.86 (AB q, *J* = 13.5 Hz, 1H, C*H*$_2$C(OH)), 2.00 – 2.13 (m, 2H, C*H*$_2$CO(C*H*$_2$)$_2$O), 2.44 (AB q, *J* = 13.5 Hz, 1H, C*H*$_2$C(OH)), 2.56 (AB q, *J* = 14.0 Hz, 1H, C*H*$_2$CO$_2$R), 2.84 (AB q, *J* = 14.0 Hz, 1H, C*H*$_2$CO$_2$R), 3.93 (s, 4H, O(C*H*$_2$)$_2$O), 3.97 – 4.08 (m, 4H, O(C*H*$_2$)$_2$O), 4.43 – 4.48 (m, 1H, CH$_3$C*H*), 5.00 (*app.* dq, *J* = 4.5, 9.0 Hz, 1H, C*H*OR), 5.42 – 5.49 (m, 1H, CH=C*H*COR), 5.65 – 5.72 (m, 1H, C*H*=CHCOR); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6, 21.1, 21.7, 30.3, 32.4, 36.5, 36.6, 39.5, 40.8, 46.9, 64.1, 64.3, 64.5, 64.8, 68.8, 71.7, 96.3, 107.5, 111.9, 131.0, 131.8, 169.3; MS (CI) *m/z* 427 $[M+H]^+$, 444 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{22}H_{38}NO_8$ $[M+NH_4]^+$: 444.2584, found: 444.2588; Anal. calculated for $C_{22}H_{34}O_8$: C, 61.95; H, 8.04; found: C, 62.01; H, 8.02%.

Diastereoisomer **280b**:

R_f 0.25 (EtOAc : hexanes, 2 : 3); m.p. 137–138 °C (*t*BuOMe); $[\alpha]_D$ –14.7 (*c* = 1.14, CH_2Cl_2); IR (film) ν_{max} 3442, 1705, 1435, 1209, 1065 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (d, *J* = 7.0 Hz, 3H, C*H*$_3$CH), 1.37 – 1.56 (m, 12H, C*H*$_2$), 1.59 – 2.03 (m, 4H, C*H*$_2$C(OH) + C*H*$_2$CO$_2$R), 2.08 – 2.16 (m, 2H, C*H*$_2$CO(C*H*$_2$)$_2$O), 3.88 – 4.05 (m, 8H, O(C*H*$_2$)$_2$O × 2), 4.13 (td, *J* = 6.0, 7.5 Hz, 1H, C*H*CH=CH), 4.50 – 4.55 (m, 1H, CH$_3$C*H*), 5.15 – 5.22 (m, 1H, O*H*), 5.43 (dd, *J* = 6.0, 7.5 Hz, 1H, CH=C*H*COR), 5.63 – 5.70 (m, 1H, C*H*=CHCOR); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 21.7 (2C), 30.8, 33.4, 37.0, 37.3, 40.3, 43.1, 45.2, 63.8, 64.6, 64.7, 65.2, 68.8, 71.7, 96.0, 106.6, 111.7, 131.7, 132.9, 171.9; MS (CI) *m/z* 427 $[M+H]^+$, 444 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{22}H_{38}NO_8$ $[M+NH_4]^+$: 444.2597, found: 444.2597; Anal. calculated for $C_{22}H_{34}O_8$: C, 61.95; H, 8.04; found: C, 61.88; H, 7.97%; X-ray crystal structure data: $C_{22}H_{34}O_8$, M = 294.38, monoclinic, $P2_1$, *a* = 8.4675(5) Å, *b* = 0.1087(13) Å, *c* = 9.7796(8) Å, V = 1665.0(2) $Å^3$, Z = 4, D_c = 1.174 gcm^{-3}, μ(Cu-Kα) = 0.663 mm^{-1}, T = 173(2) K, colourless blocky needles, reflections collected / unique: 16705 / 6009 [R(int) = 0.0840], reflections observed [F>4σ(F)]: 5315, full-matrix least-squares on F^2, data / restraints / parameters: 6009 / 3 / 392, final R indices [F>4σ(F)]: R_1 = 0.0936, *w*R^2 = 0.2312, R_1^+ = 0.0936, *w*R_2^+ = 0.2312, R_1^- = 0.0936, *w*R_2^- = 0.2313, R indices (all data): R_1 = 0.0977, *w*R_2 = 0.2342.

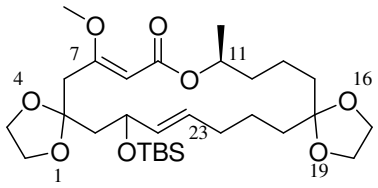


4-{2-[2-(*tert*-Butyldimethylsilanyloxy)pent-3-enyl]
-[1,3]dioxolan-2-yl}-3-methoxybut-2-enoic acid ethyl ester (289)



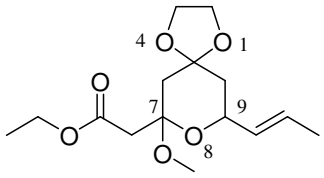
To a solution of 4-{2-[2-(*tert*-butyldimethylsilanyloxy)pent-3-enyl]-[1,3]dioxolan-2-yl}-3-oxobutyric acid ethyl ester (**272**) (160 mg, 0.40 mmol) in MeCN (2.7 mL) and MeOH (0.3 mL) was added *N,N*-di*iso*propylethylamine (77 μL, 0.44 mmol), followed by trimethylsilyldiazomethane (2.0 M in Et_2O, 220 μL, 0.44 mmol). After 18 h, the yellow reaction mixture was quenched by addition of brine (10 mL), extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts dried (Na_2SO_4). Concentration *in vacuo* was followed by flash column chromatography (EtOAc : hexanes, 1 : 9) to afford enol ether **289** (16 mg, 10 %) as a colourless oil: R_f 0.70 (EtOAc : hexanes, 1 : 3); IR (film) ν_{max} 1711, 1626, 1378, 1254, 1148, 1057 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.06 (d, *J* = 3.0 Hz, 6H, $(CH_3)_2$), 0.89 (d, *J* = 3.0, 9H, $C(CH_3)_3$), 1.29 (t, *J* = 7.0 Hz, 3H, CH_3CH_2), 1.62 – 1.69 (m, 3H, CH_3C=CH), 1.95 – 2.20 (m, 2H, CH_2CHOTBS), 3.20 (AB q, *J* = 13.0 Hz, 1H, CH_2C(OMe)=CH), 3.27 (AB q, *J* = 13.0 Hz, 1H, CH_2C(OMe)=CH), 3.66 (s, 3H, OCH_3), 3.83 – 4.05 (m, 4H, $O(CH_2)_2O$), 4.15 (q, 2H, *J* = 7.0, CH_3CH_2), 4.31 – 4.37 (m, 1H, CHOTBS), 5.12 (s, 1H, CH=COMe), 5.37 – 5.57 (m, 2H, CH=CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ –4.7, –4.1, 13.3, 14.4, 17.6, 25.9, 26.0 (2C), 39.4, 46.3, 55.4, 59.4, 64.7, 64.9, 70.0, 93.4, 109.3, 124.2, 135.5, 167.5, 171.0; MS (CI) *m/z* 415 $[M+H]^+$, 432 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{21}H_{42}SiNO_6$ $[M+NH_4]^+$: 432.2782, found: 432.2782; Anal. calculated for $C_{21}H_{38}SiO_6$: C, 60.83; H, 9.24; found: C, 60.09; H, 9.14%.

7-Methoxy-25-(*tert*-butyldimethylsilanyloxy)-11-methyl-1,4,10,16,19-pentaoxa-dispiro[4.9.4.7]hexacos-7,23-dien-9-one (286)



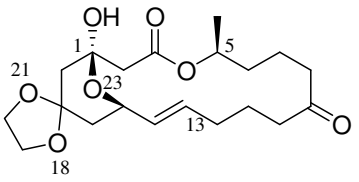
To a solution of 25-(*tert*-butyldimethylsilanyloxy)-11-methyl-1,4,10,16,19-pentaoxa-dispiro[4.9.4.7]hexacos-23-ene-7,9-dione (**278**) (105 mg, 0.19 mmol) in CH_3CN (1.8 mL) and MeOH (0.2 mL) was added *N,N*-di*iso*propylethylamine (37 μL, 0.21 mmol), followed by trimethylsilyldiazomethane (**181**) (2.0 M in Et_2O, 107 μL, 0.21 mmol). After 18 h, the yellow reaction mixture was quenched by addition of brine (5 mL), extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts dried (Na_2SO_4). Concentration *in vacuo* was followed by flash column chromatography (EtOAc : hexanes, 3 : 7) to afford enol ether **286** (7 mg, 5 %) as an inseparable mixture of diastereoisomers: *Rf* 0.75 (EtOAc: hexanes 1:2); IR (film) ν_{max} 2955, 1710, 1623, 1593, 1119, 1036 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *both diastereoisomers (see Appendix 2e):* δ 0.07 (d, *J* = 10.0 Hz, 6H, $(CH_3)_2$), 0.90 (s, 9H, $C(CH_3)_3$), 1.21 (d, *J* = 6.5 Hz, 3H, CH_3CH), 1.29 – 1.58 (m, 10H, CH_2), 1.77 – 2.22 (m, 4H, $CH_2CHOTBS + CH_2CH=CH$), 2.64 (AB q, *J* = 15.5 Hz, 1H, $CH_2C(OMe)=CH$), 2.71 (AB q, *J* = 15.5 Hz, 1H, $CH_2C(OMe)=CH$), 3.65 (s, 3H, OCH_3), 3.90 – 3.95 (m, 8H, $O(CH_2)_2O$ × 2), 4.24 – 4.30 (m, 1H, CHOTBS), 4.03 – 4.06 (m, 1H, CH_3CH), 5.06 (s, 1H, CH=COMe), 5.27 – 5.45 (m, 2H, CH=CHR); ^{13}C NMR (100 MHz, $CDCl_3$) *both diastereoisomers:* δ –4.6, –4.2, 14.2, 21.1, 21.5, 26.0 (3C), 27.3, 31.7, 34.8, 37.3, 38.2, 40.1, 44.9, 45.2, 55.3, 60.7, 64.8, 65.0, 65.2, 68.2, 70.0, 93.6, 109.5, 111.9, 129.6, 135.5, 167.2, 170.0, 171.9; MS (CI) *m/z* 555 $[M+H]^+$, 572 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{29}H_{51}SiO_8$ $[M+H]^+$: 555.3375, found: 555.3372.

7-Methoxy-9-propenyl-1,4,8-trioxa-spiro[4.5]dec-7-yl)acetic acid methyl ester (290)



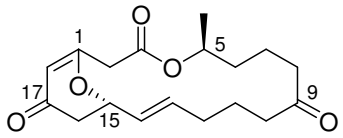
To a solution of 4-{2-[2-(*tert*-butyldimethylsilanyloxy)pent-3-enyl]-[1,3]dioxolan-2-yl}-3-methoxybut-2-enoic acid ethyl ester (**289**) (12 mg, 0.03 mmol) in THF (0.5 mL) was added TBAF (1.0 M in THF, 145 μL, 0.14 mmol). After 18 h, the orange reaction mixture was quenched by addition of brine (5 mL), extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts dried (Na_2SO_4). Concentration *in vacuo* was followed by flash column chromatography (EtOAc : hexanes, 1 : 2) to afford ketal **290** (6 mg, 69%) as an inseparable 5 : 3 mixture of two diastereoisomers: R_f 0.15 (EtOAc : hexanes, 1 : 3); IR (film) ν_{max} 1736, 1370, 1225, 1043, 998 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *major diastereoisomer (see Appendix 2f):* δ 1.28 (t, *J* = 7.0 Hz, 3H, CH_3CH_2), 1.55 – 1.62 (m, 3H, CH_3C=CH), 1.70 – 1.80 (m, 2H, CH_2CHC=C), 2.05 (AB q, *J* = 14.5 Hz, 1H, CH_2C(OMe)OR), 2.22 (AB q, *J* = 14.5 Hz, 1H, CH_2C(OMe)OR), 2.59 (AB q, *J* = 13.5 Hz, 1H, CH_2CO_2Et), 2.87 (AB q, *J* = 13.5 Hz, 1H, CH_2CO_2Et), 3.64 (s, 3H, OCH_3), 3.90 – 3.96 (m, 4H, $O(CH_2)_2O$), 4.17 (q, 2H, *J* = 7.0, CH_3CH_2), 4.22 – 4.28 (m, 1H, CHOR), 5.51 (ddd, *J* = 15.5, 7.0, 1.5 Hz, 1H, CH=CHMe), 5.74 – 5.83 (m, 1H, CH=CHMe); ^{13}C NMR (100 MHz, $CDCl_3$) *both diastereoisomers:* δ 13.5, 14.2, 17.9, 39.7, 39.8, 42.1, 42.2, 42.6, 48.4, 60.6, 63.7, 64.4, 65.2, 69.3, 99.0, 99.1, 106.2, 106.3, 127.6, 128.4, 129.8, 130.4, 169.0; MS (CI) *m/z* 300 $[M+H]^+$, 318 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{15}H_{28}NO_6$ $[M+NH_4]^+$: 318.1917, found: 318.1921.

(1*R*,5*S*,15*R*)-1-Hydroxy-5-methyl-4,18,21,23-tetraoxa-bicyclo-spiro[13.1.4.1.1]tricos-13-en-3,9-dione (293)



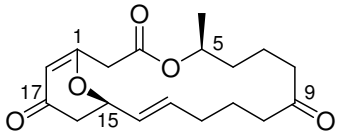
To a solution of (1*R*,5*S*,19*R*)-1-hydroxy-5-methyl-4,10,13,22,25,27-hexaoxa-bicyclo-dispiro[7.4.5.1.4.1.1]heptacos-17-en-3-one (**280b**) (85 mg, 0.20 mmol) in acetone : H_2O, 5 : 1 (1 mL) was added PPTS (125 mg, 0.50 mmol). After 18 h, the reaction mixture was quenched by addition of brine (8 mL), extracted with CH_2Cl_2 (3 × 8 mL) and the combined organic extracts dried (Na_2SO_4). Concentration *in vacuo* was followed by flash column chromatography (EtOAc : hexanes, 1 : 2) to afford hemi-ketal **293** (72 mg, 94 %) as colourless needles: R_f 0.25 (EtOAc : hexanes, 2 : 3); m.p. 85–86 °C (*t*BuOMe); $[\alpha]_D$ –6.7 (*c* = 0.87, CH_2Cl_2); IR (film) ν_{max} 3454, 1709, 1212, 1066, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.21 (d, *J* = 6.0 Hz, 3H, C*H*$_3$CH), 1.48 – 1.82 (m, 8H, C*H*$_2$), 1.90 – 2.82 (m, 10H, C*H*$_2$), 3.88 – 4.13 (m, 4H, O(C*H*$_2$)$_2$O), 4.44 – 4.57 (m, 1H, CH$_3$C*H*), 5.07 – 5.13 (m, 1H, C*H*(OR)CH=CH), 5.27 – 5.36 (m, 1H, CH(OR)C*H*=CH), 5.45 (ddd, *J* = 5.5, 10.0, 13.0 Hz, 1H, CH(OR)CH=C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7 (2C), 21.5, 30.1, 36.0, 38.4, 39.6, 42.9, 43.4, 45.8, 63.8, 65.1, 69.1, 70.5, 96.0, 106.6, 131.5, 131.9, 171.5, 211.0; MS (CI) *m/z* 383 $[M+H]^+$, 400 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{20}H_{34}NO_7$ $[M+NH_4]^+$: 400.2335, found: 400.2342; Anal. calculated for $C_{20}H_{30}O_7$: C, 62.81; H, 7.91; found: C, 62.91; H, 7.81%.

(5*S*,15*S*)-5-Methyl-4,19-dioxa-bicyclo[13.3.1]nonadeca -1(18),13-diene-3,9,17-trione (294a)



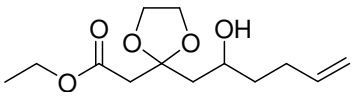
To a solution of (1*S*,5*S*,19*S*)-1-hydroxy-5-methyl-4,10,13,22,25,27-hexaoxa-bicyclo-dispiro[7.4.5.1.4.1.1]heptacos-17-en-3-one (**280a**) (58 mg, 0.14 mmol) in glacial acetic acid (1.5 mL) was added $NaClO_4$ (56 mg, 0.46 mmol). After 18 h, the reaction mixture was quenched by addition of pH 7.2 buffer (10 mL), extracted with CH_2Cl_2 (3 × 8 mL) and the combined organic extracts dried (Na_2SO_4). Concentration *in vacuo* was followed by flash column chromatography (EtOAc : hexanes, 1 : 2) to afford hemi-ketal **294a** (43 mg, 97 %) as a colourless needles: *Rf* 0.35 (EtOAc : hexanes, 1 : 1); $[\alpha]_D$ +52.4 (*c* = 1.03, CH_2Cl_2); IR (film) ν_{max} 1732, 1710, 1669, 1612, 1392, 1230, 978 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (d, *J* = 6.0 Hz, 3H, C*H*$_3$CH), 1.48 – 1.94 (m, 6H, C*H*$_2$), 2.20 – 2.29 (m, 2H, C*H*$_2$CH=CH), 2.43 – 2.51 (m, 4H, C*H*$_2$COC*H*$_2$), 2.54 (AB q, *J* = 12.0 Hz, 1H, C*H*$_2$CO$_2$R), 2.58 (AB q, *J* = 12.0 Hz, 1H, C*H*$_2$CO$_2$R), 3.26 (AB q, *J* = 15.0 Hz, 1H, C*H*$_2$COCH=CH), 3.35 (AB q, *J* = 15.0 Hz, 1H, C*H*$_2$C(O)CH=C), 4.85 (dt, *J* = 12.5, 5.0 Hz, 1H, C*H*(OR)CH=CH), 4.97 – 5.07 (m, 1H, CH$_3$C*H*), 5.43 (s, 1H, C(O)C*H*=COR), 5.54 – 5.67 (m, 2H, C*H*=C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7 (2C), 21.0, 31.3, 35.5, 39.8, 40.9, 41.7, 43.0, 71.8, 80.2, 106.6, 128.0, 135.5, 167.6, 168.9, 192.2, 211.1; MS (CI) *m/z* 321 $[M+H]^+$, 338 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{18}H_{25}O_5$ $[M+H]^+$: 321.1702, found: 321.1706; Anal. calculated for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55; found: C, 67.58; H, 7.50%.

(5*S*,15*R*)-5-Methyl-4,19-dioxa-bicyclo[13.3.1]nonadeca -1(18),13-diene-3,9,17-trione (294b)



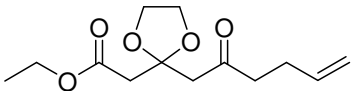
To a solution of (1*R*,5*S*,19*R*-1-hydroxy-5-methyl-4,10,13,22,25,27-hexaoxa-bicyclo-dispiro[7.4.5.1.4.1.1]heptacos-17-en-3-one (**280b**) (20 mg, 0.05 mmol) in glacial acetic acid (0.5 mL) was added $NaClO_4$ (19 mg, 0.15 mmol). After 18 h, the reaction mixture was quenched by addition of pH 7.2 buffer (3 mL), extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts dried (Na_2SO_4). Concentration *in vacuo* was followed by flash column chromatography (EtOAc : hexanes, 1 : 2) to afford hemi-ketal **294b** (15 mg, 99 %) as colourless needles: *Rf* 0.35 (EtOAc: hexanes, 1:1); $[\alpha]_D$ −54.4 (*c* = 1.18, CH_2Cl_2); IR (film) ν_{max} 1730, 1710, 1672, 1611, 1392, 1230, 978 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.24 (d, *J* = 6.0 Hz, 3H, C*H*$_3$CH), 1.48 – 1.94 (m, 6H, C*H*$_2$), 2.23 – 2.31 (m, 2H, C*H*$_2$CH=CH), 2.40 – 2.50 (m, 4H, C*H*$_2$COC*H*$_2$), 2.53 (AB q, *J* = 12.0 Hz, 1H, C*H*$_2$CO$_2$R), 2.58 (AB q, *J* = 12.0 Hz, 1H, C*H*$_2$CO$_2$R), 3.25 (AB q, *J* = 15.0 Hz, 1H, C*H*$_2$C(O)CH=C), 3.33 (AB q, *J* = 15.0 Hz, 1H, C*H*$_2$COCH=CH), 4.85 (dt, *J* = 12.5, 5.0 Hz, 1H, C*H*(OR)CH=CH), 4.97 – 5.05 (m, 1H, CH$_3$C*H*), 5.42 (s, 1H, C*H*=C(O)R), 5.52 – 5.65 (m, 2H, C*H*=C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 20.7, 20.9, 31.4, 35.5, 39.7, 40.3, 41.8, 43.0, 71.4, 79.8, 106.6, 127.8, 135.2, 167.5, 168.9, 192.4, 210.9; MS (CI) *m/z* 321 $[M+H]^+$, 338 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{18}H_{25}O_5$ $[M+H]^+$: 321.1702, found: 321.1705; Anal. calculated for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55; found: C, 67.54; H, 7.55%.

[2-(2-Hydroxy-hex-5-enyl)-[1,3]dioxolan-2-yl]acetic acid ethyl ester (300)



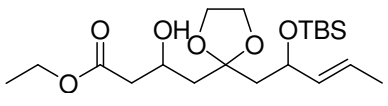
To a solution of [2-(2-oxo-ethyl)-[1,3]dioxolan-2-yl]acetic acid ethyl ester (**91**) (1.59 g, 7.9 mmol) in THF (25 mL) at –78 °C was added a solution of 4-pentenyl magnesium bromide (**96**) [freshly prepared from 5-bromo-1-pentane (878 μL, 8.6 mmol) and Mg (268 mg, 11.0 mmol) in Et_2O (15 mL)] *via* syringe pump over 2.5 h. After a further 30 min at that temperature the reaction mixture was quenched by the addition of sat. aq. NH_4Cl (20 mL) and H_2O (20 mL). The aqueous layer was extracted with Et_2O (3 × 20 mL) and the combined organic extracts washed with H_2O (2 × 20 mL), then dried (Na_2SO_4). Concentration *in vacuo* afforded an inseparable 2 : 1 mixture of starting aldehyde **91** : alcohol **300** (1.60 g, 79% by mass) as a pale yellow oil which was used crude without purification: *Rf* 0.35 (EtOAc : hexanes, 1:2); MS (CI) *m/z* 259 $[M+H]^+$, 276 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{13}H_{23}O_5$ $[M+H]^+$: 259.1545, found: 259.1545.

[2-(2-Oxo-hex-5-enyl)-[1,3]dioxolan-2-yl]acetic acid ethyl ester (299)



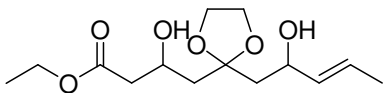
To a solution of crude [2-(2-hydroxy-hex-5-enyl)-[1,3]dioxolan-2-yl]acetic acid ethyl ester (**300**) (<33% purity, 1.35 g, 1.73 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added Dess-Martin periodinane (2.23 g, 5.25 mmol). The solution was stirred at 0 °C for 20 min then allowed to warm to 23 °C for 30 min, before quenching by the addition of a 1 : 1 mixture of sat. aq. $Na_2S_2O_3$ and sat. aq. $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts dried (Na_2SO_4). Concentration *in vacuo* was followed by flash column chromatography (EtOAc : hexanes, 1 : 9) to afford ketone **299** (178 mg, 11 % over 2 steps) as a colourless oil: *Rf* 0.50 (EtOAc : hexanes, 1 : 2); IR (film) ν_{max} 3077, 1733, 1371, 1210, 1099, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.0 Hz, 3H, CH_3CH_2), 2.31 – 2.37 (m, 2H, $CH_2CH{=}CH_2$), 2.61 (t, *J* = 6.5 Hz, 2H, $CH_2CH_2CH_2{=}CH_2$), 2.89 (s, 2H, CH_2CO_2R), 3.07 (s, 2H, CH_2COR), 4.01 – 4.07 (m, 4H, $O(CH_2)_2O$), 4.17 (q, *J* = 7.0 Hz, 2H, CH_3CH_2), 5.00 (dd, *J* = 1.5, 10.0 Hz, 1H, $CH{=}CH_2$, *cis*), 5.05 (dd, *J* = 1.5, 17.0 Hz, 1H, $CH{=}CH_2$, *trans*), 5.83 (tdd, *J* = 6.5, 10.0, 17.0 Hz, 1H, $CH{=}CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 27.4, 42.2, 43.5, 49.2, 60.6, 65.0 (2C), 107.1, 115.2, 137.1, 169.5, 206.6; MS (CI) *m/z* 257 $[M+H]^+$, 274 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{13}H_{21}O_5$ $[M+H]^+$: 257.1389, found: 257.1392; Anal. calculated for $C_{13}H_{20}O_5$: C, 60.92; H, 7.97; found: C, 60.87; H, 7.91%.

4-{2-[2-(*tert*-Butyldimethylsilanyloxy)pent-3-enyl]
-[1,3]dioxolan-2-yl}-3-hydroxy-butyric acid ethyl ester (304)



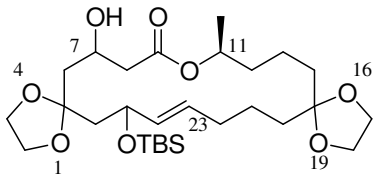
To a solution of 4-{2-[2-(*tert*-butyldimethylsilanyloxy)pent-3-enyl]-[1,3]dioxolan-2-yl}-3-oxobutyric acid ethyl ester (**272**) (38 mg, 0.10 mmol) in EtOH (2 mL) at 0 °C was added $NaBH_4$ (29 mg, 0.76 mmol). After 20 min at that temperature, the reaction mixture was quenched by addition of sat. aq. NH_4Cl (2 mL), extracted with CH_2Cl_2 (3 × 3 mL) and the combined organic extracts dried (Na_2SO_4). Concentration *in vacuo* was followed by flash column chromatography (EtOAc : hexanes, 1 : 3) to afford alcohol **304** (34 mg, 89%) as an inseparable mixture of diastereoisomers: *Rf* 0.80 (EtOAc : hexanes 1 : 2); IR (film) ν_{max} 3498, 2957, 1735, 1253, 1031, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *see Appendix 2g*; ^{13}C NMR (100 MHz, $CDCl_3$) *all diastereoisomers:* δ –4.6, –4.5, –4.2, –3.9, 14.2, 17.5, 26.0 (3C), 27.3, 30.6, 42.2, 42.3, 43.1, 43.2, 45.2, 45.4, 60.5, 60.7, 64.2, 64.3, 65.1, 65.2, 70.5, 70.6, 110.6, 110.7, 125.1, 125.3, 135.0, 171.7, 172.0; MS (CI) *m/z* 403 $[M+H]^+$, 420 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{20}H_{39}SiO_6$ $[M+H]^+$: 403.2529, found: 403.2526.

3-Hydroxy-4-[2-(2-hydroxy-pent-3-enyl)
-[1,3]dioxolan-2-yl]butyric acid ethyl ester (305)



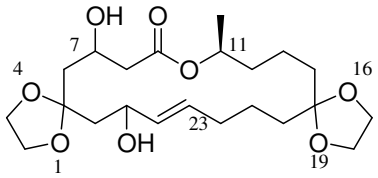
To a solution of 4-{2-[2-(*tert*-butyldimethylsilanyloxy)pent-3-enyl]-[1,3]dioxolan-2-yl}-3-hydroxy-butyric acid ethyl ester (**304**) (30 mg, 0.07 mmol) in THF (0.5 mL) was added TBAF (1.0 M in THF, 0.75 mL, 0.75 mmol). After 18 h, the orange reaction mixture was quenched by addition of brine (2 mL), extracted with CH_2Cl_2 (3 × 2 mL) and the combined organic extracts dried (Na_2SO_4). Concentration *in vacuo* was followed by flash column chromatography (EtOAc) to afford diol **305** (10 mg, 47%) as ^{1}H NMR spectroscopically indistinguishable mixture of diastereoisomers: *Rf* 0.15 (EtOAc : hexanes, 1 : 1); IR (film) ν_{max} 3454, 2922, 1728, 1283, 1028, 820 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *both diastereoisomers (see Appendix 2h):* δ 1.30 (t, *J* = 7.0 Hz, 3H, C*H*$_3$CH$_2$), 1.71 (d, *J* = 7.0 Hz, 3H, C*H*$_3$CH=C), 1.88 – 2.03 (m, 4H, C*H*$_2$), 2.44 – 2.62 (m, 2H, C*H*$_2$CO$_2$Et), 3.29 (*br.* s, 1H, O*H*), 3.54 *(br.* s, 1H, O*H*), 4.06 – 4.10 (m, 4H, O(C*H*$_2$)$_2$O), 4.19 (q, *J* = 7.0 Hz, 2H, CH$_3$C*H*$_2$), 4.29 – 4.38 (m, 2H, C*H*OH), 5.41 – 5.59 (m, 1H, CH=C*H*Me), 5.69 – 5.77 (m, 1H, C*H*=CHMe); ^{13}C NMR (100 MHz, $CDCl_3$) *both diastereoisomers:* δ 14.2, 17.7, 41.9, 42.0, 42.6, 42.8, 43.3, 43.5, 60.7, 63.9, 64.5, 64.8, 64.9, 68.8, 111.3, 111.4, 125.7, 126.4, 133.1, 171.9; MS (CI) *m/z* 289 $[M+H]^+$, 306 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{14}H_{28}NO_6$ $[M+NH_4]^+$: 306.1930, found: 306.1926.

7-Hydroxy-25-(*tert*-butyldimethylsilanyloxy)-11-methyl-1,4,10,16,19-pentaoxa-dispiro[4.9.4.7]hexacos-23-ene-9-one (302)



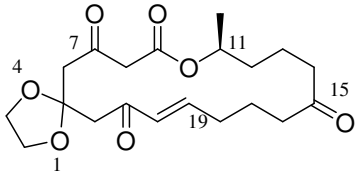
To a solution of 25-(*tert*-butyldimethylsilanyloxy)-11-methyl-1,4,10,16,19-pentaoxa-dispiro[4.9.4.7]hexacos-23-ene-7,9-dione (**278**) (40 mg, 0.07 mmol) in EtOH (1 mL) at 0 °C was added $NaBH_4$ (14 mg, 0.37 mmol). After 20 min at that temperature, the reaction mixture was quenched by addition of sat. aq. NH_4Cl (2 mL), extracted with CH_2Cl_2 (3 × 3 mL) and the combined organic extracts dried (Na_2SO_4). Concentration *in vacuo* was followed by flash column chromatography (EtOAc : hexanes, 1 : 3) to afford alcohol **302** (34 mg, 88 %) as a spectroscopically indistinguishable mixture of diastereoisomers: *Rf* 0.25 (EtOAc : hexanes, 1 : 2); IR (film) ν_{max} 3500, 2952, 1728, 1254, 1039, 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *all diastereoisomers (see Appendix 2i):* δ 0.06 (s, 3H, $Si(CH_3)_2$), 0.09 (s, 3H, $(CH_3)_2$), 0.90 (s 9H, $C(CH_3)_3$), 1.23 (d, *J* = 6.0 Hz, 3H, CH_3CH), 1.49 – 1.64 (m, 10H, CH_2), 1.75 (dd, *J* = 14.5, 9.5Hz, 1H, CH_2CHOH), 1.92 – 2.01 (m, 3H, CH_2), 2.05 (dd, *J* = 14.5, 4.0 Hz, 1H, CH_2CHOSi), 2.10 – 2.17 (m, 1H, CH_2), 2.50 *(app.* qd, *J* = 15.5, 7.0 Hz, 2H, CH_2CO_2R), 3.93 *(app.* d, *J* = 2.0 Hz, 4H, $O(CH_2)_2O$), 3.99 – 4.03 (m, 4H, $O(CH_2)_2O$), 4.20 – 4.31 (m, 2H, CH_3CH + $CHOTBS$), 5.01 – 5.09 (m, 1H, $CHOCOR$), 5.45 – 5.56 (m, 2H, CH=CH); ^{13}C NMR (100 MHz, $CDCl_3$) *all diastereoisomers:* δ –4.7, –4.3, 18.2, 20.4, 20.6, 22.9, 25.9 (3C), 31.9, 35.0, 36.0, 36.5, 42.2, 42.8, 45.8, 64.0, 64.6 (2C), 65.1 (2C), 69.8, 70.5, 110.4, 111.8, 130.5, 134.5, 171.1; MS (CI) *m/z* 543 $[M+H]^+$, 560 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{28}H_{51}SiO_8$ $[M+H]^+$: 543.3367, found: 543.3365; Anal. calculated for $C_{28}H_{50}SiO_8$: C, 61.96; H, 9.29; found: C, 62.04; H, 9.33%.

7,25-Dihydroxy-11-methyl-1,4,10,16,19-pentaoxa-dispiro [4.9.4.7]hexacos-23-ene-9-one (301)



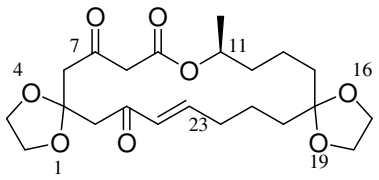
To a solution of 7-hydroxy-25-(*tert*-butyldimethylsilanyloxy)-11-methyl-1,4,10,16,19-pentaoxa-dispiro[4.9.4.7]hexacos-23-ene-9-one (**302**) (163 mg, 0.30 mmol) in THF (2 mL) was added TBAF (1.0 M in THF, 3.0 mL, 3.0 mmol). After 18 h, the orange reaction mixture was quenched by addition of brine (5 mL), extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts dried (Na_2SO_4). Concentration *in vacuo* was followed by flash column chromatography (EtOAc) to afford diol **301** (128 mg, 99%) as an inseparable mixture of diastereoisomers: *Rf* 0.50 (EtOAc); IR (film) ν_{max} 3455, 3414, 1726, 1125, 1032, 949 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *see Appendix 2j*; ^{13}C NMR (100 MHz, $CDCl_3$) *all diastereoisomers:* 20.0, 20.1, 20.5, 20.7, 21.4, 21.7, 22.1, 31.3, 31.6, 34.3, 34.6, 36.3, 37.1, 37.7, 38.0, 42.1, 42.5, 43.0, 43.3, 43.7, 43.8, 64.4, 64.6, 64.9, 65.1, 65.4, 65.5, 65.7, 110.9, 111.1, 111.2, 111.5, 131.3, 131.8, 133.6, 170.6, 171.4; MS (CI) *m/z* 429 $[M+H]^+$, 446 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{22}H_{40}NO_8$ $[M+NH_4]^+$: 446.2764, found: 446.2764.

(*S*)-11-Methyl-1,4,10-trioxa-spiro[4.17]docos-19-ene -7,9,15,21-tetraone (306)



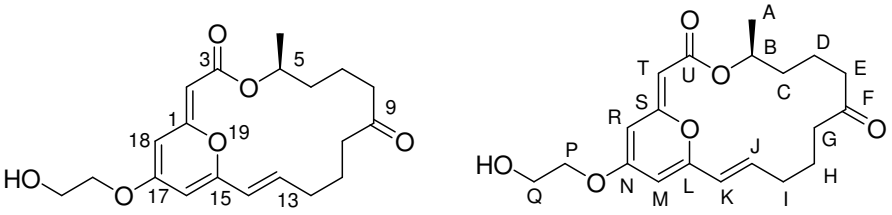
To a solution of oxalyl chloride (60 μL, 0.70 mmol) in CH_2Cl_2 (2.5 mL) at –78 °C was added DMSO (115 μL, 1.65 mmol). After 30 min, a solution of 7,25-dihydroxy-11-methyl-1,4,10,16,19-pentaoxa-dispiro[4.9.4.7]hexacos-23-ene-9-one (**301**) (115 mg, 0.27 mmol) in CH_2Cl_2 (2.5 mL) was added and after a further 30 min Et_3N (400 μL, 2.8 mmol) was added. The reaction mixture was stirred at –78 °C for 1 h then warmed slowly to 0 °C during 1 h. After 30 min at 0 °C, the reaction mixture was quenched by addition of H_2O (10 mL), extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts dried (Na_2SO_4). Concentration *in vacuo* was followed by flash column chromatography (EtOAc : hexanes, 1 : 3) to afford triketone **306** (15 mg, 15%) as a colourless oil: *Rf* 0.20 (EtOAc : hexanes, 1 : 2); $[\alpha]_D$ +14.0 (*c* 0.95, CH_2Cl_2); IR (film) ν_{max} 3434, 2937, 1760, 1710, 1664, 1623, 1369, 1251, 1124, 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.33 (d, *J* = 6.5 Hz, 3H, C*H*$_3$CHOR), 1.52 – 1.70 (m, 8H, C*H*$_2$), 1.83 – 1.93 (m, 2H, C*H*$_2$), 2.15 – 2.56 (m, 4H, C*H*$_2$C(=O)), 3.00 (AB q, *J* = 16.5 Hz, 1H, C(O)C*H*$_2$CO$_2$R), 3.48 (AB q, *J* = 18.0 Hz, 1H, C*H*$_2$C(O)C=C), 3.52 (AB q, *J* = 18.0 Hz, 1H, C*H*$_2$C(O)C=C), 3.61 (AB q, *J* = 16. Hz, 1H, C(O)C*H*$_2$CO$_2$R), 3.86 – 4.10 (m, 4H, O(C*H*$_2$)$_2$O), 4.90 – 5.11 (m, 1H, C*H*OR), 6.01 – 6.10 (m, 1H, C(O)C*H*=CH), 6.75 – 6.88 (m, 1H, C(O)CH=C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 20.6, 21.0, 31.7, 35.1, 39.8, 41.6, 43.2, 45.6 (2C), 64.7, 65.1, 66.4, 107.2, 132.6, 148.5, 162.5, 192.2, 197.0, 210.4; MS (CI) *m/z* 381 $[M+H]^+$, 398 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{20}H_{29}O_7$ $[M+H]^+$: 381.1913, found: 381.1908.

(*S*)-11-Methyl-1,4,10,16,19-pentaoxa-dispiro
[4.9.4.7]hexacos-23-ene-7,9,25-trione (86)



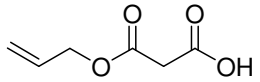
To a solution of oxalyl chloride (12 μL, 138 μmol) in CH_2Cl_2 (0.5 mL) at –78 °C was added DMSO (23 μL, 330 μmol). After 30 min, a solution of 7,25-dihydroxy-11-methyl-1,4,10,16,19-pentaoxa-dispiro[4.9.4.7]hexacos-23-ene-9-one (**301**) (20 mg, 47 μmol) in CH_2Cl_2 (0.5 mL) was added and after a further 30 min Et_3N (78 μL, 560 μmol) was added. The reaction mixture was stirred at –78 °C for 1 h then warmed slowly to 0 °C during 1 h. After 30 min at 0 °C, the reaction mixture was quenched by addition of H_2O (2 mL), extracted with CH_2Cl_2 (3 × 2 mL) and the combined organic extracts dried (Na_2SO_4). Concentration *in vacuo* was followed immediately by flash column chromatography (EtOAc : hexanes, 1 : 1) to afford diketone **86** (18 mg, 91 %) as a colourless oil: *Rf* 0.20 (EtOAc: hexanes, 1:2); $[\alpha]_D$ +12.5 (*c* = 0.89, CH_2Cl_2); IR (film) ν_{max} 3407, 2939, 1762, 1747, 1710, 1660, 1619, 1388, 1243, 1085 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.33 (d, *J* = 6.0 Hz, 3H, C*H*$_3$CHOR), 1.21 – 1.39 (m, 2H, C*H*$_2$), 1.46 – 1.73 (m, 8H, C*H*$_2$), 2.06 – 2.62 (m, 4H, C*H*$_2$), 3.05 (AB q, *J* = 15.0 Hz, 1H, C(O)C*H*$_2$CO$_2$R), 3.40 (AB q, *J* = 17.0 Hz, 1H, C*H*$_2$C(O)C=C), 3.44 (AB q, *J* = 17.0 Hz, 1H, C*H*$_2$C(O)C=C), 3.56 (AB q, *J* = 15.0 Hz, 1H, C(O)C*H*$_2$CO$_2$R), 3.94 (s, 4H, O(C*H*$_2$)$_2$O), 3.96 – 4.05 (m, 4H, O(C*H*$_2$)$_2$O), 5.04 – 5.14 (m, 1H, C*H*OR), 6.10 (d, *J* = 16.0 Hz, 1H, C(O)C*H*=CH), 6.98 (td, *J* = 7.5, 16.0 Hz, 1H, C(O)CH=C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 20.4, 21.5, 32.2, 34.4, 36.0, 37.2, 42.2, 45.5 (2C), 64.7 (2C), 64.8 (2C), 65.2, 107.4, 111.3, 132.9, 150.0, 162.6, 191.4, 197.5; MS (CI) *m/z* 425 [M+H], 442 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{22}H_{33}O_8$ $[M+H]^+$: 425.2175, found: 425.2179.

(*S*)-17-(2-Hydroxyethoxy)-5-methyl-4,19-dioxa-bicyclo [13.3.1]nonadeca-1,13,15,17-tetraene-3,9-dione (315)



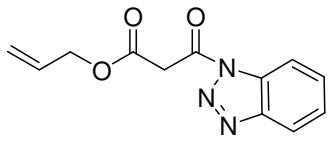
To a solution of (*S*)-11-Methyl-1,4,10,16,19-pentaoxa-dispiro[4.9.4.7]hexacos-23-ene-7,9,25-trione (**86**) (46 mg, 0.11 mmol) in CH_2Cl_2 : *i*PrOH, 5 : 3 (24 mL) was added K_2CO_3 (450 mg, 3.26 mmol). After 72 h, 1.2 M HCl aq. (12 mL) was added dropwise and the resultant reaction mixture was stirred at 23 °C for a further 4 h. After this time, the reaction mixture was diluted with H_2O (25 mL), extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic extracts dried (Na_2SO_4). Concentration *in vacuo* was followed by flash column chromatography (EtOAc) to afford pyrone derivative **315** (31 mg, 80%) as a colourless oil: *Rf* 0.25 (EtOAc); $[\alpha]_D$ −2.5 (*c* = 1.00, CH_2Cl_2); IR (film) ν_{max} 3424, 3090, 1755, 1709, 1654, 1553, 1427, 1253 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.33 (d, *J* = 6.0 Hz, 3H, H_A), 1.58 – 1.81 (m, 6H, H_C, H_D + H_H), 2.13 (*br.* s, 1H, O*H*), 2.25 (*app*. q, *J* = 7.5 Hz, 2H, H_I), 2.46 (t, *J* = 7.0 Hz, 4H, H_E + H_G), 3.97 – 4.02 (m, 2H, H_Q), 4.10 (t, *J* = 4.0 Hz, 2H, H_P), 4.95 – 5.06 (m, 1H, H_B), 5.47 (d, *J* = 2.0 Hz, 1H, H_R), 5.83 (d, *J* = 2.0 Hz, 1H, H_M), 5.94 (s, 1H, H_T), 5.98 (d, *J* = 15.5 Hz, 1H, H_K), 6.68 (td, *J* = 7.0, 15.5 Hz, 1H, H_J); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4 (C_A), 19.6 (C_D), 22.6 (C_C), 32.1 (C_H), 35.1 (C_I), 41.9 (C_E), 42.3 (C_G), 60.7 (C_P), 64.8 (C_T), 70.3 (C_Q), 75.0 (C_B), 89.4 (C_R), 100.1 (C_M), 122.3 (C_K), 139.2 (C_J), 158.8 (C_L), 164.3 (C_U), 164.4 (C_S), 170.5 (C_N), 210.0 (C_F); (*See Appendix 3 for 2D NMR spectra*); Anal. calculated for $C_{20}H_{26}O_6$: C, 66.28; H, 7.23; found: C, 66.26; H, 7.31%.

Malonic acid monoallyl ester (351)[192]



A solution of 2,2-dimethyl-[1,3]dioxane-4,6-dione (**350**) (10 g, 0.07 mol) in allylic alcohol (20 mL) was gently refluxed for 6 h. After this time, the reaction was concentrated *in vacuo* and the oily residue was re-dissolved in H_2O (20 mL) and washed with hexane : Et_2O, 1 : 1 (2 × 20 mL). The aqueous layer was acidified to ~pH 4 with 1 M aq. HCl, extracted with Et_2O (2 × 50 mL) and the combined organic extracts were dried ($MgSO_4$). Concentration *in vacuo* afforded allylic ester **351** (6.2 g, 62%) as a colourless oil which was used crude without further purification: *Rf* 0.10 (EtOAc : hexanes, 1 : 3); IR (film) ν_{max} 3545, 2951, 1738, 1154, 993 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.49 (s, 2H, C*H*$_2$CO$_2$H), 4.69 (d, *J* = 6.0 Hz, 2H, C*H*$_2$CH=C), 5.30 (dd, *J* = 1.0, 10.0 Hz, 1H, CH=C*H*$_2$), 5.38 (dd, *J* = 1.0, 17.0 Hz, 1H, CH=C*H*$_2$), 5.94 (tdd, *J* = 6.0, 10.0, 17.0 Hz, 1H, C*H*=CH$_2$), 7.09 (*br.* s, 1H, CO$_2$*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.8, 66.5, 119.2, 131.4, 166.5, 171.0; MS (CI) *m/z* 145 $[M+H]^+$, 162 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_6H_{12}NO_4$ $[M+NH_4]^+$: 162.0766, found: 162.0764.

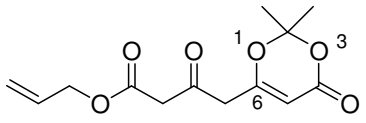
3-Benzo[1,2,3]triazol-1-yl-3-oxo-propionic acid allyl ester (348)



To a solution of benzo[1,2,3]triazole (20.5 g, 168 mmol) in CH_2Cl_2 (100 mL), was added thionyl chloride (3.65 ml, 84 mmol) dropwise. After 30 min, malonic acid monoallyl ester (**351**) (6.0 g, 42 mmol) was added and a solid precipitated. After a further 4 h, the reaction mixture was filtered, the filtrate washed with 0.5 M aq. NaOH (2 × 50 mL) and dried ($MgSO_4$). Concentration *in vacuo* was followed by flash column chromatography stabilised by Et_3N (EtOAc : hexanes, 3 : 7) to afford acyl-benzotriazole **348** (6.2 g, 60 %) as a colourless oil: *Rf* 0.45 (EtOAc : hexanes, 3 : 7); IR (film) ν_{max} 3461, 2952, 1752, 1737, 1486, 1153, 993 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.46 (s, 2H, C*H*$_2$CO$_2$Bt), 4.70 (d, *J* = 6.0 Hz, 2H, C*H*$_2$CH=C), 5.25 (dd, *J* = 1.0, 10.5 Hz, 1H, CH=C*H*$_2$), 5.33 (dd, *J* = 1.0, 17.0 Hz, 1H, CH=C*H*$_2$), 5.89 (tdd, *J* = 6.0, 10.5, 17.0 Hz, 1H, C*H*=CH$_2$), 7.57 (*app*. t, *J* = 8.5 Hz, 1H, Ar*H*), 7.72 (*app*. t, *J* = 8.5 Hz, 1H, Ar*H*), 8.17 (d, *J* = 8.5 Hz, 1H, Ar*H*), 8.33 (d, *J* = 8.5 Hz, 1H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.7, 66.6, 114.3, 119.0, 120.3, 126.6, 130.8, 131.2, 131.5, 146.3, 164.9, 165.6; MS (CI) *m/z* 246 $[M+H]^+$, 263 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{12}H_{12}N_3O_3$ $[M+H]^+$: 246.0879, found: 246.0882.

Note : The product is partially hydrolyzed on the column, hence at least 1% of Et_3N is added to the eluent mixture for chromatography.

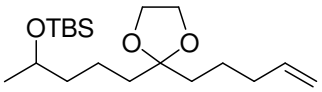
4-(2,2-Dimethyl-4-oxo-6*H*-[1,3]dioxin-6-yl)-3-oxobutyric acid allyl ester (339)



To a solution of HMDS (1.9 mL, 9.1 mmol) in THF (140 mL) at –78 ºC, was added *n*-BuLi (2.5 M in hexanes, 3.8 mL, 9.5 mmol) and the resultant solution was stirred at that temperature for 30 min. After this period, 2,2,6-trimethyl-[1,3]dioxin-4-one (**316**) (1.0 ml, 7.6 mmol) was added dropwise and the solution was stirred at –78 ºC for a further 1.5 h. 3-Benzo[1,2,3]triazol-1-yl-3-oxo-propionic acid allyl ester (**348**) (480 mg, 1.90 mmol) was added in one portion and the reaction was allowed to warm to 23 °C over 18 h and then quenched by addition of sat. aq. NH_4Cl (3 mL). The reaction was acidified to ~pH 4 with 1 M aq. HCl, extracted with EtOAc (2 × 40 mL) and the combined organic extracts dried ($MgSO_4$). Concentration *in vacuo* was followed by flash column chromatography (EtOAc : hexanes, 1 : 4) to afford dioxinone analogue **339** (300 mg, 65%) as a pale yellow oil: *Rf* 0.40 (EtOAc : hexanes, 3 : 7); IR (film) ν_{max} 3451, 3000, 1725, 1639, 1392, 1274, 1203, 1016 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.71 (s, 6H, 3.49 (CH_3)$_2$C), 3.53 (s, 2H, CH_2C(=O)CO_2Allyl), 3.57 (s, 2H, CH_2CO_2Allyl), 4.68 (d, *J* = 6.0 Hz, 2H, CH_2CH=C), 5.29 (dd, *J* = 1.0, 10.5 Hz, 1H, CH=CH_2), 5.35 (dd, *J* = 1.0, 17.0 Hz, 1H, CH=CH_2), 5.37 (s, 1H, C=C*H*C(=O)), 5.90 (tdd, *J* = 6.0, 10.5, 17.0 Hz, 1H, C*H*=CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0 (2C), 47.0, 49.0, 66.4, 97.2, 107.4, 119.4, 131.2, 160.5, 163.4 (2C), 195.5; MS (CI) *m/z* 269 $[M+H]^+$, 286 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{13}H_{17}O_6$ $[M+H]^+$: 269.1026, found: 269.1025.

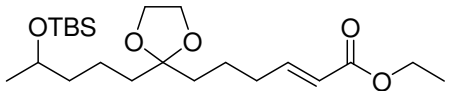
Note: This yield is calculated based on a 90 % purity of 3-benzo[1,2,3]triazol-2-yl-3-oxo-propionic acid allyl ester **348** after column chromatography.

(±)-5-[2-(4-*tert*-Butyldimethylsilanyloxypentyl)
-[1,3]dioxolan-2-yl]pent-1-ene, (110)[84]



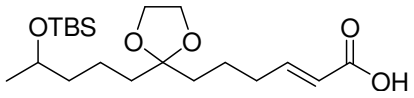
To a solution of (±)-5-(2-pent-4-enyl-[1,3]dioxolan-2-yl)pentan-2-ol (**93**) (500 mg, 2.19 mmol) in CH_2Cl_2 (5 mL) was added 2,6-lutidine (508 μL, 4.37 mmol) followed by TBSOTf (754 μL, 3.28 mmol) and the resultant solution was stirred at 23 °C for 20 min. After this time the reaction was diluted with brine (25 mL), the aqueous layer extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic extracts washed with brine (2 × 25 mL), then dried (Na_2SO_4). Concentration *in vacuo* was followed by flash column chromatography (EtOAc : hexanes, 1 : 9) to afford (±)-silyl ether **110** (647 mg, 86%) as a colourless oil: *Rf* 0.85 (EtOAc : hexanes, 1 : 4); IR (film) ν_{max} 3436, 1641, 1253, 1051 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 6H, $(CH_3)_2Si$), 0.90 (s, 9H, $(CH_3)_3C$), 1.13 (d, *J* = 6.0 Hz, 3H, CH_3CH), 1.26 – 1.71 (m, 10H, CH_2), 2.08 (*app.* q, *J* = 7.0 Hz, 2H, $CH_2CH{=}C$), 3.80 (q, *J* = 6.0 Hz, 1H, $CHCH_3$), 3.94 (s, 4H, $O(CH_2)_2O$), 4.98 (dd, *J* = 1.5, 10.0 Hz, 1H, $CH{=}CH_2$), 5.03 (dd, *J* = 1.5, 17.0 Hz, 1H, $CH{=}CH_2$), 5.82 (tdd, *J* = 7.0, 10.0, 17.0 Hz, 1H, $CH{=}CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ –4.7, –4.4, 14.1, 20.2, 23.2, 23.8, 25.9 (3C), 33.9, 36.7, 37.3, 40.0, 65.0, 68.6 (2C), 111.7, 114.6, 138.7; MS (CI) *m/z* 343 $[M+H]^+$, 360 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{19}H_{39}SiO_3$ $[M+H]^+$: 343.2668, found: 343.2667.

6-{2-[4-(*tert*-Butyldimethylsilanyloxy)pentyl]
-[1,3]dioxolan-2-yl}hex-2-enoic acid ethyl ester (353)



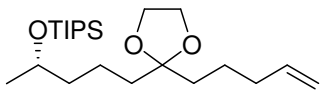
To a solution of (±)-5-[2-(4-*tert*-butyldimethylsilanyloxypentyl)-[1,3]dioxolan-2-yl]pent-1-ene (**110**) (200 mg, 0.58 mmol) and ethyl acrylate (**349**) (159 μL, 1.46 mmol) in CH_2Cl_2 (100 mL) at 40 °C with a slow stream of argon bubbled through, was added Hoveyda Grubbs' second generation catalyst (**197**) (37 mg, 10 mol %) in CH_2Cl_2 (10 mL) *via* syringe pump over 2.5 h. After this time, the reaction was concentrated *in vacuo* and purified by flash column chromatography (EtOAc : hexanes, 1 : 9) to afford ester **353** (186 mg, 77%) as a colourless oil: *Rf* 0.75 (EtOAc : hexanes, 1 : 4); IR (film) ν_{max} 2952, 1722, 1583, 1255, 1047 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 6H, $(CH_3)_2Si$), 0.90 (s, 9H, $(CH_3)_3C$), 1.13 (d, *J* = 6.0 Hz, 3H, CH_3CH), 1.30 (t, *J* = 7.0Hz, 3H, CH_3CH_2),1.34 – 1.67 (m, 10H, CH_2), 2.22 (*app.* q, *J* = 7.0 Hz, 2H, CH_2CH=C), 3.79 (q, *J* = 6.0 Hz, 1H, $CHCH_3$), 3.94 (s, 4H, $O(CH_2)_2O$), 4.20 (q, *J* = 7.0 Hz, 2H, CH_3CH_2), 5.84 (d, *J* = 15.5Hz, 1H, CH=CHCO_2Et), 6.97 (td, *J* = 7.0, 15.5 Hz, 1H, C*H*=CHCO_2Et); ^{13}C NMR (100 MHz, $CDCl_3$) δ –4.7, –4.4, 14.3, 18.2, 20.2, 22.3, 23.8, 25.9 (3C), 32.3, 36.7, 37.4, 39.9, 60.2, 65.0 (2C), 68.5, 111.5, 121.5, 148.9, 166.7; MS (CI) *m/z* 415 $[M+H]^+$, 432 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{22}H_{43}SiO_5$ $[M+H]^+$: 415.2880, found: 415.2876; Anal. calculated for $C_{22}H_{42}SiO_5$: C, 63.72; H, 10.21; found: C, 63.66; H, 10.15%.

6-{2-[4-(*tert*-Butyldimethylsilanyloxy)pentyl]
-[1,3]dioxolan-2-yl}hex-2-enoic acid (352)



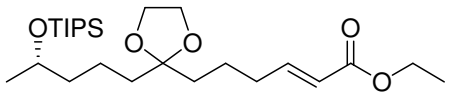
To a solution of 6-{2-[4-(*tert*-butyldimethylsilanyloxy)pentyl]-[1,3]dioxolan-2-yl}hex-2-enoic acid ethyl ester (**353**) (104 mg, 0.25 mmol) in EtOH (11 mL) at 0 °C was added NaOH (2 M aq, 6 mL) dropwise. After 18 h, the reaction was diluted with H_2O (20 mL) and extracted with Et_2O (3 × 20 mL). The aqueous layer was acidified to ~pH 4 with 1 M aq. HCl, then re-extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts dried (Na_2SO_4). Concentration *in vacuo* was followed by flash column chromatography (MeOH : CH_2Cl_2, 1 : 20) to afford acid **352** (76 mg, 78%) as a colourless oil: *Rf* 0.40 (MeOH : CH_2Cl_2, 1 : 20); IR (film) ν_{max} 3299, 2952, 2858, 1698, 1650, 1253, 1056 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 6H, $(CH_3)_2Si$), 0.89 (s, 9H, $(CH_3)_3C$), 1.12 (d, *J* = 6.0 Hz, 3H, CH_3CH), 1.29 – 1.66 (m, 10H, CH_2), 2.22 (*app.* q, *J* = 7.0 Hz, 2H, $CH_2CH{=}C$), 3.78 (q, *J* = 6.0 Hz, 1H, $CHCH_3$), 3.93 (s, 4H, $O(CH_2)_2O$), 5.83 (d, *J* = 15.5Hz, 1H, $CH{=}CHCO_2Et$), 7.06 (td, *J* = 7.0, 15.5 Hz, 1H, $CH{=}CHCO_2Et$), 9.12 (*br.* s, 1H, CO_2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ –4.7, –4.4, 18.1, 20.2, 22.1, 23.8, 25.9 (3C), 32.4, 36.6, 37.3, 39.9, 65.0 (2C), 68.6, 111.5, 120.9, 151.7, 171.6; MS (CI) *m/z* 387 $[M+H]^+$, 404 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{20}H_{39}SiO_5$ $[M+H]^+$: 387.2567, found: 387.2562.

(*S*)-5-[2-(4-Tri*iso*propylsilanyloxypentyl)
-[1,3]dioxolan-2-yl]pent-1-ene (359)



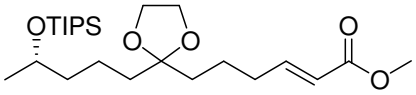
To a solution of (*S*)-*5*-(2-pent-4-enyl-[1,3]dioxolan-2-yl)pentan-2-ol (**93**) (604 mg, 2.64 mmol) in CH_2Cl_2 (6 mL), was added imidazole (450 mg, 6.60 mmol), followed by TIPS-Cl (849 μL, 4.00 mmol. After 72 h, the reaction was diluted with brine (25 mL), the aqueous layer extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic extracts were washed with brine (2 × 25 mL), then dried (Na_2SO_4). Concentration *in vacuo* was followed by flash column chromatography (EtOAc : hexanes, 1 : 20) to afford silyl ether **359** (1.00 g, 99%) as a colourless oil: *Rf* 0.85 (EtOAc : hexanes, 1 : 4); $[\alpha]_D$ +0.9 (*c* 0.97, CH_2Cl_2); IR (film) ν_{max} 2944, 2867, 1461, 1376, 1137, 1056 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (s, 18H, $(CH_3)_2C$), 1.18 (d, *J* = 6.0 Hz, 3H, CH_3CH), 1.59 (s, 3H, $(CH_3)_2CH$), 1.41 – 1.65 (m, 10H, CH_2), 2.08 (*app.* q, *J* = 7.0 Hz, 2H, $CH_2CH{=}C$), 3.95 (*app.* s, 5H, $O(CH_2)_2O + CHCH_3$), 4.98 (dd, *J* = 1.5, 10.0 Hz, 1H, $CH{=}CH_2$), 5.03 (dd, *J* = 1.5, 17.0 Hz, 1H, $CH{=}CH_2$), 5.82 (tdd, *J* = 7.0, 10.0, 17.0 Hz, 1H, $CH{=}CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.5 (3C), 18.1 (6C), 19.7, 23.2, 23.5, 33.9, 36.9, 37.4, 40.2, 64.9 (2C), 68.5, 111.7, 114.6, 138.7; MS (CI) *m/z* 385 $[M+H]^+$, 402 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{22}H_{45}SiO_3$ $[M+H]^+$: 385.3138, found: 385.3138; Anal. calculated for $C_{22}H_{44}SiO_3$: C, 68.69; H, 11.53; found: C, 68.70; H, 11.57%.

(*S*)-6-[2-(4-Tri*iso*propylsilanyloxypentyl)
-[1,3]dioxolan-2-yl]hex-2-enoic acid ethyl ester (360)



To a solution of (*S*)-5-[2-(4-tri*iso*propylsilanyloxypentyl)-[1,3]dioxolan-2-yl]pent-1-ene (**359**) (1.07 g, 2.78 mmol) and ethyl acrylate (**349**) (758 µL, 6.97 mmol) in CH_2Cl_2 (200 mL) at 40 °C with a slow stream of argon bubbled through, was added Hoveyda Grubbs' second generation catalyst (**197**) (100 mg, 6 mol %) in CH_2Cl_2 (15 mL) *via* syringe pump over 2.5 h. After this time, the reaction was concentrated *in vacuo* and purified by flash column chromatography (EtOAc : hexanes, 1 : 9) to afford ester **360** (926 mg, 78%) as a colourless oil: *Rf* 0.75 (EtOAc: hexanes, 1 : 4); $[\alpha]_D$ +1.0 (*c* 1.74, CH_2Cl_2); IR (film) ν_{max} 3517, 2944, 2867, 1722, 1654, 1463, 1047 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 21H, $(CH_3)_2CH$), 1.16 (d, *J* = 6.0 Hz, 3H, CH_3CH), 1.28 (t, *J* = 7.0Hz, 3H, CH_3CH_2), 1.35 – 1.65 (m, 10H, CH_2), 2.20 (*app.* q, *J* = 7.0 Hz, 2H, CH_2CH=C), 3.93 (*app.* s, 5H, $O(CH_2)_2O$ + $CHCH_3$), 4.18 (q, *J* = 7.0 Hz, 2H, CH_3CH_2), 5.82 (d, *J* = 15.5 Hz, 1H, CH=$CHCO_2Et$), 6.97 (td, *J* = 7.0, 15.5 Hz, 1H, CH=$CHCO_2Et$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.5 (3C), 14.3, 18.2 (6C), 19.7, 22.3, 23.5, 32.3, 36.6, 37.5, 40.1, 60.1, 65.0 (2C), 68.5, 111.5, 121.5, 148.9, 166.7; MS (CI) *m/z* 457 $[M+H]^+$, 474 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{25}H_{49}SiO_5$ $[M+H]^+$: 457.3363, found: 457.3357; Anal. calculated for $C_{25}H_{48}SiO_5$: C, 65.74; H, 10.59; found: C, 65.82; H, 10.65%.

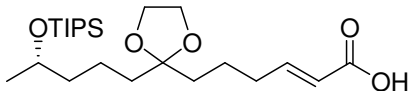
(*S*)-6-[2-(4-Tri*iso*propylsilanyloxypentyl)
-[1,3]dioxolan-2-yl]hex-2-enoic acid methyl ester (361)



To a solution of **(*S*)-**6-[2-(4-tri*iso*propylsilanyloxypentyl)-[1,3]dioxolan-2-yl]hex-2-enoic acid ethyl ester (**360**) (2.75 g, 6.0 mmol) in MeOH (55 mL) at 0 °C was added NaOH (2 M aq, 30 mL) dropwise. After 18 h, the reaction mixture was diluted with H_2O (100 mL), acidified to ~pH 4 with 1 M aq. HCl, extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts dried (Na_2SO_4). Concentration *in vacuo* was followed by flash column chromatography (MeOH : CH_2Cl_2, 1 : 99) to afford methyl ester **361** (1.55 g, 58%) as a colourless oil: *Rf* 0.70 (EtOAc : hexanes, 1 : 4); $[\alpha]_D$ +1.1 (*c* 1.11, CH_2Cl_2); IR (film) ν_{max} 2942, 2865, 1727, 1656, 1463, 1380, 1051 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (s, 18H, $(CH_3)_2C$), 1.18 (d, *J* = 6.0 Hz, 3H, CH_3CH), 1.61 (s, 3H, $(CH_3)_2CH$), 1.30 – 1.67 (m, 10H, CH_2), 2.23 (*app.* q, *J* = 7.0 Hz, 2H, CH_2CH=C), 3.75 (s, 3H, CH_3OCOR), 3.95 (*app.* s, 5H, $O(CH_2)_2O$ + $CHCH_3$), 5.85 (d, *J* = 15.5Hz, 1H, CH=CHCO_2Et), 6.98 (td, *J* = 7.0, 15.5Hz, 1H, C*H*=$CHCO_2Et$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.5 (3C), 17.7 + 18.2 (6C), 19.7, 22.3, 23.5, 32.3, 36.6, 37.5, 40.1, 51.4, 65.0 (2C), 68.5, 111.5, 121.1, 149.2, 167.1; MS (CI) *m/z* 443 $[M+H]^+$, 460 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{24}H_{47}SiO_5$ $[M+H]^+$: 443.3206, found: 443.3202; Anal. calculated for $C_{24}H_{46}SiO_5$: C, 65.11; H, 10.47; found: C, 65.01; H, 10.39%.

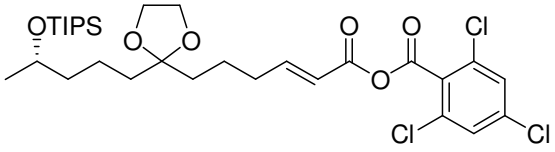
Note : The transesterification product **361** was obtained because of poor starting material solubility. Increasing the amount of MeOH resulted in desired hydroylsis.

(*S*)-6-[2-(4-Tri*iso*propylsilanyloxypentyl)
-[1,3]dioxolan-2-yl]hex-2-enoic acid (362)



To a solution of **(*S*)-**6-[2-(4-tri*iso*propylsilanyloxypentyl)-[1,3]dioxolan-2-yl]hex-2-enoic acid ethyl ester (**360**) (2.00 g, 4.39 mmol) in MeOH (100 mL) at 0 °C was added NaOH (2 M aq, 30 mL) dropwise. After 18 h, the reaction was diluted with H_2O (100 mL), acidified to ~pH 4 with 1 M aq. HCl, extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts dried (Na_2SO_4). Concentration *in vacuo* was followed by flash column chromatography (MeOH : CH_2Cl_2, 1 : 99) to afford acid **362** (1.80 g, 96%) as a colourless oil: *Rf* 0.40 (MeOH : CH_2Cl_2, 1 : 20); $[\alpha]_D$ +1.1 (*c* 1.00, CH_2Cl_2); IR (film) ν_{max} 3691, 2944, 2867, 1698, 1650, 1463, 1056 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.04 (s, 21H, $(CH_3)_2CH$), 1.15 (d, *J* = 6.0 Hz, 3H, CH_3CH), 1.36 – 1.64 (m, 10H, CH_2), 2.23 (*app.* q, *J* = 6.5 Hz, 2H, CH_2CH=C), 3.92 (*app.* s, 5H, $O(CH_2)_2O$ + $CHCH_3$), 5.82 (d, *J* = 15.5 Hz, 1H, CH=$CHCO_2Et$), 7.05 (td, *J* = 6.5, 15.5 Hz, 1H, CH=$CHCO_2Et$), 10.39 (*br.* s, 1H, CO_2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.5 (3C), 18.1 (6C), 19.6, 22.1, 23.5, 32.3, 36.5, 37.4, 40.0, 65.0 (2C), 68.5, 111.5, 121.0, 151.6, 171.7; MS (CI) *m/z* 429 $[M+H]^+$, 446 $[M+NH_4]^+$; HRMS (CI) *m/z* calculated for $C_{23}H_{45}SiO_5$ $[M+H]^+$: 429.3018, found: 429.3025.

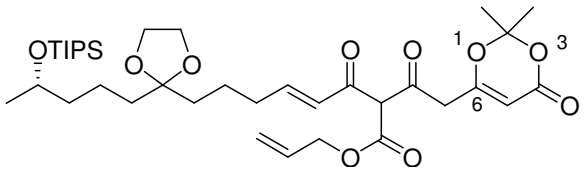
(*S*)-6-[2-(4-Tri*iso*propylsilanyloxypentyl)-[1,3]dioxolan-2-yl]hex-2-enoic 2,4,6-trichlorobenzoic anhydride (366)



To a solution of **(*S*)-**6-[2-(4-tri*iso*propylsilanyloxypentyl)-[1,3]dioxolan-2-yl]hex-2-enoic acid (**362**) (137 mg, 0.32 mmol) in THF (8 mL) was added Et_3N (53 μL, 0.38 mmol) followed by 2,4,6-trichlorobenzoyl chloride (**365**) (50 μL, 0.32 mmol). After 2.5 h, the reaction was concentrated *in vacuo* and purified by flash column chromatography (EtOAc : hexanes, 2 : 3) to afford mixed anhydride **366** (215 mg, >100% by mass) as a colourless oil which was used crude without further purification: *Rf* 0.80 (EtOAc : hexanes, 1 : 3); IR (film) ν_{max} 2923, 1815, 1755, 1576, 1547, 1211, 1081, 984 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.07 (s, 21H, $(CH_3)_2CH$), 1.17 (d, J = 6.0 Hz, 3H, CH_3CH), 1.39 – 1.67 (m, 10H, CH_2), 2.28 (*app.* q, J = 7.0 Hz, 2H, CH_2CH=C), 3.95 (*app.* s, 5H, $O(CH_2)_2O + CHCH_3$), 5.90 (d, J = 15.5 Hz, 1H, CH=C*H*CO_2Et), 7.14 (td, J = 7.0, 15.5 Hz, 1H, C*H*=$CHCO_2Et$), 7.41 (s, 2H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.5 (3C), 18.2 (6C), 19.7, 22.0, 23.5, 32.6, 36.6, 37.5, 40.1, 65.0 (2C), 68.5, 111.4, 120.6, 130.8, 133.1, 137.4, 137.6, 153.8, 156.0, 157.6, 162.0, 164.6; MS (ESI, Na^+) *m/z* 635, 637 $[M+H]^+$, 657, 659 $[M+Na]^+$; HRMS (ESI, Na^+) *m/z* calculated for $C_{30}H_{47}(^{35}Cl)_3SiO_6$ $[M+H]^+$: 635.2138, found: 635.2136.

Note : The product obtained was contaminated with excess 2,4,6-trichlorobenzoyl chloride (**365**), or its acid derivative.

2-[2-(2,2-Dimethyl-4-oxo-6H-[1,3]dioxin-6-yl)-acetyl]
-3-oxo-8-[2-(4-tri*iso*propylsilanyloxypentyl)
-[1,3]dioxolan-2-yl]oct-4-enoic acid allyl ester (368)

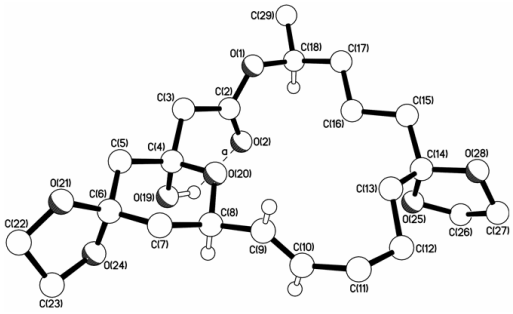


To a solution of 4-(2,2-dimethyl-4-oxo-6I-[1,3]dioxin-6-yl)-3-oxobutyric acid allyl ester (**339**) (54 mg, 0.20 mmol) in CH_2Cl_2 (0.3 mL) was added $MgCl_2$ (21 mg, 0.22 mmol) and the resultant suspension cooled to 0 °C for the addition of pyridine (34 μL, 0.42 mmol). After 30 min (*S*)-6-[2-(4-tri*iso*propylsilanyloxypentyl)-[1,3]dioxolan-2-yl]hex-2-enoic 2,4,6-trichlorobenzoic anhydride (**366**) (140 mg, 0.22 mmol) in CH_2Cl_2 (0.3 mL) was added and the reaction was allowed to warm to 23 °C for 2 h before quenching by the addition of sat. aq. NH_4Cl (2 mL). The reaction was poured into pH 7.0 buffer (10 mL), extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were washed with sat. aq. NH_4Cl (2 × 10 mL), then dried (Na_2SO_4). Concentration *in vacuo* afforded the crude reaction products, which were analysed by MS and shown to include acyl dioxinone **368**, along with starting materials and other unknown products (196 mg >100% by mass): MS (ESI, Na^+) *m/z* 679 $[M+H]^+$, 701 $[M+Na]^+$; HRMS (ESI, Na^+) *m/z* calculated for $C_{36}H_{58}NaSiO_{10}$ $[M+Na]^+$: 701.3697, found: 701.3699.

Appendices

Appendix 1: Crystal Structure Data

Crystal data and structure refinement for hemi-ketal **280b**:



Empirical formula C22 H34 O8

Formula weight 426.49

Temperature 173(2) K

Diffractometer, wavelength OD Xcalibur PX Ultra, 1.54248 Å

Crystal system, space group Monoclinic, P2(1)

Unit cell dimensions a = 5.6741(1) Å α = 90°

b = 10.1286(1) Å β = 93.8525(6)°

c = 19.5581(1) Å γ = 90°

Volume, Z 1121.477(12) $Å^3$, 2

Density (calculated) 1.263 Mg/m^3

Absorption coefficient 0.790 mm^{-1}

F(000) 460

Crystal colour / morphology Colourless platy needles

Crystal size 0.29 x 0.14 x 0.04 mm^3

θ range for data collection 2.27 to 71.65°

Index ranges -6<=h<=6, -12<=k<=12, -23<=l<=24

Reflns collected / unique 32188 / 4296 [R(int) = 0.0397]

Reflns observed [F>4σ(F)] 3591

Absorption correction Semi-empirical from equivalents

Max. and min. transmission 1.00000 and 0.83092

Refinement method Full-matrix least-squares on F^2

Data / restraints / parameters 4296 / 46 / 294

Goodness-of-fit on F^2 0.962

Final R indices [F>4σ(F)] R1 = 0.0297, wR2 = 0.0719

R1+ = 0.0297, wR2+ = 0.0719

R1- = 0.0299, wR2- = 0.0724

R indices (all data) R1 = 0.0371, wR2 = 0.0744

Absolute structure parameter x+ =0.00(13), x- = 1.01(13)

Largest diff. peak, hole 0.104, -0.145 eÅ^{-3}

Mean and maximum shift/error 0.000 and 0.001

Table 1: Bond Lengths [Å]:

BOND	BOND LENGTH
O(1)-C(2)	1.3356(19)
O(1)-C(18)	1.4746(17)
C(2)-O(2)	1.2112(17)
C(2)-C(3)	1.506(2)
C(3)-C(4)	1.514(2)
C(4)-O(19)	1.4153(17)
C(4)-O(20)	1.4190(18)
C(4)-C(5)	1.525(2)
C(5)-C(6)	1.512(2)
C(6)-O(24)	1.421(2)
C(6)-O(21)	1.4454(17)
C(6)-C(7)	1.505(2)
C(7)-C(8)	1.528(2)
C(8)-O(20)	1.443(2)
C(8)-C(9)	1.493(2)
C(9)-C(10)	1.305(2)
C(10)-C(11)	1.499(3)
C(11)-C(12)	1.537(2)
C(12)-C(13)	1.525(2)
C(13)-C(14)	1.513(2)
C(14)-O(28)	1.434(2)
C(14)-O(25)	1.4358(19)
C(14)-C(15)	1.517(2)
C(15)-C(16)	1.531(2)
C(16)-C(17)	1.519(2)
C(17)-C(18)	1.510(2)
C(18)-C(29)	1.514(2)
O(21)-C(22)	1.419(2)
C(22)-C(23)	1.489(2)
C(23)-O(24)	1.422(2)
O(25)-C(26')	1.388(10)
O(25)-C(26)	1.449(5)

BOND	BOND LENGTH
C(26)-C(27)	1.514(7)
C(27)-O(28)	1.410(4)
C(26')-C(27')	1.485(9)
C(27')-O(28)	1.492(8)

Table 2: Bond Angles [º]:

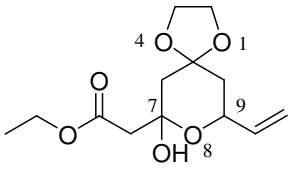
BOND	BOND ANGLE
C(2)-O(1)-C(18)	117.88(11)
O(2)-C(2)-O(1)	123.85(14)
O(2)-C(2)-C(3)	124.02(14)
O(1)-C(2)-C(3)	112.11(12)
C(2)-C(3)-C(4)	113.30(12)
O(19)-C(4)-O(20)	111.01(11)
O(19)-C(4)-C(3)	112.14(12)
O(20)-C(4)-C(3)	104.77(12)
O(19)-C(4)-C(5)	107.54(12)
O(20)-C(4)-C(5)	110.92(12)
C(3)-C(4)-C(5)	110.50(12)
C(6)-C(5)-C(4)	114.61(12)
O(24)-C(6)-O(21)	105.71(12)
O(24)-C(6)-C(7)	112.29(14)
O(21)-C(6)-C(7)	108.81(13)
O(24)-C(6)-C(5)	110.38(13)
O(21)-C(6)-C(5)	108.94(12)
C(7)-C(6)-C(5)	110.54(13)
C(6)-C(7)-C(8)	112.07(14)
O(20)-C(8)-C(9)	105.48(13)
O(20)-C(8)-C(7)	109.87(13)
C(9)-C(8)-C(7)	110.86(14)
C(10)-C(9)-C(8)	126.03(18)
C(9)-C(10)-C(11)	124.5(2)
C(10)-C(11)-C(12)	111.00(15)
C(13)-C(12)-C(11)	110.99(14)
C(14)-C(13)-C(12)	116.21(13)
O(28)-C(14)-O(25)	106.00(12)
O(28)-C(14)-C(13)	110.52(15)
O(25)-C(14)-C(13)	109.21(14)
O(28)-C(14)-C(15)	108.85(13)
O(25)-C(14)-C(15)	109.39(15)
C(13)-C(14)-C(15)	112.65(13)
C(14)-C(15)-C(16)	113.70(13)
C(17)-C(16)-C(15)	113.23(13)

BOND	BOND ANGLE
C(18)-C(17)-C(16)	114.09(13)
O(1)-C(18)-C(17)	108.76(12)
O(1)-C(18)-C(29)	106.55(13)
C(17)-C(18)-C(29)	113.24(14)
C(4)-O(20)-C(8)	114.65(11)
C(22)-O(21)-C(6)	108.44(11)
O(21)-C(22)-C(23)	103.59(13)
O(24)-C(23)-C(22)	103.10(14)
C(6)-O(24)-C(23)	106.22(12)
C(26')-O(25)-C(14)	111.0(4)
C(26')-O(25)-C(26)	18.8(7)
C(14)-O(25)-C(26)	107.2(3)
O(25)-C(26)-C(27)	102.5(4)
O(28)-C(27)-C(26)	102.1(4)
O(25)-C(26')-C(27')	101.2(7)
C(26')-C(27')-O(28)	103.6(6)
C(27)-O(28)-C(14)	109.0(2)
C(27)-O(28)-C(27')	28.2(3)
C(14)-O(28)-C(27')	103.8(4)

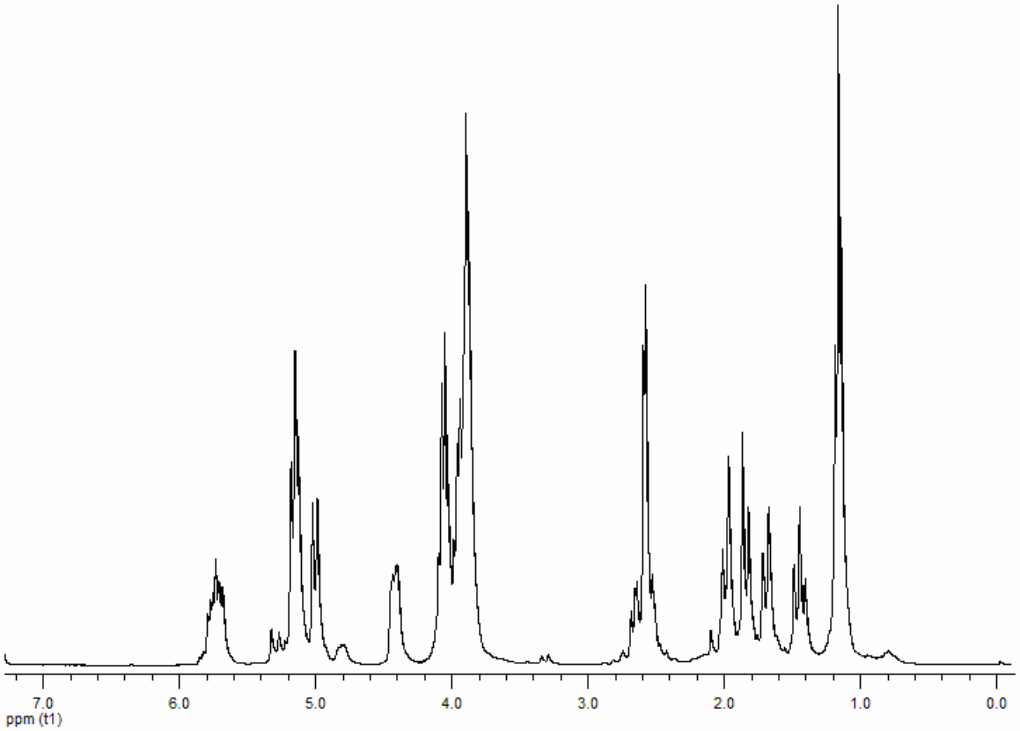
Appendix 2: ^{1}H NMR data for Diastereotopic Compounds.

Appendix 2a

(7-Hydroxy-9-vinyl-1,4,8-trioxaspiro[4,5]dec-7-yl)-acetic acid ethyl ester (269)

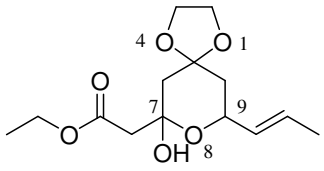


^{1}H NMR Spectrum (300 MHz, $CDCl_3$):

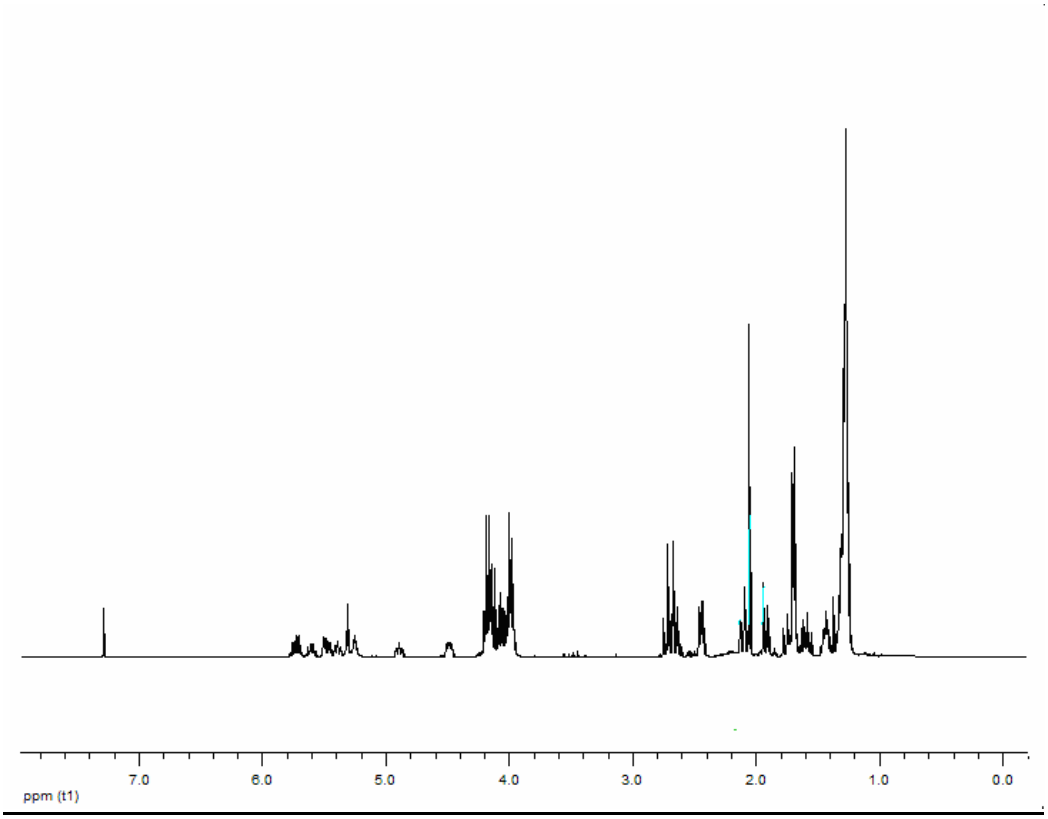


Appendix 2b

(7-Hydroxy-9-propenyl-1,4,8-trioxa-spiro[4.5]dec-7-yl)-acetic acid ethyl ester (275)

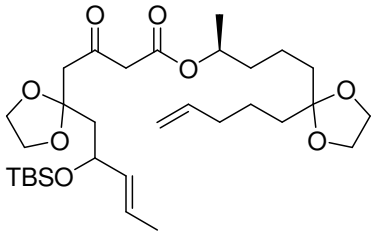


^{1}H NMR Spectrum (400 MHz, $CDCl_3$):

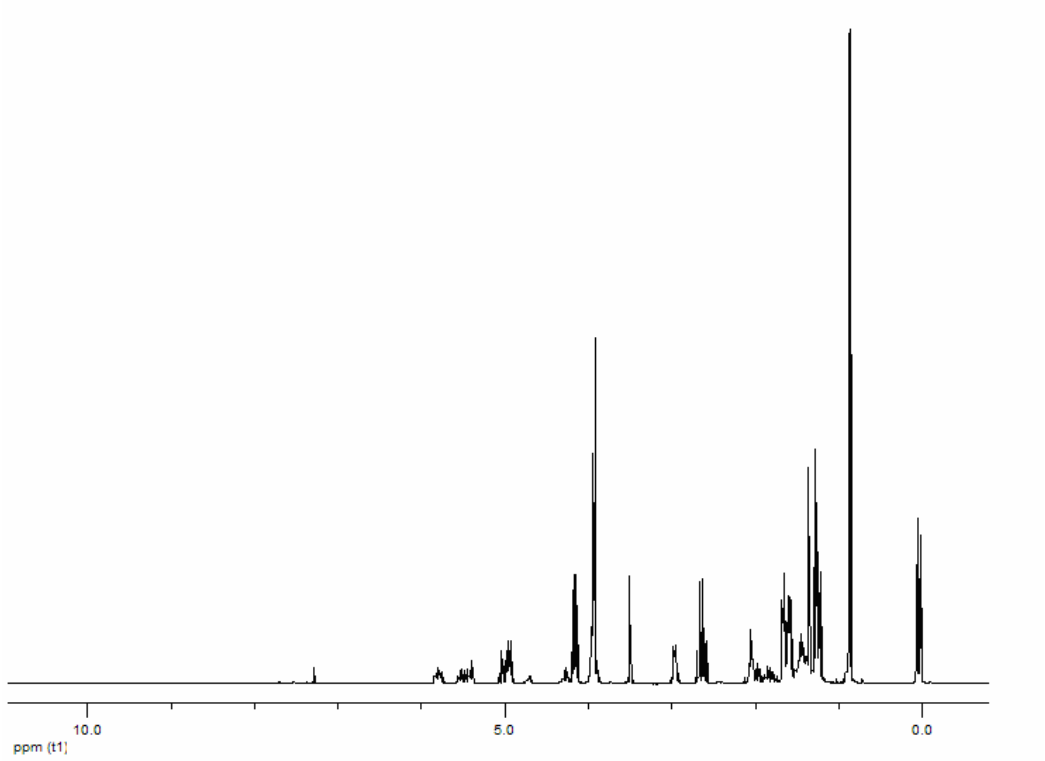


Appendix 2c

4-{2-[2-(*tert*Butyldimethylsilanyloxy)-pent-3-enyl]-[1,3]dioxolan-2-yl}-3-oxobutyric acid 1-methyl-4-(2-pent-4-enyl-[1,3]dioxolan-2-yl)-butyl ester (277)

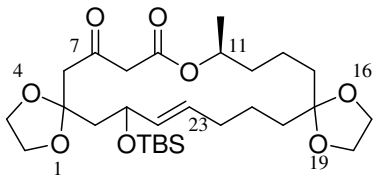


^{1}H NMR Spectrum (400 MHz, $CDCl_3$):

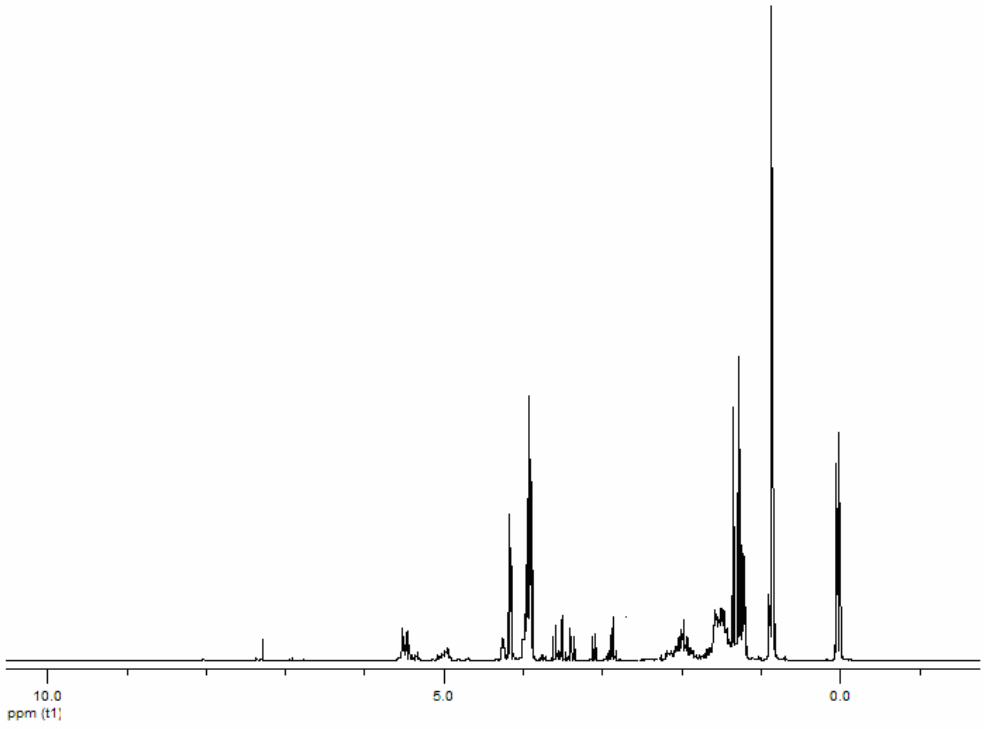


Appendix 2d

25-(*tert*-Butyldimethylsilanyloxy)-11-methyl-1,4,10,16,19-pentaoxa-dispiro[4.9.4.7]hexacos-23-ene-7,9-dione (278)

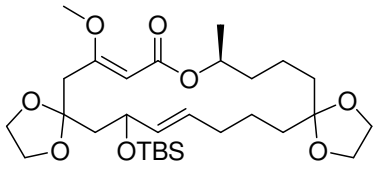


^{1}H NMR Spectrum (400 MHz, $CDCl_3$):

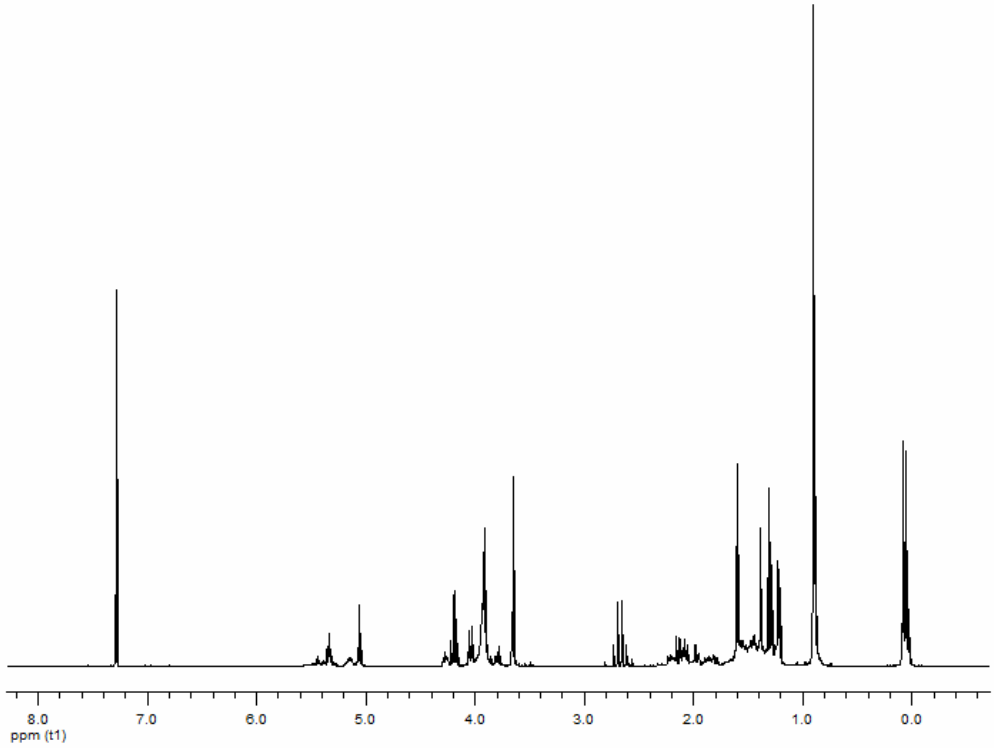


Appendix 2e

7-Methoxy-25-(*tert*-butyldimethylsilanyloxy)-11-methyl-1,4,10,16,19-pentaoxa-dispiro[4.9.4.7]hexacos-7,23-dien-9-one (286)

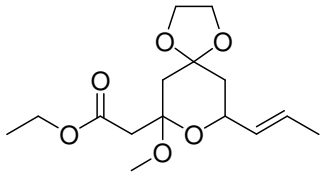


^{1}H NMR Spectrum (400 MHz, $CDCl_3$):

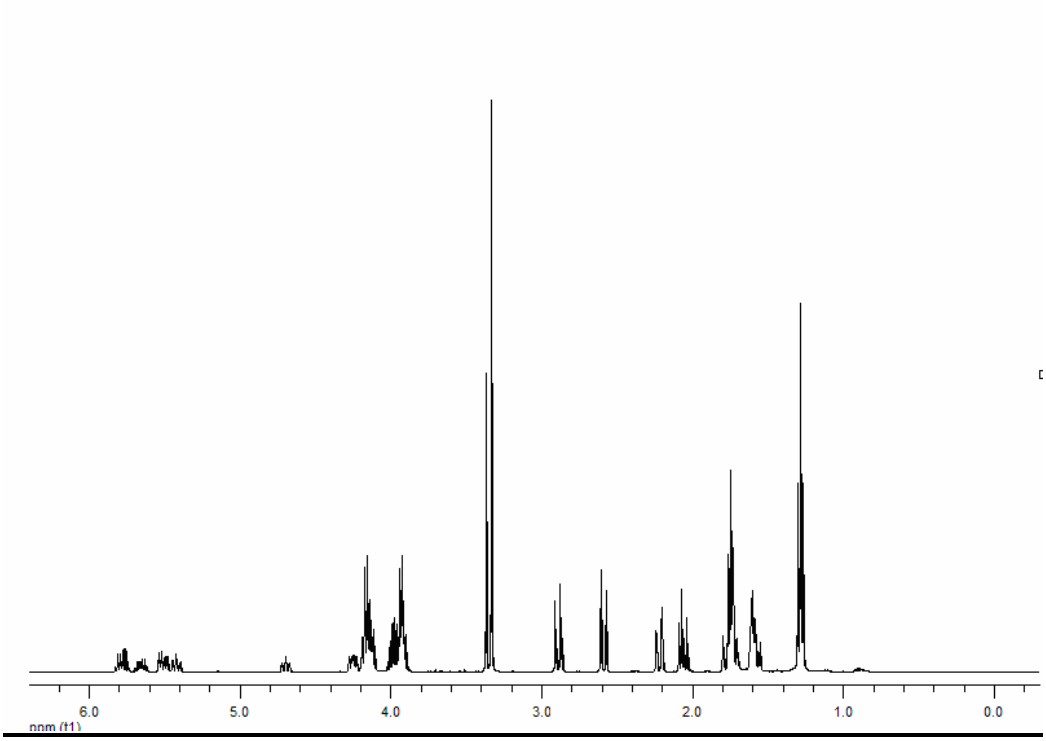


Appendix 2f

7-Methoxy-9-propenyl-1,4,8-trioxa-spiro[4.5]dec-7-yl)-acetic acid methyl ester (290)

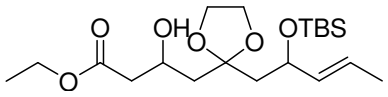


^{1}H NMR Spectrum (400 MHz, $CDCl_3$):

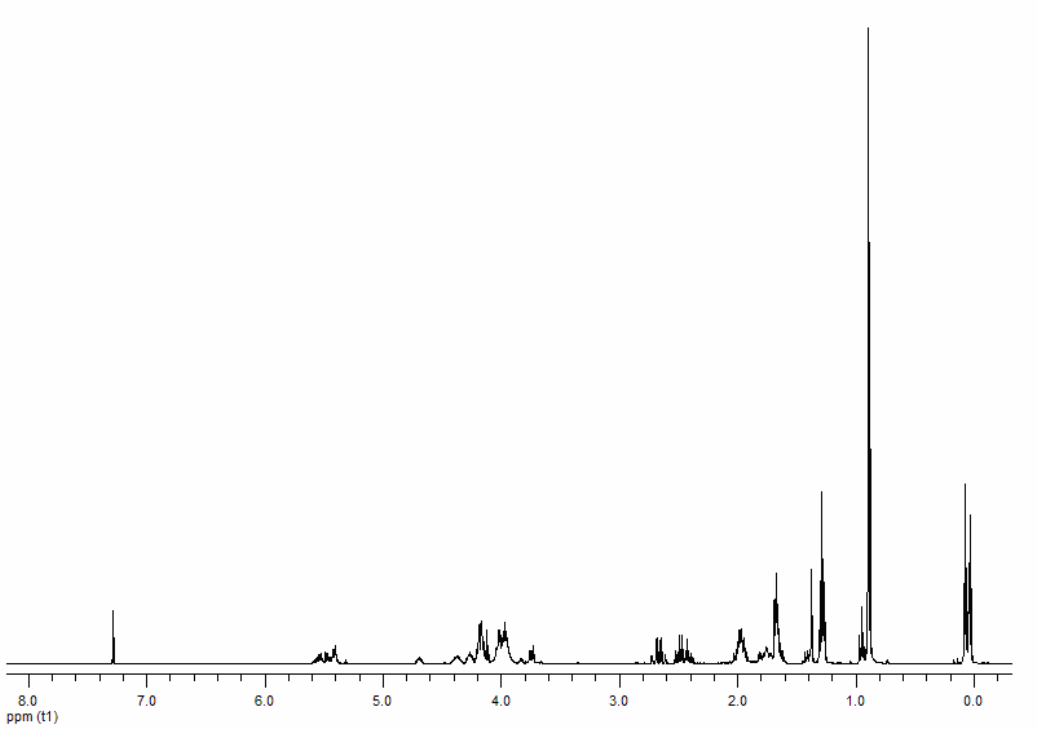


Appendix 2g

4-{2-[2-(*tert*-Butyldimethylsilanyloxy)-pent-3-enyl]-[1,3]dioxolan-2-yl}-3-hydroxy-butyric acid ethyl ester (304)

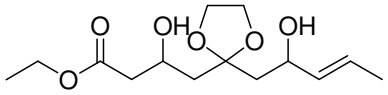


^{1}H NMR Spectrum (400 MHz, $CDCl_3$):

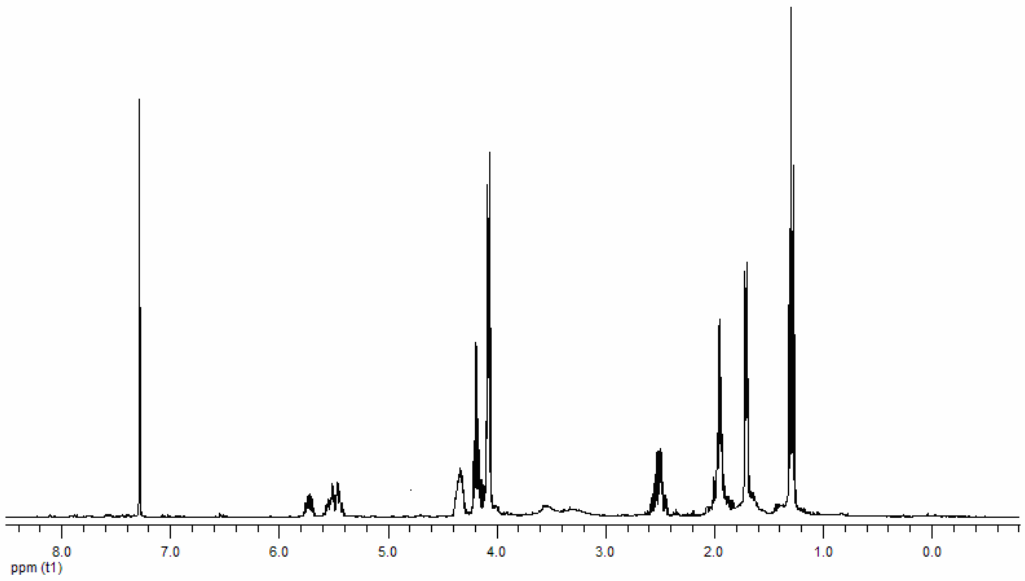


Appendix 2h

3-Hydroxy-4-[2-(2-hydroxy-pent-3-enyl)-
[1,3]dioxolan-2-yl]-butyric acid ethyl ester (305)

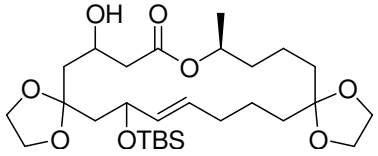


^{1}H NMR Spectrum (400 MHz, $CDCl_3$):

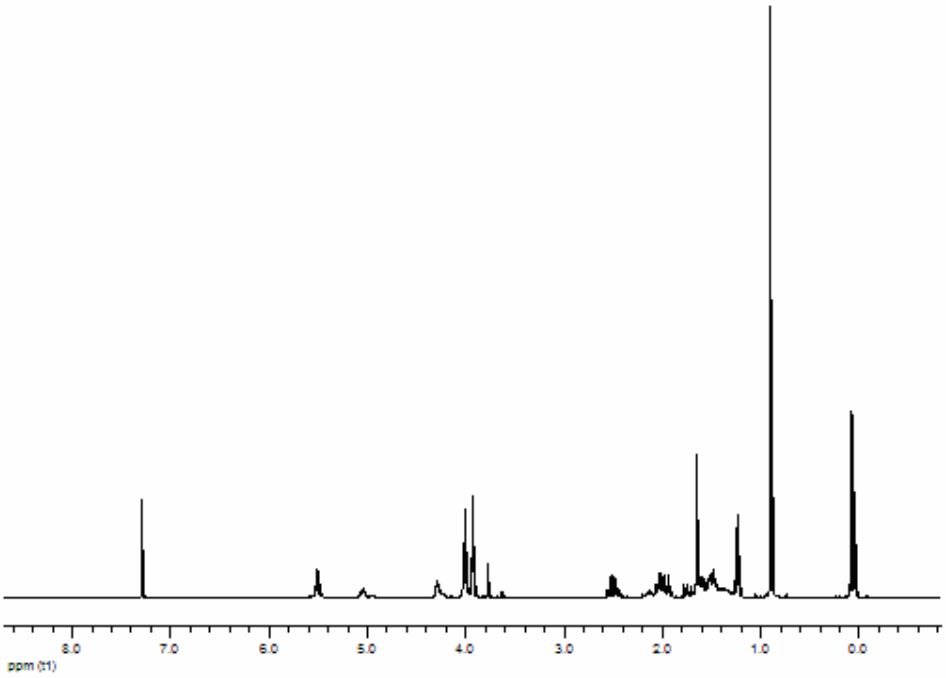


Appendix 2i

7-Hydroxy-25-(*tert*-butyldimethylsilanyloxy)-11-methyl-1,4,10,16,19-pentaoxa-dispiro[4.9.4.7]hexacos-23-ene-9-one (302)

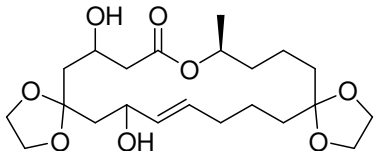


^{1}H NMR Spectrum (400 MHz, $CDCl_3$):

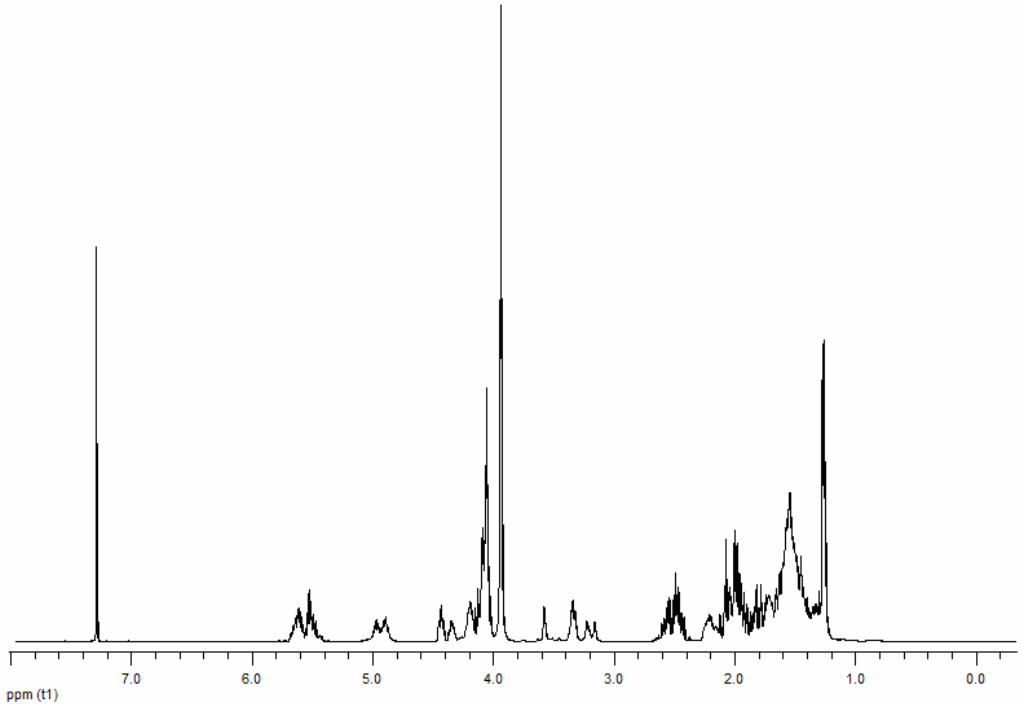


Appendix 2j

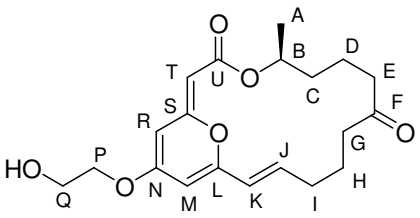
7,25-Dihydroxy-11-methyl-1,4,10,16,19-pentaoxa-dispiro[4.9.4.7]hexacos-23-ene-9-one (301)



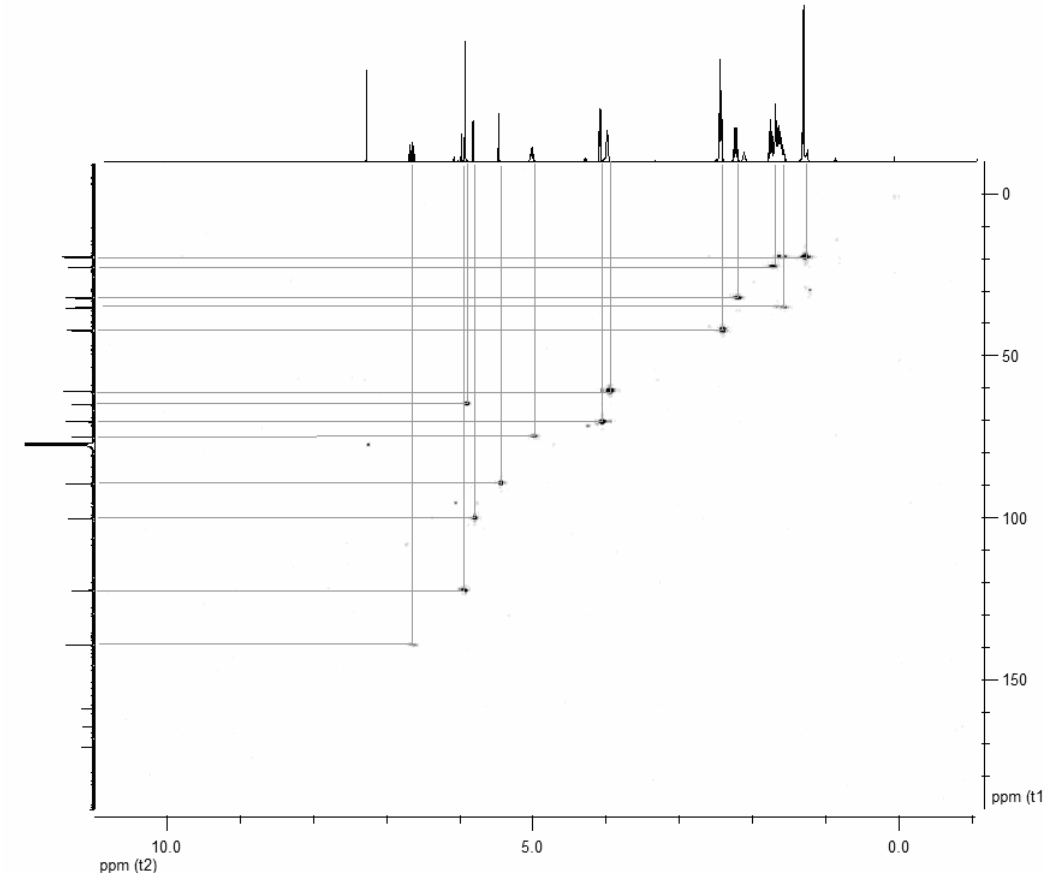
^{1}H NMR Spectrum (400 MHz, $CDCl_3$):



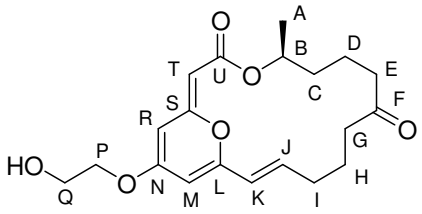
Appendix 3: Further NMR Data for Unexpected Product 'b' (**315**)

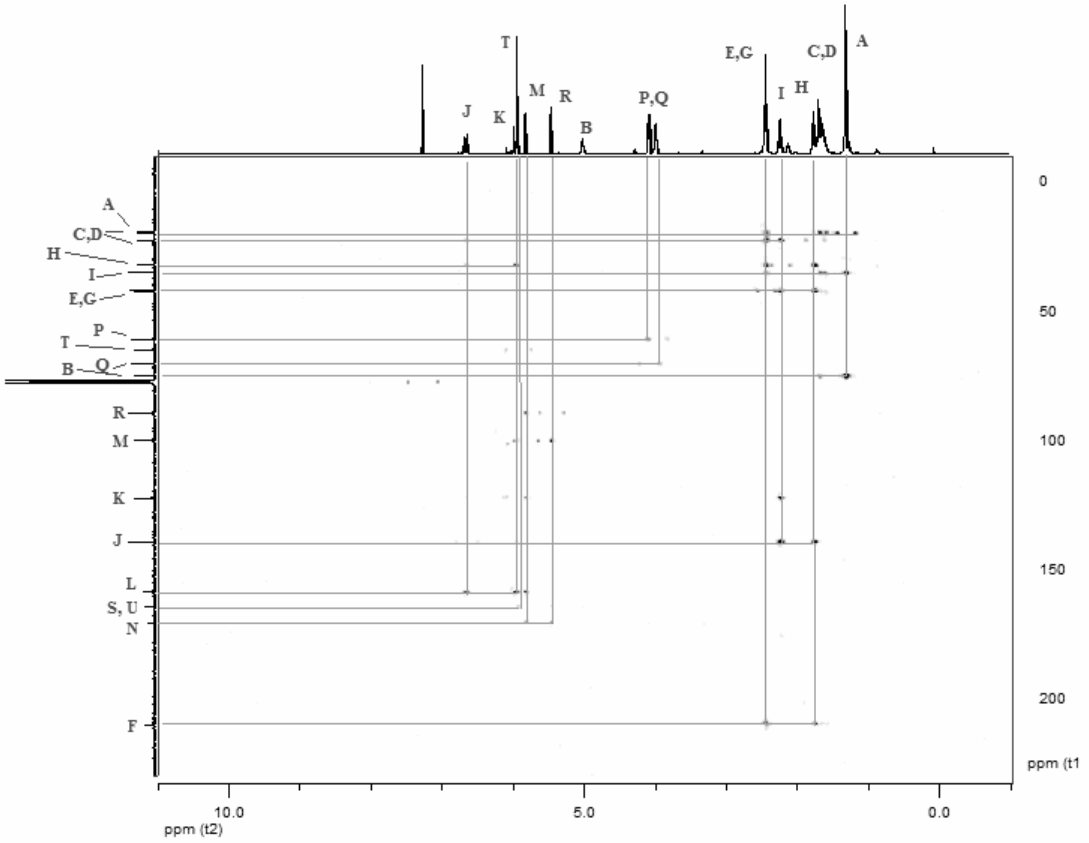


HMQC Spectrum:



HMBC Spectrum:





References

References

1) Birch, A. J., *Proc. Chem. Soc.* **1962**, 3.

2) Stob, M.; Baldwin, R. S.; Tuite, J.; Andrews, F. N.; Gillette, K. G., *Nature (London)* **1962**, *196*, 1318.

3) Turner, W. B.; Aldridge, D. C.; Galt, M. S.; Giles, D., *J. Chem. Soc., Org.* **1971**, 1623.

4) Takahashi, T.; Kasuga, K.; Takahashi, M.; Tsuji, J., *J. Am. Chem. Soc.* **1979**, *101*, 5072.

5) Mirrington, R. N.; Ritchie, E.; Shoppee, C. W.; Taylor, W. C.; Sternhell, S., *Tetrahedron Lett.* **1964**, 365.

6) Abbanat, D.; Leighton, M.; Maiese, W.; Jones, E. B. G.; Pearce, C.; Greenstein, M., *J. Antibiot.* **1998**, *51*, 296.

7) Delmotte, P.; Delmotte-Plaquee, J., *Nature (London)* **1953**, *171*, 344.

8) Mirocha, C. J.; Christensen, C. M.; Nelson, G. H., *Appl. Microbiol.* **1967**, *15*, 497.

9) Schoental, R., *Adv. Cancer Research* **1985**, *45*, 217.

10) Urry, W. H.; Wehrmeister, H. L.; Hodge, E. B.; Hidy, P. H., *Tetrahedron Lett.* **1966**, 3109.

11) Isaka, M.; Suyarnsestakorn, C.; Tanticharoen, M.; Kongsaeree, P.; Thebtaranonth, Y., *J. Org. Chem.* **2002**, *67*, 1561.

12) Hellwig, V.; Mayer-Bartschmid, A.; Mueller, H.; Greif, G.; Kleymann, G.; Zitzmann, W.; Tichy, H.-V.; Stadler, M., *J. Nat. Prod.* **2003**, *66*, 829.

13) Nair, M. S. R.; Carey, S. T., *Tetrahedron Lett.* **1980**, *21*, 2011.

14) Winssinger, N.; Barluenga, S., *Chem. Commun.* **2007**, 22.

15) Schlingmann, G.; Milne, L.; Williams, D. R.; Carter, G. T., *J. Antibiot.* **1998**, *51*, 303.

16) Albaugh, D.; Albert, G.; Bradford, P.; Cotter, V.; Froyd, J.; Gaughran, J.; Kirsch, D. R.; Lai, M.; Rehnig, A.; Sieverding, E.; Silverman, S., *J. Antibiot.* **1998**, *51*, 317.

17) Breinholt, J.; Jensen, G. W.; Nielsen, R. I.; Olsen, C. E.; Frisvad, J. C., *J. Antibiot.* **1993**, *46*, 1101.

18) Ito, M.; Maruhashi, M.; Sakai, N.; Mizoue, K.; Hanada, K., *J. Antibiot.* **1992**, *45*, 1559.

19) Ito, M.; Tsuchida, Y.; Mizoue, K.; Hanada, K., *J. Antibiot.* **1992**, *45*, 1566.

20) Kondo, H.; Kurama, M.; Nakajima, S.; Osada, K.; Ookura, A.; Suda, H. Estrogenic BE-26263 and its manufacture with Scedosporium apiospermum. 91-19106105032658, 19910705., 1993.

21) Collie, J. N., *Proc. Chem. Soc.* **1907**, *23*, 203.

22) Collie, J. N., *J. Chem. Soc.* **1891**, *59*, 179.

23) Collie, J. N., *J. Chem. Soc.* **1891**, *59*, 607.

24) Collie, J. N.; Hilditch, T. P., *J. Chem. Soc.* **1907**, *91*, 787.

25) Collie, J. N.; Hilditch, T. P., *Proc. Chem. Soc.* **1907**, *23*, 92.

26) Collie, J. N.; Chrystall, E. R., *Proc. Chem. Soc.* **1908**, *23*, 231.

27) Collie, J. N., *J. Chem. Soc.* **1900**, *77*, 961.

28) Robinson, R., *J. Roy. Soc. Arts* **1948**, 795.

29) Robinson, R., *The Structural Relations of Natural Products*. Clarendon Press, Oxford: **1955**.

30) Birch, A. J.; Donovan, F. W., *Austral. J. Chem.* **1953**, *6*, 360.

31) Birch, A. J., *Fortschr. Chem. Org. Naturst.* **1957**, *14*, 186.

32) Bentley, R.; Zwitkowits, P. M., *J. Am. Chem. Soc.* **1967**, *89*, 681.

33) Birch, A. J.; Massy-Westropp, R. A.; Moye, C. J., *Austral. J. Chem.* **1955**, *8*, 539.

34) Mirocha, C. J.; Pathre, S. V., *J. Food Prot.* **1979**, *42*, 821.

35) Vleggar, R. S. P. S., *Biosynthesis of Mycotoxins: A Study in Secondary Metabolism*. Academic Press: N.Y., **1980**.

36) Steele, J. A.; Lieberman, J. R.; Mirocha, C. J., *Can. J. Microbiol.* **1974**, *20*, 531.

37) Harris, T. M.; Harris, C. M., *Tetrahedron* **1977**, *33*, 2159.

38) Douglas, J. L.; Money, T., *Tetrahedron* **1967**, *23*, 3545.

39) Harris, T. M.; Murry, T. P.; Harris, C. M.; Gumulka, M., *J. Chem. Soc., Chem. Commun.* **1974**, 362.

40) Harris, T. M.; Carney, R. L., *J. Am. Chem. Soc.* **1966**, *88*, 2053.

41) Harris, T. M.; Carney, R. L., *J. Am. Chem. Soc.* **1966**, *88*, 5686.

42) Howarth, T. T.; Murphy, G. P.; Harris, T. M., *J. Am. Chem. Soc.* **1969**, *91*, 517.

43) Harris, T. M.; Carney, R. L., *J. Am. Chem. Soc.* **1967**, *89*, 6734.

44) Douglas, J. L.; Money, T., *Can. J. Chem.* **1967**, *45*, 1990.

45) Barrett, A. G. M.; Morris, T. M.; Barton, D. H. R., *J. Chem. Soc., Perkin Trans. 2* **1980**, 2272.
46) Scott, A. I.; Guilford, H.; Ryan, J. J.; Skingle, D., *Tetrahedron* **1971**, *27*, 3025.
47) Scott, A. I.; Pike, D. G.; Ryan, J. J.; Guilford, H., *Tetrahedron* **1971**, *27*, 3051.
48) Scott, A. I.; Guilford, H.; Skingle, D., *Tetrahedron* **1971**, *27*, 3039.
49) Fleet, G. W. J.; Harding, P. J. C., *Tetrahedron Lett.* **1979**, 975.
50) Bram, G., *Tetrahedron Lett.* **1967**, 4069.
51) Schmidt, U.; Schwochau, M., *Monatsh. Chem.* **1967**, *98*, 1492.
52) Schmidt, U.; Schwochau, M., *Tetrahedron Lett.* **1967**, 4491.
53) Stetter, H.; Vestner, S., *Chem. Ber.* **1964**, *97*, 169.
54) Stephen, J. F.; Marcus, E., *J. Org. Chem.* **1970**, *35*, 258.
55) Griffin, D. A.; Staunton, J., *J. Chem. Soc., Chem. Commun.* **1975**, 675.
56) Chan, T.-H.; Brownbridge, P., *J. Chem. Soc., Chem. Commun.* **1981**, 20.
57) Chan, T. H.; Chaly, T., *Tetrahedron Lett.* **1982**, *23*, 2935.
58) Batelaan, J. G., *Synth. Commun.* **1976**, *6*, 81.
59) Brownbridge, P.; Chan, T. H.; Brook, M. A.; Kang, G. J., *Can. J. Chem.* **1983**, *61*, 688.
60) Chan, T. H.; Stossel, D., *J. Org. Chem.* **1986**, *51*, 2423.
61) Yamaguchi, M.; Shibato, K.; Hirao, I., *Chem. Lett.* **1985**, 1145.
62) Yamaguchi, M.; Shibato, K.; Nakashima, H.; Minami, T., *Tetrahedron* **1988**, *44*, 4767.
63) Tatsuta, K.; Kojima, N.; Chino, M.; Kawazoe, S.; Nakata, M., *Tetrahedron Lett.* **1993**, *34*, 4961.
64) Brimble, M. A.; Nairn, M. R.; Prabaharan, H., *Tetrahedron* **2000**, *56*, 1937.
65) Krohn, K.; Bernhard, S.; Floerke, U.; Hayat, N., *J. Org. Chem.* **2000**, *65*, 3218.
66) Barrett, A. G. M.; Atkinson, C., *Unpublished results.*, 2004.
67) Vlattas, I.; Harrison, I. T.; Tokes, L.; Fried, J. H.; Cross, A. D., *J. Org. Chem.* **1968**, *33*, 4176.
68) Taub, D.; Girotra, N. N.; Hoffsommer, R. D., Jr.; Kuo, C.-H.; Slates, H. L.; Weber, S.; Wendler, N. L., *Tetrahedron* **1968**, *24*, 2443.
69) Masamune, S.; Kamata, S.; Schilling, W., *J. Am. Chem. Soc.* **1975**, *97*, 3515.
70) Arnold, L. D.; Assil, H. I.; Vederas, J. C., *J. Am. Chem. Soc.* **1989**, *111*, 3973.
71) Corey, E. J.; Nicolaou, K. C., *J. Am. Chem. Soc.* **1974**, *96*, 5614.

72) Hitchcock, S. A.; Pattenden, G., *J. Chem. Soc., Perkin Trans. 2* **1992**, 1323.

73) Takahashi, T.; Ikeda, H.; Tsuji, J., *Tetrahedron Lett.* **1981**, *22*, 1363.

74) Takahashi, T.; Nagashima, T.; Ikeda, H.; Tsuji, J., *Tetrahedron Lett.* **1982**, *23*, 4361.

75) Rao, A. V. R.; Deshmukh, M. N.; Sharma, G. V. M., *Tetrahedron* **1987**, *43*, 779.

76) Hitchcock, S. A.; Pattenden, G., *Tetrahedron Lett.* **1990**, *31*, 3641.

77) Kalivretenos, A.; Stille, J. K.; Hegedus, L. S., *J. Org. Chem.* **1991**, *56*, 2883.

78) Fuerstner, A.; Thiel, O. R.; Kindler, N.; Bartkowska, B., *J. Org. Chem.* **2000**, *65*, 7990.

79) Taub, D.; Girotra, N. N.; Hoffsommer, R. D.; Kuo, C. H.; Slates, H. L.; Weber, S.; Wendler, N. L., *Tetrahedron* **1968**, *24*, 2443.

80) Garbaccio, R. M.; Stachel, S. J.; Baeschlin, D. K.; Danishefsky, S. J., *J. Am. Chem. Soc.* **2001**, *123*, 10903.

81) Barluenga, S.; Lopez, P.; Moulin, E.; Winssinger, N., *Angew. Chem., Int. Ed.* **2004**, *43*, 3467.

82) Hwu, J. R.; Leu, L. C.; Robl, J. A.; Anderson, D. A.; Wetzel, J. M., *J. Org. Chem.* **1987**, *52*, 188.

83) Buchwald, S. L.; LaMaire, S. J., *Tetrahedron Lett.* **1987**, *28*, 295.

84) Furstner, A.; Thiel, O. R.; Kindler, N.; Bartkowska, B., *J. Org. Chem.* **2000**, *65*, 7990.

85) Keinan, E.; Sinha, S. C.; Sinha-Bagchi, A., *J. Chem. Soc., Perkin Trans. 2* **1991**, 3333.

86) Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A., *J. Org. Chem.* **1991**, *56*, 2656.

87) Liu, R.; Berglund, P.; Hoegberg, H.-E., *Tetrahedron: Asymmetry* **2005**, *16*, 2607.

88) Kourist, R.; Gonzalez-Sabin, J.; Liz, R.; Rebolledo, F., *Adv. Synth. Catal.* **2005**, *347*, 695.

89) Dale, J. A.; Dull, D. L.; Mosher, H. S., *J. Org. Chem.* **1969**, *34*, 2543.

90) Lenger, S.; Linke, S.; *AstraZeneca, Bristol*.

91) Mitsunobu, O., *Synthesis* **1981**, 1.

92) Pamies, O.; Backvall Jan, E., *J. Org. Chem.* **2002**, *67*, 1261.

93) Martin-Matute, B.; Edin, M.; Bogar, K.; Baeckvall, J.-E., *Angew. Chem., Int. Ed.* **2004**, *43*, 6535.

94) Paetzold, J.; Backvall Jan, E., *J. Am. Chem. Soc.* **2005**, *127*, 17620.

95) Brutcher, F. V., Jr.; Vanderwerff, W. D.; Dreikorn, B., *J. Org. Chem.* **1972**, *37*, 297.

96) Wang, W.; Xiong, C.; Hruby, V. J., *Tetrahedron Lett.* **2001**, *42*, 3159.

97) Mosettig, E.; Mozingo, R., *Org. Reactions* **1948**, *4*, 362.

98) Corey, E. J.; Fuchs, P. L., *Tetrahedron Lett.* **1972**, 3769.

99) Fritsch, P., *Ann. Chem.* **1894**, *279*, 310.

100) Ohira, S., *Synth. Commun.* **1989**, *19*, 561.

101) Gilbert, J. C.; Weerasooriya, U., *J. Org. Chem.* **1982**, *47*, 1837.

102) Roth, G. J.; Liepold, B.; Mueller, S. G.; Bestmann, H. J., *Synthesis* **2004**, 59.

103) Callant, P.; D'Haenens, L.; Vandewalle, M., *Synth. Commun.* **1984**, *14*, 155.

104) McElwee-White, L.; Dougherty, D. A., *J. Am. Chem. Soc.* **1984**, *106*, 3466.

105) Nicolaou, K. C.; Fylaktakidou, K. C.; Monenschein, H.; Li, Y.; Weyershausen, B.; Mitchell, H. J.; Wei, H.-X.; Guntupalli, P.; Hepworth, D.; Sugita, K., *J. Am. Chem. Soc.* **2003**, *125*, 15433.

106) Peterson, D. J., *J. Org. Chem.* **1968**, *33*, 780.

107) Ohira, S.; Okai, K.; Moritani, T., *J. Chem. Soc., Chem. Commun.* **1992**, 721.

108) Cordova, A.; Janda, K. D., *J. Org. Chem.* **2001**, *66*, 1906.

109) Nanda, S.; Scott, A. I., *J. Mol. Catal. B: Enzym.* **2004**, *30*, 1.

110) Krasik, P., *Tetrahedron Lett.* **1998**, *39*, 4223.

111) Bandgar, B. P.; Sadavarte, V. S., *J. Chem. Res., Synop.* **2001**, 16.

112) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M., *J. Am. Chem. Soc.* **1990**, *112*, 3875.

113) Grubbs, R. H.; Miller, S. J.; Fu, G. C., *Acc. Chem. Res.* **1995**, *28*, 446.

114) Taylor, R. E.; Haley, J. D., *Tetrahedron Lett.* **1997**, *38*, 2061.

115) Fuerstner, A.; Langemann, K., *J. Org. Chem.* **1996**, *61*, 8746.

116) Barrett, A. G. M.; Beall, J. C.; Gibson, V. C.; Giles, M. R.; Walker, G. L. P., *Chem. Commun.* **1996**, 2229.

117) Nicolaou, K. C.; He, Y.; Vourloumis, D.; Vallberg, H.; Roschangar, F.; Sarabia, F.; Ninkovic, S.; Yang, Z.; Trujillo, J. I., *J. Am. Chem. Soc.* **1997**, *119*, 7960.

118) Herisson, J. L.; Chauvin, Y., *Makromol. Chem.* **1971**, *141*, 161.

119) Katz, T. J.; Hacker, S. M.; Kendrick, R. D.; Yannoni, C. S., *J. Am. Chem. Soc.* **1985**, *107*, 2182.

120) Grubbs, R. H., *Handbook of Metathesis*. Wiley-Vch: Weinheim, **2003**.

121) Katz, T. J.; Sivavec, T. M., *J. Am. Chem. Soc.* **1985**, *107*, 737.

122) Kinoshita, A.; Mori, M., *J. Org. Chem.* **1996**, *61*, 8356.

123) Hansen, E. C.; Lee, D., *J. Am. Chem. Soc.* **2003**, *125*, 9582.

124) Hansen, E. C.; Lee, D., *J. Am. Chem. Soc.* **2004**, *126*, 15074.

125) Mori, M.; Sakakibara, N.; Kinoshita, A., *J. Org. Chem.* **1998**, *63*, 6082.

126) Kinoshita, A.; Sakakibara, N.; Mori, M., *J. Am. Chem. Soc.* **1997**, *119*, 12388.

127) Lippstreu, J. J.; Straub, B. F., *J. Am. Chem. Soc.* **2005**, *127*, 7444.

128) Morimoto, Y.; Kitao, S.; Okita, T.; Shoji, T., *Org. Lett.* **2003**, *5*, 2611.

129) Ahrendt, K. A.; Williams, R. M., *Org. Lett.* **2004**, *6*, 4539.

130) Yang, D.; Wong, M.-K.; Yip, Y.-C., *J. Org. Chem.* **1995**, *60*, 3887.

131) Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y. L., *J. Am. Chem. Soc.* **2002**, *124*, 2245.

132) Frigerio, M.; Santagostino, M.; Sputore, S., *J. Org. Chem.* **1999**, *64*, 4537.

133) Petasis, N. A.; Bzowej, E. I., *J. Am. Chem. Soc.* **1990**, *112*, 6392.

134) Payack, J. F.; Huffman, M. A.; Cai, D.; Hughes, D. L.; Collins, P. C.; Johnson, B. K.; Cottrell, I. F.; Tuma, L. D., *Org. Process. Res.* **2004**, *8*, 256.

135) Ndakala, A. J.; Hashemzadeh, M.; So, R. C.; Howell, A. R., *Org. Lett.* **2002**, *4*, 1719.

136) Evarts, J. B.; Fuchs, P. L., *Tetrahedron Lett.* **2001**, *42*, 3673.

137) Frohn, M.; Dalkiewicz, M.; Tu, Y.; Wang, Z.-X.; Shi, Y., *J. Org. Chem.* **1998**, *63*, 2948.

138) Neipp, C. E.; Martin, S. F., *J. Org. Chem.* **2003**, *68*, 8867.

139) Brenneman, J. B.; Machauer, R.; Martin, S. F., *Tetrahedron* **2004**, *60*, 7301.

140) Andersson, P. G.; Sharpless, K. B., *J. Am. Chem. Soc.* **1993**, *115*, 7047.

141) Nicolaou, K. C.; Bulger, P. G.; Brenzovich, W. E., *Org. Biomol. Chem.* **2006**, *4*, 2158.

142) Toyooka, N.; Okumura, M.; Nemoto, H., *J. Org. Chem.* **2002**, *67*, 6078.

143) Royer, F.; Vilain, C.; Elkaiem, L.; Grimaud, L., *Org. Lett.* **2003**, *5*, 2007.

144) Dess, D. B.; Martin, J. C., *J. Org. Chem.* **1983**, *48*, 4155.

145) Sakamoto, S.; Sakazaki, H.; Hagiwara, K.; Kamada, K.; Ishii, K.; Noda, T.; Inoue, M.; Hirama, M., *Angew. Chem., Int. Ed.* **2004**, *43*, 6505.

146) Hoye, T. R.; Hu, M., *J. Am. Chem. Soc.* **2003**, *125*, 9576.

147) Ranu, B. C.; Jana, U.; Majee, A., *Tetrahedron Lett.* **1999**, *40*, 1985.

148) DattaGupta, A.; Singh, R.; Singh, V. K., *Synlett* **1996**, 69.

149) Julian, L. D.; Newcom, J. S.; Roush, W. R., *J. Am. Chem. Soc.* **2005**, *127*, 6186.

150) Vincent, G.; Mansfield, D. J.; Vors, J.-P.; Ciufolini, M. A., *Org. Lett.* **2006**, *8*, 2791.

151) Mehta, G.; Pallavi, K.; Umarye, J. D., *Chem. Commun.* **2005**, 4456.

152) Mintz, M. J.; Walling, C., *Org. Synth.* **1969**, *49*, 9.

153) Milovanovic, J. N.; Vasojevic, M.; Gojkovic, S., *J. Chem. Soc., Perkin Trans. 2* **1988**, 533.

154) Matsuo, J.-i.; Iida, D.; Yamanaka, H.; Mukaiyama, T., *Tetrahedron* **2003**, *59*, 6739.

155) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F., *J. Chem. Soc.* **1915**, *107*, 1080.

156) Pearson, A. J.; Lai, Y. S.; Lu, W.; Pinkerton, A. A., *J. Org. Chem.* **1989**, *54*, 3882.

157) Karimi, B.; Rajabi, J., *Org. Lett.* **2004**, *6*, 2841.

158) Muzart, J., *Synthesis* **1993**, 11.

159) Paterson, I.; Cowden, C. J.; Rahn, V. S.; Woodrow, M. D., *Synlett* **1998**, 915.

160) Piva, O.; Amougay, A.; Peter, J. P., *Tetrahedron Lett.* **1991**, *32*, 3993.

161) Kocienski, P.; Narquizian, R.; Raubo, P.; Smith, C.; Farrugia, L. J.; Muir, K.; Boyle, F. T., *J. Chem. Soc., Perkin Trans. 1* **2000**, 2357.

162) Harris, C. R.; Kuduk, S. D.; Savin, K.; Balog, A.; Danishefsky, S. J., *Tetrahedron Lett.* **1999**, *40*, 2263.

163) Voight, E. A.; Seradj, H.; Roethle, P. A.; Burke, S. D., *Org. Lett.* **2004**, *6*, 4045.

164) Curran, D. P.; Yu, H., *Synthesis* **1992**, 123.

165) Nicolaou, K. C.; Montagnon, T.; Baran, P. S., *Angew. Chem., Int. Ed.* **2002**, *41*, 1386.

166) Chai, L.; Zhao, Y.; Sheng, Q.; Liu, Z.-Q., *Tetrahedron Lett.* **2006**, *47*, 9283.

167) Singleton, D. A.; Hang, C., *J. Org. Chem.* **2000**, *65*, 7554.

168) Shing, T. K. M.; Yeung, Y.-Y.; Su, P. L., *Org. Lett.* **2006**, *8*, 3149.

169) Tullis, J. S.; Vares, L.; Kann, N.; Norrby, P.-O.; Rein, T., *J. Org. Chem.* **1998**, *63*, 8284.

170) Tan, D. S.; Dudley, G. B.; Danishefsky, S. J., *Angew. Chem., Int. Ed.* **2002**, *41*, 2185.

171) Clemens, R. J.; Hyatt, J. A., *J. Org. Chem.* **1985**, *50*, 2431.

172) Hyatt, J. A.; Feldman, P. L.; Clemens, R. J., *J. Org. Chem.* **1984**, *49*, 5105.

173) Singer, R. A.; Carreira, E. M., *J. Am. Chem. Soc.* **1995**, *117*, 12360.

174) Sato, M.; Sakaki, J.; Sugita, Y.; Yasuda, S.; Sakoda, H.; Kaneko, C., *Tetrahedron* **1991**, *47*, 5689.

175) Katritzky, A. R.; Wang, Z.; Wang, M.; Hall, C. D.; Suzuki, K., *J. Org. Chem.* **2005**, *70*, 4854.

176) Denmark, S. E.; Heemstra, J. R., Jr.; Beutner, G. L., *Angew. Chem., Int. Ed.* **2005**, *44*, 4682.

177) Barrett, A. G. M.; Bassett, J.-F., *Unpublished results*, 2007.

178) Barrett, A. G. M.; Navarro-Fuertes, I., *Unpublished results*, 2007.

179) McNab, H., *Chem. Soc. Rev.* **1978**, *7*, 345.

180) Corey, E. J.; Cho, H.; Ruecker, C.; Hua, D. H., *Tetrahedron Lett.* **1981**, *22*, 3455.

181) Connon, S. J.; Blechert, S., *Angew. Chem., Int. Ed.* **2003**, *42*, 1900.

182) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H., *J. Am. Chem. Soc.* **2000**, *122*, 3783.

183) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M., *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

184) Suzuki, K.; Tomooka, K.; Katayama, E.; Matsumoto, T.; Tsuchihashi, G., *J. Am. Chem. Soc.* **1986**, *108*, 5221.

185) Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C., *J. Org. Chem.* **1986**, *51*, 432.

186) Carr, D. B.; Schwartz, J., *J. Am. Chem. Soc.* **1979**, *101*, 3521.

187) Kametani, T.; Huang, S. P.; Nakayama, A.; Honda, T., *J. Org. Chem.* **1982**, *47*, 2328.

188) Regitz, M.; Anschuetz, W.; Liedhegener, A., *Chem. Ber.* **1968**, *101*, 3734.

189) Ames, D. E.; Goodburn, T. G., *J. Chem. Soc., Org.* **1967**, 1556.

190) Linstead, R. P.; Rydon, H. N., *J. Chem. Soc.* **1934**, 1995.

191) Mookherjee, B. D.; Patel, R. R.; Ledig, W. O., *J. Org. Chem.* **1971**, *36*, 4124.

192) Newman, M. S.; Magerlein, B. J.; Wheatley, W. B., *J. Am. Chem. Soc.* **1946**, *68*, 2112.