Towards the synthesis of anthecularin and anthecotulides

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Abstract

Towards the synthesis of anthecularin and anthecotulides

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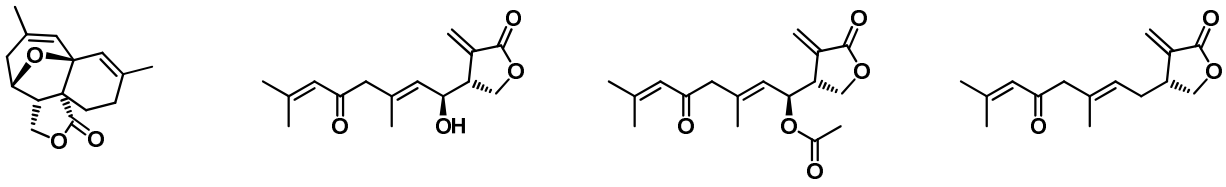
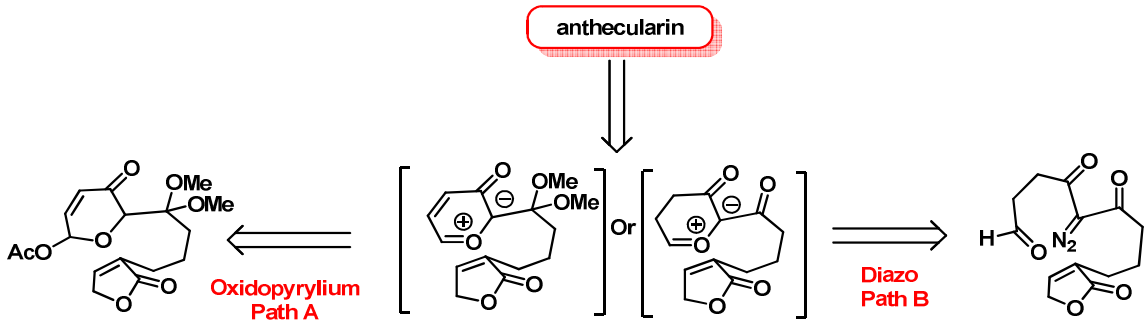
The work presented in this thesis mainly describes the discovery and development of methodology for the synthesis of anthecularin and anthecotulides, a family of unusual sesquiterpene lactones.

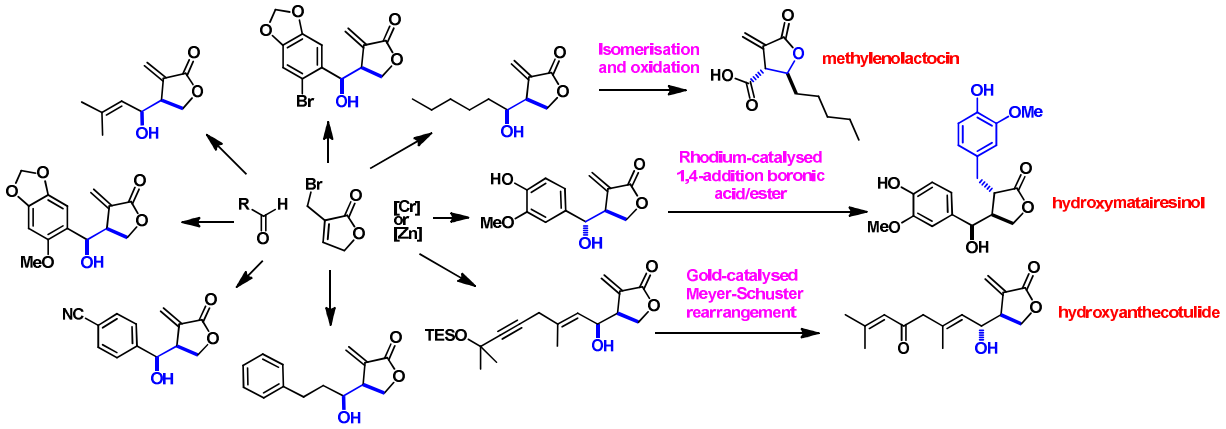


Firstly, two 1,3-dipolar cycloaddition approaches toward anthecularin have been evaluated, using either oxidopyrylium ylide chemistry (Path A) or carbonyl ylides, generated by rhodium-catalysed decomposition of diazo ketones (Path B). Synthesis of the key precursor for the diazo strategy was achieved but unfortunately no desired cycloadduct was isolated.

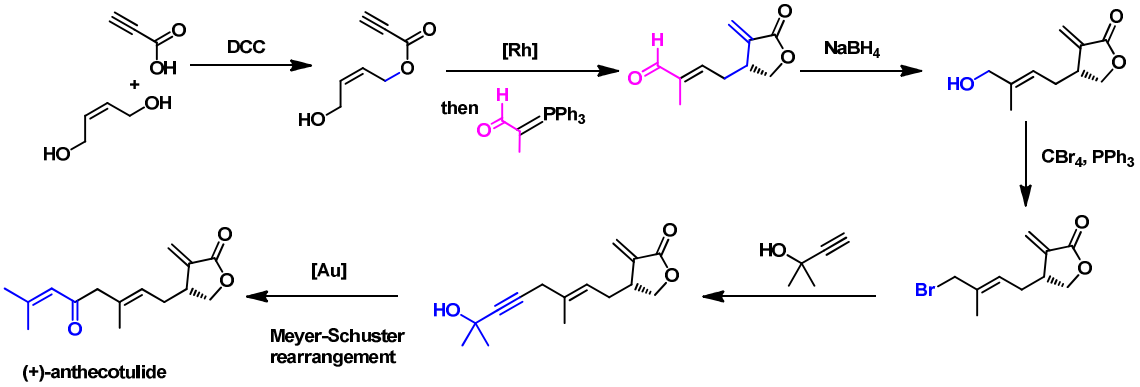


Secondly, an experimentally straightforward method to stereoselectively synthesise β-hydroxymethyl-α-methylene-γ-butyrolactones was developed using chromium or zinc. The synthetic utility of this methodology was demonstrated in syntheses of (±)-

methylenolactocin, (±)-hydroxymatairesinol and, ultimately, (±)-hydroxyanthecotulide using a gold-catalysed Meyer-Schuster rearrangement.



Finally, the first asymmetric synthesis of (+)-anthecotulide has been achieved, in 6 steps from commercially available materials. During this synthesis the absolute configuration was established. Furthermore, a novel rhodium-catalysed enantioselective ene-yne cycloisomerisation was used to form the α-methylene-γ-butyrolactone core.



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I would like to thank my industrial supervisor, Barry Clark, for helpful advice and great support during my placement at Eli Lilly.

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Abbreviations

μ	micro
ABSA	*p*-acetamidobenzenesulfonyl azide
acac	acetylacetone
Ac	acetyl
AcOH	acetic acid
aq.	aqueous
ATPH	aluminium tris(2,6-diphenyl phenoxide)
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINIM-4Me-2NQ	*N*,*N*′-bis(2-quinolylmethylene)-1,1′-binaphthyl-2,2′-diamine–Ni(II)
Boc	*tert*-butyloxycarbonyl
bp	boiling point
brsm	based on recovered starting material
t-Bu	*tert*-butyl
Bn	benzyl
Bz	benzoyl
c	celsius
cap	caprolactam
cat	catalyst/catalytic
CBz	carboxybenzyl
CI	chemical ionization
cod	cyclooctadiene
Cp	cyclopentadienyl
m-CPBA	*m*-chloroperoxybenzoic acid
Δ	heat
d	days
DBU	1,8-diazabicyclo[5,4,0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DDBNP	1,1-binaphthyl-2,2-diylphosphate
DIAD	diisopropyl azodicarboxylate

DMMAP	dimethylallyl diphosphate
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
dppf	1,1'-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
er	enantiomeric ratio
EI	electron impact
equiv.	equivalent(s)
ES	electrospray
Et	ethyl
GPP	geranyl diphosphate
h	hour(s)
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
IR	infra-red (spectroscopy)
LDA	lithium diisopropylamide
lit.	literature
M	molar concentration (mol/dm^3)
m	medium/metal
Me	methyl
min.	minute(s)
mole	mole/molar
MOM	methoxymethyl ether
m.p.	melting point
MS	mass spectrometry/molecular sieve
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
NMO	*N*-methylmorpholine
p-	*para*-
PCC	pyridinium chlorochromate

PDC	pyridinium dichromate
Ph	phenyl
ppm	parts per million
Pr	propyl
i-Pr	isopropyl
p-TSA	*para*-toluenesulfonic acid
R	generic alkyl group
rac	racemic
R*f*	retention factor
rt	room temperature
s	strong
sat.	saturated
SLs	sesquiterpene lactones
TBAB	tetrabutyl ammonium bromide
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TC-PTTL	*N*-tetrachlorophthaloyl-*tert*-leucinate
TES	triethylsilyl
TFP	tris(2-furyl)phosphane
TMS	trimethylsilyl
TPAP	tetra propyl ammonium perruthanate
TsCl	*para*-toluenesulfonyl chloride
THF	tetrahydrofuran
TLC	thin layer chromatography
Troc	2,2,2-trichlorethoxycarbonyl
TS	transition state
w	weak

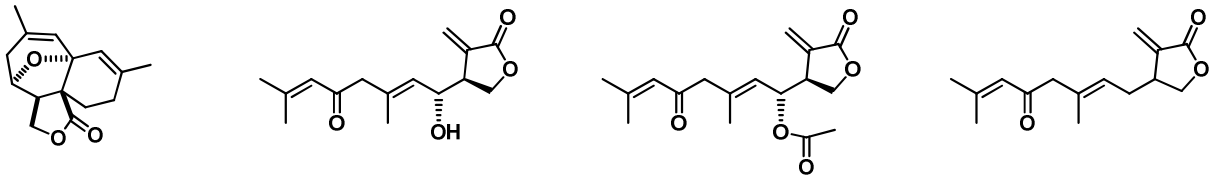
Stereochemistry

Throughout this thesis relative stereochemistry will be represented by uniform lines, whereas absolute stereochemistry will be represented by tapered lines.[1]

Contents

Chapter 1. Introduction

This thesis describes the discovery and development of methodology for the synthesis of anthecularin and anthecotulides,[2,3] a family of unusual sesquiterpene lactones (Figure 1.1: the relative and absolute stereochemistry of these natural products are drawn as originally proposed in the lit.[4,5,6]). This introduction gives brief background on sesquiterpene lactones (SLs), followed by a more detailed introduction on anthecularin and anthecotulides; their bioactivity and their proposed biosynthesis.



(1) anthecularin

(2) hydroxyanthecotulide (originally proposed structure (3S, 4R))

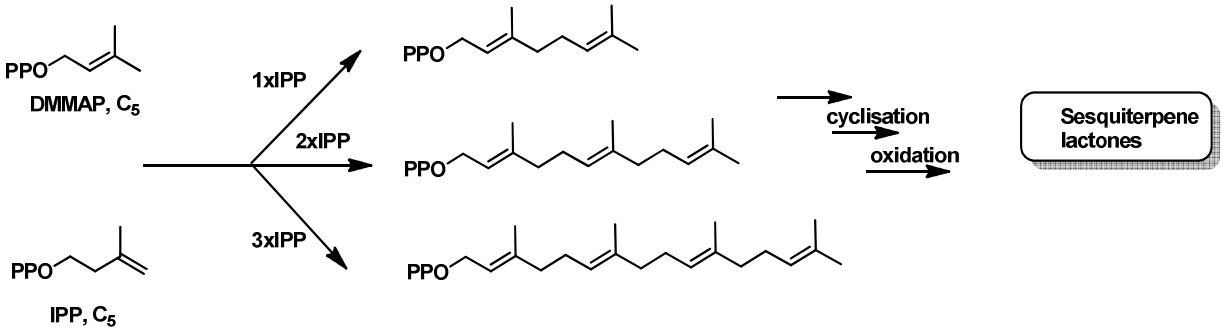
(3) acetoxyanthecotulide (originally proposed structure (3S, 4R))

(4) anthecotulide

Figure 1.1 Anthecularin and anthecotulides.

1.1 Sesquiterpene lactones

SLs constitute a large and varied group of biologically active compounds[7] that are found in a number of plant families such as *Acanthaceae*, *Anacardiaceae*, *Apiaceae*, *Euphorbiaceae*, *Lauraceae*, *Magnoliaceae*, *Menispermaceae*, *Rutaceae*, *Winteraceae* and *Hepatideae*. Sesquiterpene lactones are a class of naturally occurring plant terpenoids that represent a diverse and unique class of natural products and are important constituents of essential oils. They are typically biosynthesised by head-to-tail condensation of 3 isoprene units followed by cyclisation and oxidative transformations to produce *cis*- or *trans*-fused lactones (Scheme 1.1).



Scheme 1.1 Formation of sesquiterpene lactones from isoprene units.

These compounds tend to be classified by their carbocyclic skeletons into pseudoguainolides, guaianolides, germanocranolides, eudesmanolides, heliangolides and hyptocretenolides (Figure 1.2). However, SLs are found to have a variety of other skeletal arrangements. Different plant species generally produce SLs of one skeletal type concentrated in leaves and flower heads.

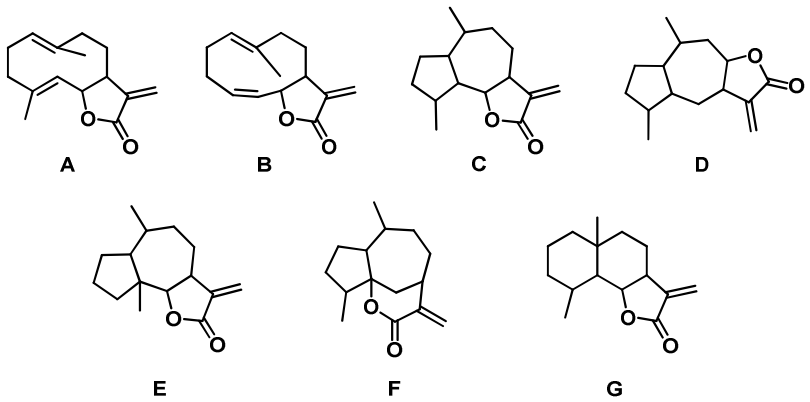


Figure 1.2 Skeletal composition of some sesquiterpene lactones: **A**: Germacranolides **B**: Heliangolides **C**+**D**: Guaianolides **E**: Pseudoguaianolides **F**: Hypocretenolides **G**: Eudesmanolides.

A common feature found in a number of SLs is a γ-lactone ring containing, in several cases, an α-methylene group (Figure 1.3). Other commonly encountered modifications are the incorporation of hydroxyl or esterified hydroxyl groups and epoxide rings. A small number of SLs occur in glycoside form, some containing halogen or sulfur atoms.

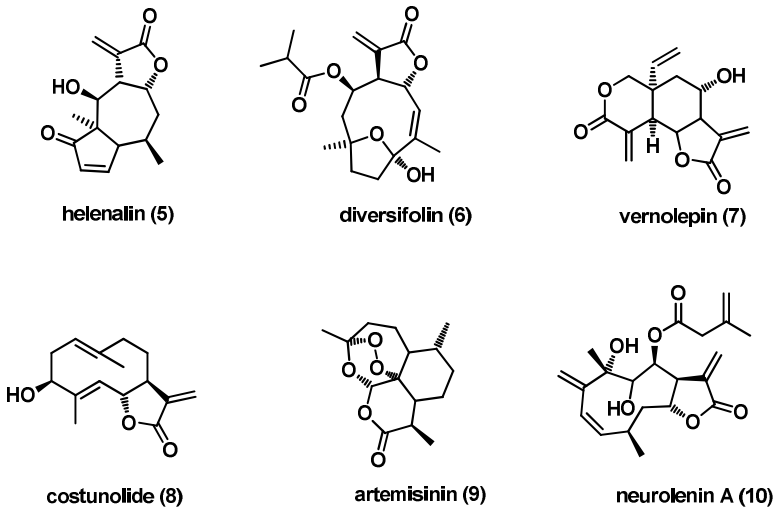


Figure 1.3 Biodiversity of sesquiterpenes lactones.

1.2. Biological activity of sesquiterpene lactones

The wide selection of SL chemical structures is mirrored in the diversity of their biological activities.[8] Compounds that have cytotoxic, anti-tumourgenic, anti-bacterial and anti-fungal properties have all been identified. A number of SLs are known to be toxic to human and animal parasites, insects and vertebrates. Many of these compounds, or plants containing them, cause allergic contact dermatitis in humans despite the fact that some of them have been used for their pharmacological activity. SLs also act as plant growth regulators and are responsible for the allelopathic properties of many plants. The variety of activities displayed by SLs suggests their significance in the evolution of plants as deterrents against herbivores and anti-fungal or anti-bacterial allelopathic agents. The majority of SLs have been shown to exhibit cytotoxic activity, with studies showing that some cytotoxic SLs react with thiols, such as cystiene residues in proteins, by a rapid Michael-type addition. These additions are chemically controlled by the α,β-unsaturated carbonyl system present in the SLs. These studies are in accordance with the theory that SLs inhibit tumour growth by selective alkylation of growth regulatory biological macromolecules such as key enzymes, which control cell division and therefore inhibit a number of cell functions, which forces the cell

into apoptosis. It is reasonable to believe that the differing activity of specific SLs could be rationalised by differing numbers of alkylating structural features. However, other factors such as lipophilicity, molecular geometry and chemical environment, or the target sulfhydryl could also play a role in the activity of SLs.

1.3. Introduction of anthecotulides and anthecularin

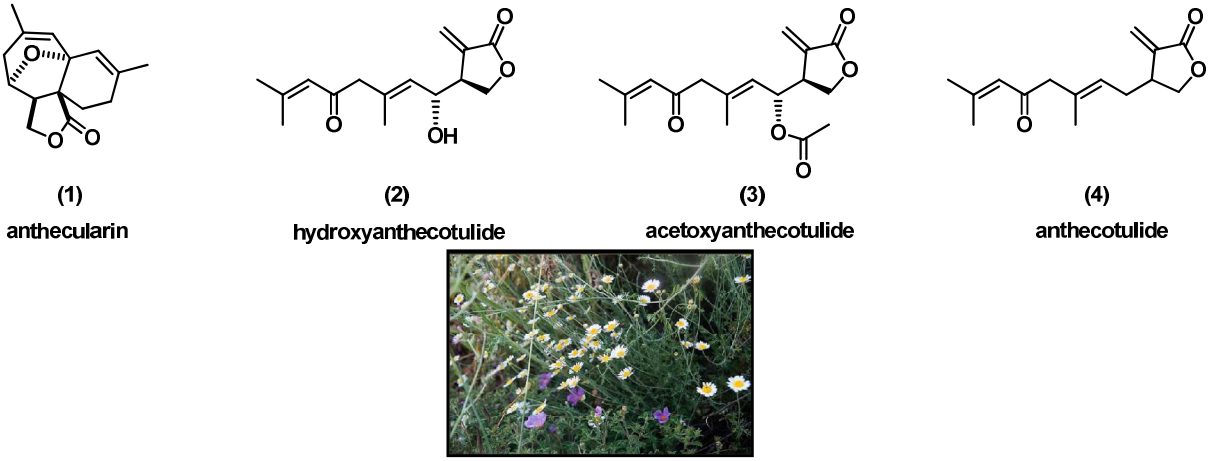
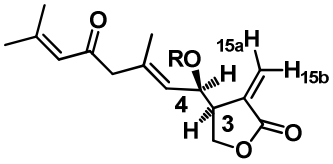


Figure 1.4: Anthecularin (**1**) and anthecotulides (top) and picture of Greek *Anthemis auriculata* (bottom).

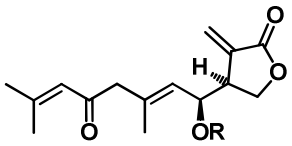
- Anthecularin (**1**), reported in 2007,[4] is an optically active minor sesquiterpene lactone with a novel ring system, isolated from the Greek *Anthemis auriculata* (Asteraceae, Figure 1.4). Its structure was deduced by NMR, HRMS and X-ray crystallography. However, due to the small amounts isolated (1.5 mg), the absolute configuration could not be determined

- Hydroxyanthecotulide (**2**) and acetoxyanthecotulide (**3**), reported in 2006, are optically active irregular linear sesquiterpene lactones isolated from the Greek *Anthemis auriculata*.[5] The structure of (**2)** and (**3)** were determined by high field NMR analysis. NOE studies show interactions between H-3/H-15b and H-4/H-15b, indicating that these protons have the same orientation (Figure 1.5). The absolute configuration at the secondary hydroxyl centre was assigned using Mosher's method.[9] Despite the fact that both diastereoisomers are drawn (in

error) in the isolation paper (Figure 1.5), we believe that the configuration of the stereocentre on the ring can be reasonably deduced from an X-ray structure of the biosynthetically related product anthecularin (**1**) (see Section 1.4, below). In an attempt to clarify this situation, both diastereoisomers were targeted.



(4*R*, 3*S*)
Structure in the Mosher Ester study (proposed structure)



(4*S*, 3*S*)
Structure in Chemical Abstracts

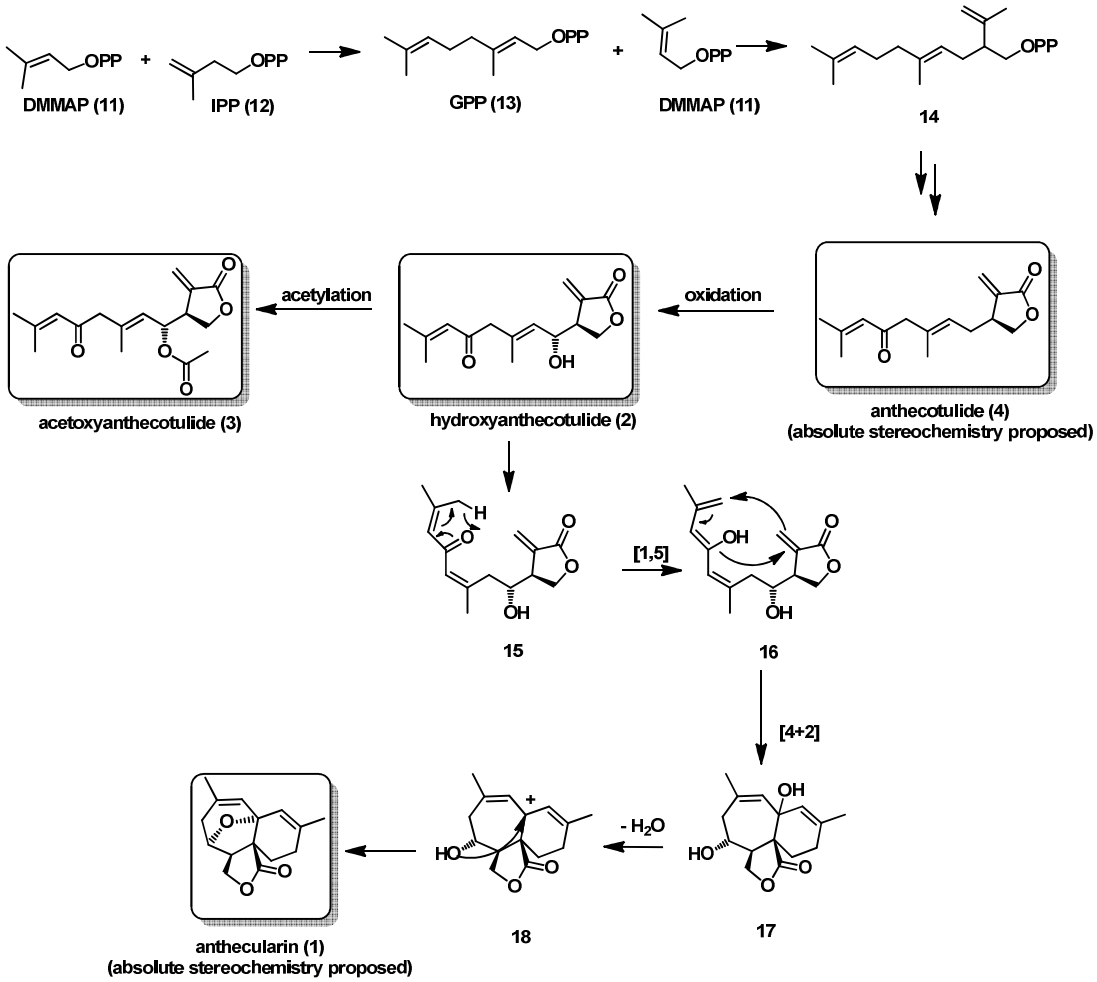
Figure 1.5 Structures shown in the isolation paper of hydroxy and acetoxyanthecotulide.

- Optically active anthecotulide (**4**), also present in Greek *Anthemis auriculata*, was first isolated in 1969 from *Anthemis cotula* L. (stinking chamomile).[6a] The structure of anthecotulide **(4)** was assigned from NMR spectroscopy.[6b] The absolute stereochemistry was unknown at the beginning of the project.[3]

1.4. Biosynthesis of anthecotulides and anthecularin

The biosynthetic origin of anthecularin (**1**) and anthecotulides (Scheme 1.2) has been of great interest in the scientific community due to their unique structures. A biosynthetic origin of anthecotulide (**4**) has been proposed by van Klink *et al.*[10] Feeding studies with various isotopically labeled glucose precursors into *A. cotula* and a deuterium-labeling experiment indicated that the isoprene building blocks of (**4**) are formed exclusively via head-to-middle coupling of geranyl diphosphate (GPP) and dimethylallyl diphosphate (DMMAP). The existence of anthecularin (**1**) with anthecotulide (**4**) and its oxygenated derivatives hydroxyanthecotulide (**2**) and acetoxyanthecotulide (**3**) in *Anthemis auriculata*[4,5] suggest the likelihood of a biosynthetic relationship. A biosynthetic relationship between anthecotulides and anthecularin (**1**) has been proposed by Tadsemir[4] and co-workers in which

hydroxyanthecotulide (**2**) is derived from anthecotulide (**4**) via oxidation. (**2)** can interconvert to **15** via double bond migration. Intermediate **15** could then tautomerise via a [1,5]-hydrogen shift to **16**, which yields the complex polycyclic core framework of **17** through a key *endo*-Diels-Alder cycloaddition. Anthecularin (**1**) could be considered as arising by formation of the cyclic ether bridge by S_N1 substitution of the stabilised *bis*-allylic carbocation intermediate **18**, itself formed through loss of water from intermediate **17.**



Scheme 1.2 Proposed biosynthetic pathways to and between anthecotulides and anthecularin (**1**).

1.5. Biological activity of anthecularin and anthecotulides

- Anthecularin (**1**) showed antitrypanosomal (IC_{50} =10.1 μg/mL; Table 1.2)[11] and antiplasmodial activity (IC_{50} = 23.3 μg/mL; Table 1.2)[12] and inhibition of two key enzymes

in the plasmodial type II fatty acid biosynthesis pathway, PfFabI (IC_{50} = 14 μg/mL; Table 1.2) and PfFabG (IC_{50} = 28.3 μg/mL; Table 1.2).[12] The inhibition of this biosynthesis is one of the most promising targets that has emerged from the recently available genome sequencing of *plasmodium falciparum*, the parasite responsible for malaria. Fatty acids are essential to parasite survival because of their role in membrane structure, energy production, and their successful invasion of the host cells. The structure of the *plasmodium* fatty acid synthase (PfFAS) differs radically from human fatty acid synthase FAS, which is a large multifunctional polypeptide, composed of distinct enzyme domains. These structural differences underpin the strategy for the development of new antimalarial agents, which are selectively toxic to the parasite.

- Anthecotulide (**4**) showed moderate antibacterial (Table 1.1),[5a] antimalarial (Table 1.2),[12] trypanocidal and leishmanicidal activity (Table 1.3),[11] and has been shown to inhibit the activation pathway of the transcription factor NF-*k*B which regulates pro-inflammatory mediators (cytokines, nitric oxide, prostaglandins).[13]

- Hydroxyanthecotulide (**2**) demonstrated the best antibacterial activity[5a] in the family, but also antimalarial (Table 1.1),[12] trypanocidal (Table 1.2)[11] and leishmanicidal activity (Table 1.3).[11]

- Acetoxyanthecotulide (**3**) showed low antibacterial (Table 1.1),[5a] antimalarial (Table 1.2),[12] trypanocidal and leishmanicidal activity (Table 1.3).[11] For this sesquiterpene family, the presence of the acetate group appears to deactivate biological activity.

	Antibacterial activities minimum inhibitory concentrations (MICs) of Compound (2) – (4) (uM)								
	Escherichia Coli	Proteus mirabilis	Agrobacterium tumefaciens	Pseudomonas aeruginosa	Pseudomonas tolaasii	Salmonella enteritidis	Staphylococcus Aureus	Micrococcus luteus	Sarcina lutea
4	101	202	101	202	202	202	101	101	51
2	189	189	94.7	189	189	189	47	94.7	47
3	81.7	163.4	81.7	163.4	163.4	163.4	81.7	81.7	40.8
Streptomycin	68.6	137.2	68.6		137.2	137.2	34.3	34.3	34.3
Bifonazole									

Table 1.1 Antibacterial activities. IC_{50} and MIC values are in mg/ml.

	Enzyme inhibitory, antimalarial, antimycobacterial and antibacterial activities of (1) – (4)							
Compound	PfFab IC_{50}	PfFabG IC_{50}	PfFabZ IC_{50}	MtFabI IC_{50}	EcFabI IC_{50}	P. falciparum IC_{50}	M tubercolis MIC	E Coli MIC
4	100	101	202	202	202	4	20.2	25
3	20	75	>50	>50	>50	2	128	51.8
2	25	50	>50	>75	>50	5.1	119.3	25.8
1	14	28.3	> 50	n. t	n. t	23.3	n. t	n. t
Triclosan	0.014							
Artemisinin						0.0022		
Rifampicin							0.06	
Streptomycin								68.6

Table 1.2 Enzyme inhibitory, antimalarial, antimycobacterial and antibacterial activities. All IC_{50} and MIC values are in mg/ml. (n.t : not tested due to low quantities available).

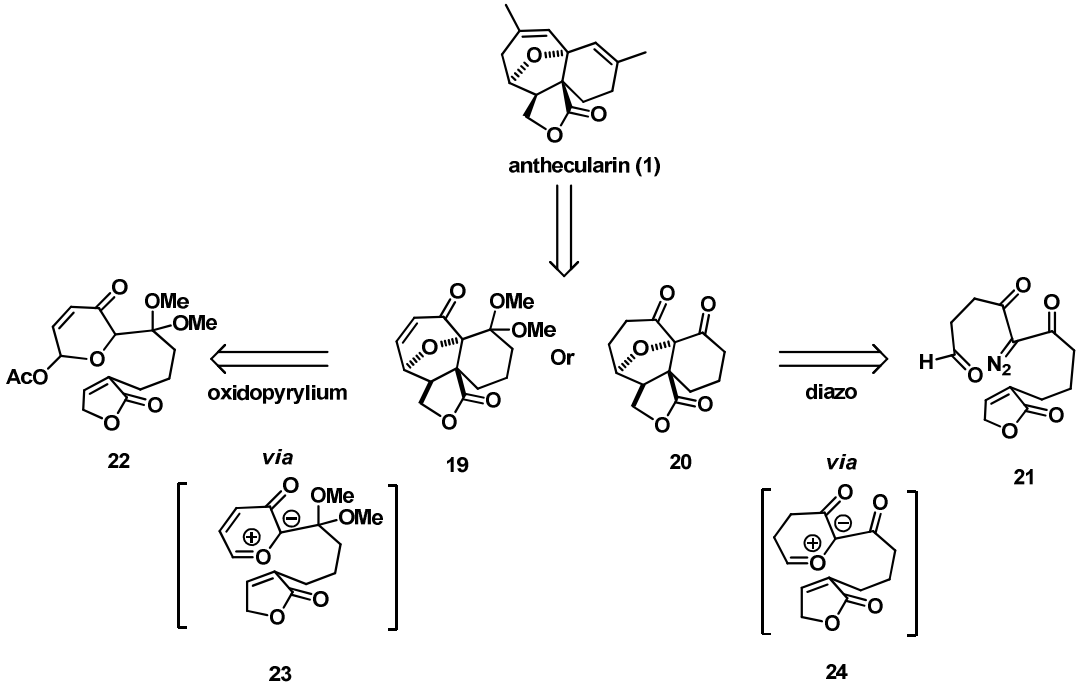
	Trypanocidal, leismanicidal and cytotoxic activities of (1) – (4).			
Compound	T. b.rhodesiense	T. cruzi	L. donovani	L6 cells
standard	0.004 (melarsoprol)	0.22 (benznidazole)	0.11 (miltefosine)	0.005 (podophyllotoxin)
4	4.11 (1.3)	18.05 (0.3)	8.18 (0.6)	5.14
3	0.56 (6.5)	5.72 (0.6)	5.27 (1.1)	3.63
2	12.11 (3.2)	> 30	12.5 (3.1)	38.3
1	10.1	n. t	n. t	> 90

Table 1.3 Trypanocidal, leismanicidal and cytotoxic activities. Selectivity indices (SI) are shown in brackets (SI: IC_{50} L6 cells/IC_{50} parasite). All IC_{50} values are in mg/ml and selectivity indices of the compounds are shown in parentheses; (n.t : not tested).

Chapter 2. Toward the synthesis of anthecularin

This chapter details the two different synthetic approaches for the synthesis of anthecularin (**1**), using a diazo and an oxidopyrylium strategy.

2.1 Introduction and key step



Scheme 2.1 Intramolecular carbonyl-ylide cycloaddition strategy to anthecularin.

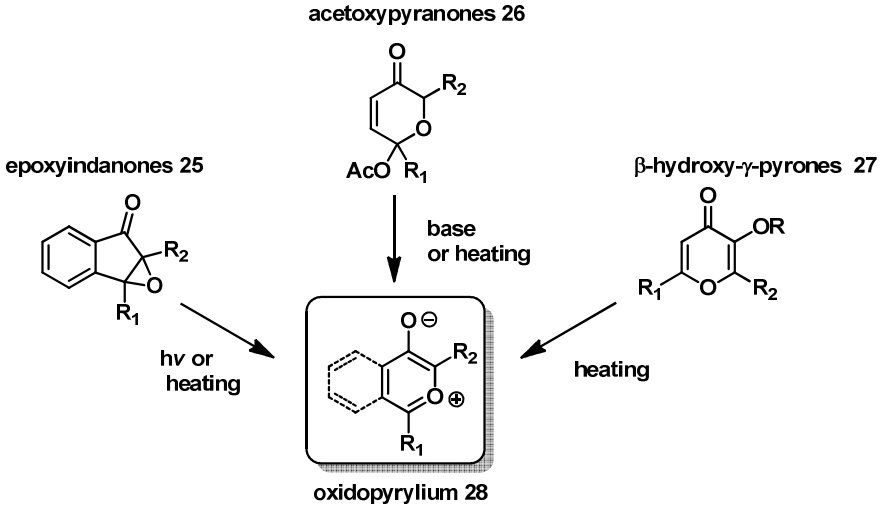
The key step of our projected synthesis of anthecularin uses a carbonyl-ylide formation-intramolecular cycloaddition to create the entire framework, including all 4 stereocentres of anthecularin (**1**), in a single step (Scheme 2.1). The resulting cycloadduct **19** or **20** could then be simultaneously manipulated (e.g. at both ketones via methylation of bis enolates or enamines for cycloadduct **20**) to generate the methylcycloalkene functionality. However, it was recognised that separate manipulation of the ketones should also be possible and potentially desirable in projected structure-activity relationship studies. To synthesise the substrate for the key step, 2 principal strategies were envisaged. These are based on

oxidopyrylium ylide chemistry (see below), or carbonyl ylides generated by rhodium-catalysed decomposition of diazo ketones (Section 2.4, p 19).

2.2 First strategy

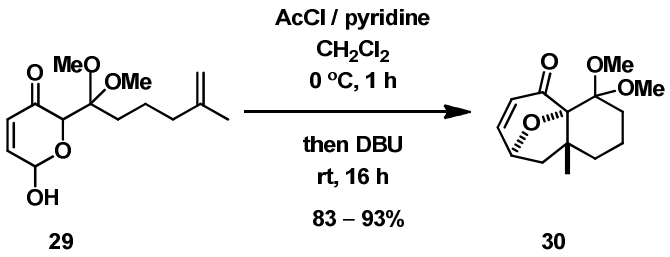
2.2.1 Introduction of the oxidopyrylium strategy

Among the various types of cycloadditions, dipolar cycloadditions of oxidopyrylium species and related carbonyl ylides have proved to be a powerful methodology for the synthesis of diverse molecular architectures which are not otherwise readily available.[14] Oxidopyryliums can be generated from epoxyindanones **25**, acetoxypyranones **26** or β-hydroxy-γ-pyrones **27** (Scheme 2.2).



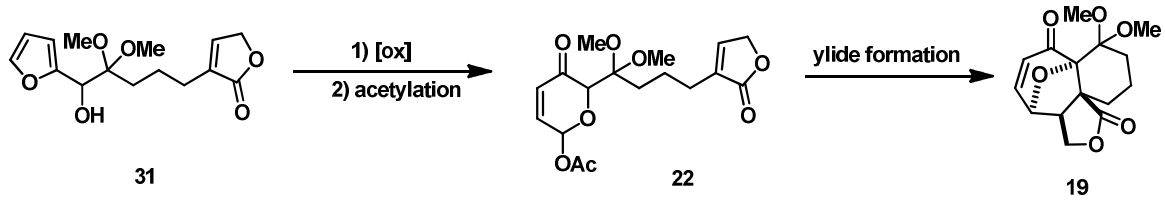
Scheme 2.2 Routes to oxidopyryliums.

In my case, I decided to investigate the synthesis of the oxidopyrylium from the acetoxypyranone **26**. Many intramolecular and intermolecular examples of carbonyl-ylide cycloadditions using acetoxypyranones are known.[14] As reported by Williams *et al.* (Scheme 2.3),[15] the dimethoxy acetal of acetoxypyranone appeared to be an excellent precursor for the synthesis of bridged ethers of bicyclo[5.4.0]undecanes also present in anthecularin (**1**). I hoped to use the same strategy for my synthesis.



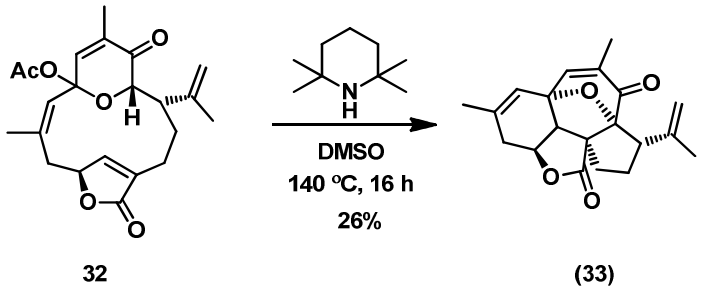
Scheme 2.3 Formation of bicyclo[5.4.0]undecanes by Williams.[15]

In my synthetic plan (Scheme 2.4), furylcarbinols **31** treated with an oxidising agent such as *m*-CPBA or *t*-BuO_2H[14] followed by acetylation would form acetoxypyranone **22**. Basic treatment or heating could hopefully generate the carbonyl ylide **23** (Scheme 2.1). Ylide **23** can then be trapped with suitable dipolarophiles such as the butenolide to form **19**.



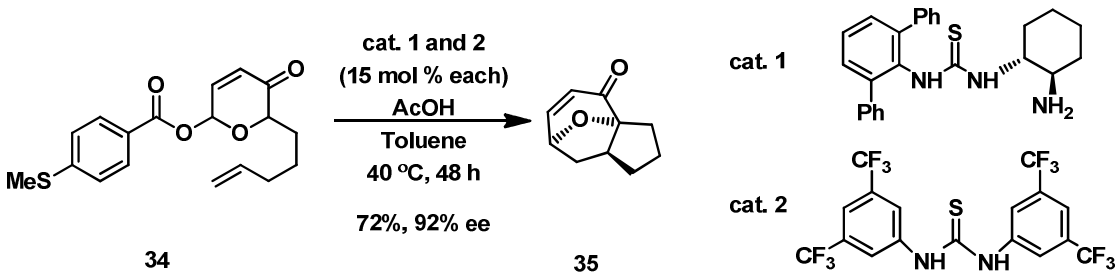
Scheme 2.4 Oxydopyrylium synthetic scheme.

Butenolide functionality has already been employed as a dipolarophile in this type of intramolecular cycloaddition, in the synthesis of (+)-intricarene (**33**) (Scheme 2.5).[16]



Scheme 2.5 Key step for the synthesis of (+)-intracarene (**33**) by Trauner.[16]

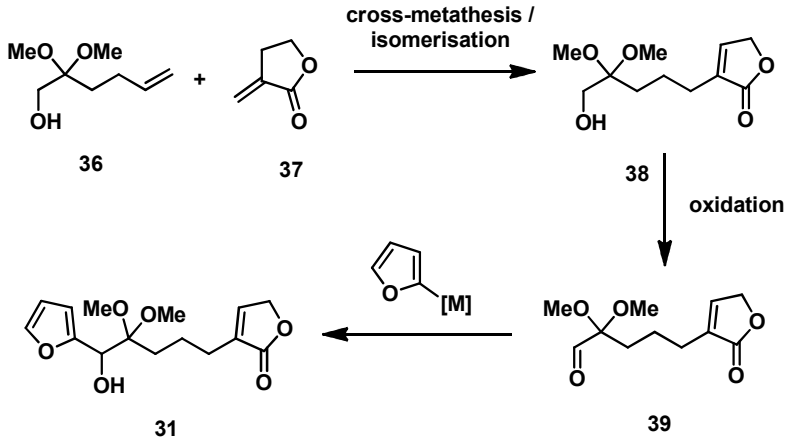
Despite its widespread use in organic synthesis, asymmetric examples have to date been limited to diastereoselective variants[14] with only one very recent (late 2011) catalytic enantioselective method having been developed by Jacobsen using a urea-type organocatalyst (Scheme 2.6).[17]



Scheme 2.6 An enantioselective oxidopyrylium-based [5 + 2] cycloaddition.[17]

2.2.2 Retrosynthesis

The synthesis of α-hydroxyl-methylfuran **31** can be envisaged as shown in the following synthetic (Scheme 2.7):

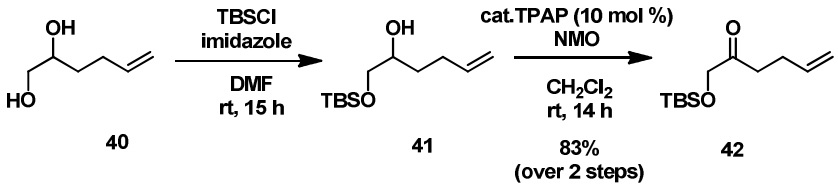


Scheme 2.7 Proposed synthetic pathway of **31**.

Cross-metathesis and isomerisation of 2,2-dimethoxy-hex-5-en-1-ol **36** with 3-methylene-dihydrofuran-2-one **37** would generate butenolide **38**. Oxidation of primary alcohol **38** followed by reaction with metalated furan would generate α-hydroxyl-methylfuran **31**.

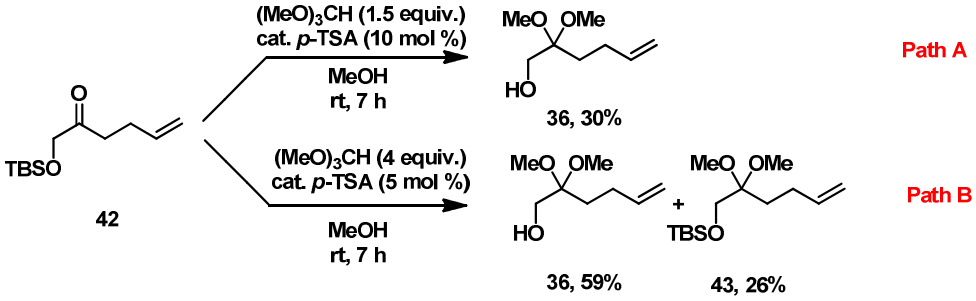
2.2.3 Synthesis of α-hydroxyl-acetal

To synthesise α-hydroxyl-acetal **31**, diol **40** was used as starting material. Selective monoprotection using TBSCl,[18] followed by oxidation with TPAP gave α-silyloxymethyl-ketone **42** in 83% yield (Scheme 2.8).



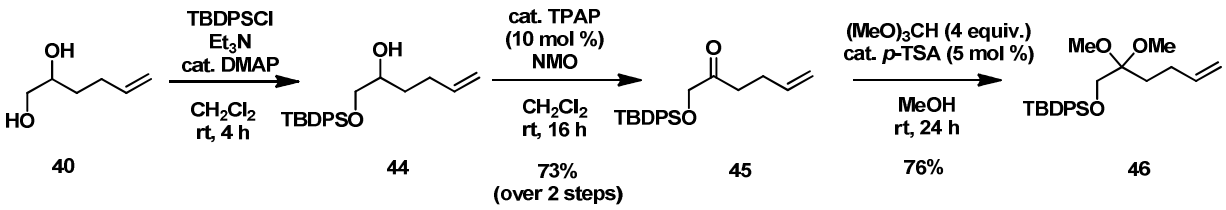
Scheme 2.8 Synthesis of α-silyloxylmetyl-ketone **42**.

Protection of the ketone as a ketal was found to be less straightfoward. On first attempt (Path A, Scheme 2.9), the TBS protecting group did not survive and the primary alcohol **36** was isolated in 30% yield. Using less acid catalyst and addition of trimethyl orthoformate in excess (Path B, Scheme 2.9) gave 26% of the desired acetal **43**, still in the presence of deprotected acetal **36** in 59%.



Scheme 2.9 Synthesis of α-silyloxylmetyl-acetal **43**.

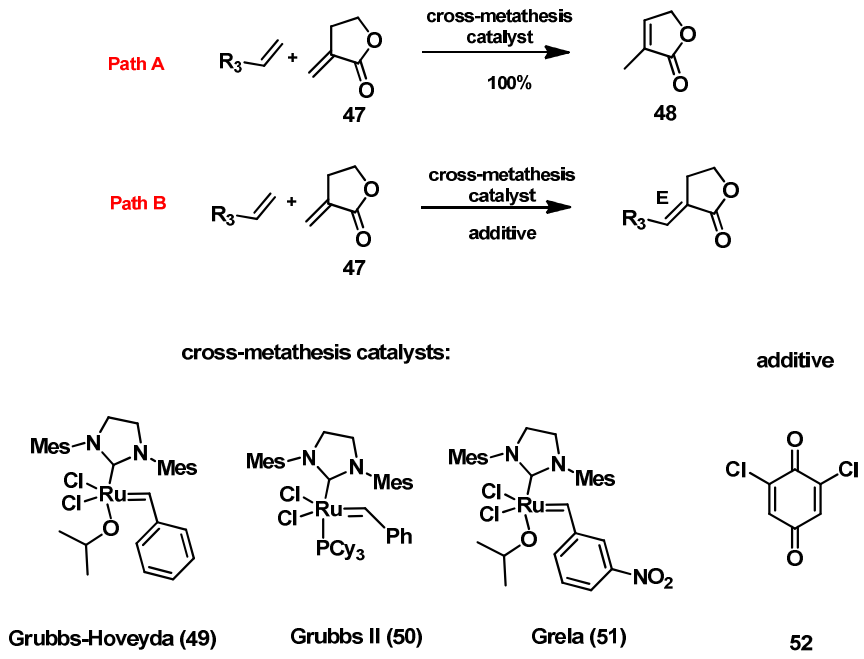
Having in mind that protecting the primary alcohol would possibly be useful during the cross-metathesis step (Scheme 2.7, p. 12), I decided to investigate a more robust protecting group such as TBDPS.[19] Pleasingly, using the same conditions (path B, Scheme 2.9), the desired acetal **46** was obtained over 3 steps in good overall yield (Scheme 2.10).



Scheme 2.10 Synthesis of acetal **46.**

2.2.4 Cross-Metathesis

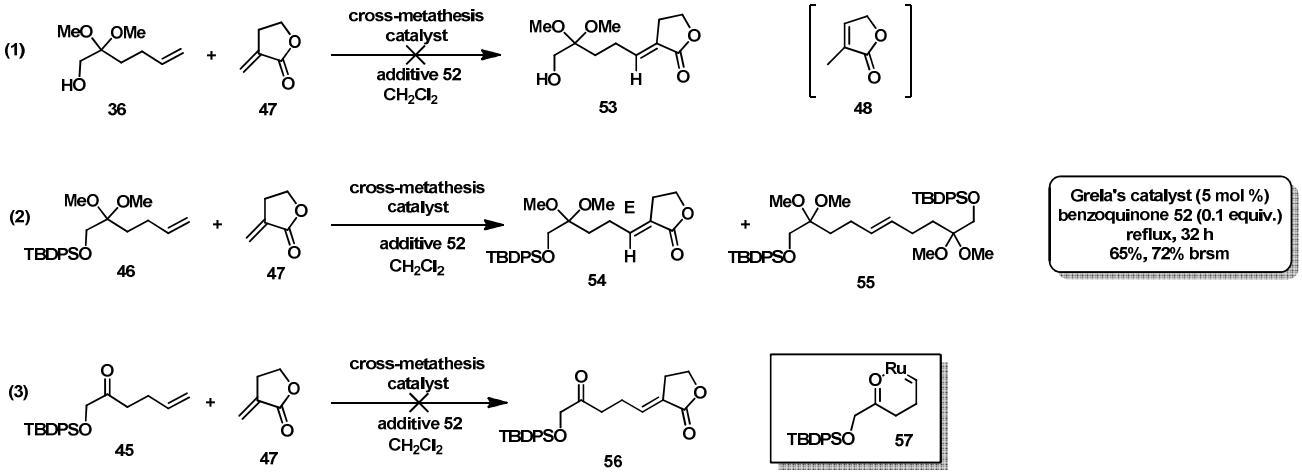
In 2007, Howell[20a] and Cossy[20b] simultaneously published methodology for cross-metathesis of 3-methylene-dihydrofuran-2-one (**47**) with simple alkenes (Scheme 2.11). Different catalysts were studied for this cross-metathesis reaction, such as Grubbs II (**50**) and Grubbs-Hoveyda (**49**). Under classic metathesis conditions (cross-partners, cross-metathesis catalyst and solvent), isomerisation of methylene lactone **47** was the sole reaction pathway observed (Path A, Scheme 2.11). There are a variety of possible explanations for this undesirable olefin isomerisation in the presence of ruthenium-based olefin metathesis catalysts but it is generally accepted that during metathesis a by-product might be responsible for the formation of a ruthenium hydride complex;[21] the latter could be responsible for the isomerisation. Electron-deficient benzoquinones such as **52** have been identified as efficient additives for preventing isomerisation in this case.[21d]



Scheme 2.11 Cross-metathesis of methylene lactone **47** and isomerisation problem.

I decided to investigate the cross-metathesis with acetal **36** made previously (Scheme 2.9, p. 13). Using acetal **36** under standard conditions (Grubbs II: 5 mol % and 2,6-dichlorobenzoquinone: 0.1 equiv.) gave the isomerisation product **48** as the only product (Scheme 2.12, Equation 1). The free hydroxyl may have reacted with the electron-deficient benzoquinone **52** in a 1,4-addition fashion. Then, α-hydroxylsilylacetal **46** was used under the same conditions (Scheme 2.12, Equation 2). A large amount of starting material and dimer **55** (ratio: 3/1) was found, but no trace of the desired product **54**. On switching to Grela's catalyst (5 mol %),[22] 65% of desired lactone **54** was isolated after 16 h under reflux (^{1}H δ 6.67, J = 6.9, 2.9 Hz, CH=, assumed to be ***E*** by analogy with previous work[20]). After 32 h, 72% of the desired product **54** was isolated. The yield under the same conditions, but using microwave heating (300 W, 100 ^{o}C, 3 h) was not improved (40%). The cross-metathesis was also examined on ketone **45** (Scheme 2.12, Equation 3). This cross-metathesis was expected to be difficult, as the cross partner α-hydroxylsilyl-ketone **45** could form a complex such as **57** with the ruthenium.[23] The same conditions (Grela's catalyst: 5 mol %) gave only recovery of starting material **45**. Using 30 mol % of $Ti(OiPr)_4$, as proposed by Fürstner for related

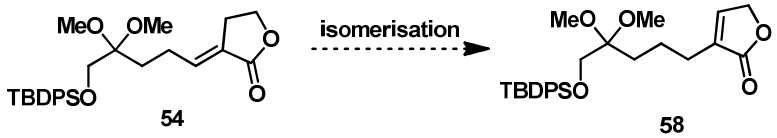
systems,[23] gave exclusively **48**. The acetal functionality appears to play an important role in the success of the present cross-metathesis.



Scheme 2.12 Cross-metathesis between alkene **36**, **46** and **45** with 3-methylene-dihydrofuran-2-one (**47**).

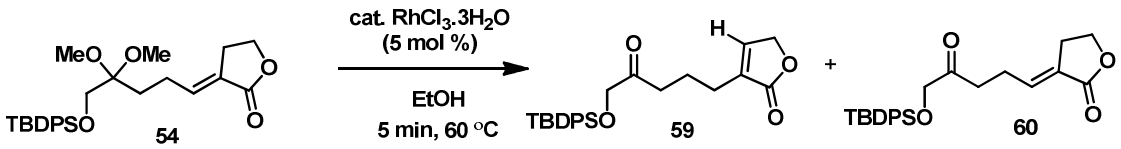
2.2.5 Isomerisation

Having successfully achieved cross-metathesis, the isomerisation of methylene lactone **54** was investigated (Scheme 2.13).



Scheme 2.13 Attempted isomerisation of lactone **54**.

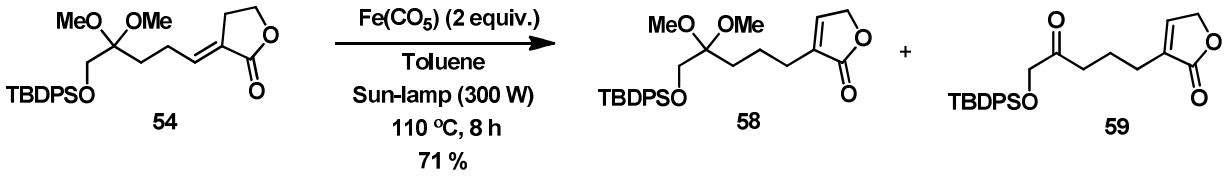
Typically, $RhCl_3$ has been used to isomerise this type of lactone.[24] Using 5 mol % of this catalyst in EtOH at 50 °C (5 min) gave an inseparable mixture of deprotected isomerised **59** (^{1}H δ 7.1) and non-isomerised deprotected starting material **60** (Scheme 2.14). Leaving the reaction mixture for a longer period of time did not improve this ratio (40% of **59** by ^{1}H–NMR data analysis of unpurified reaction mixture).



Scheme 2.14 Attempted isomerisation with $RhCl_3$.

With the aim of finding a mild way to isomerise **54**, the possibility of forming a ruthenium hydride species such as that seen in the previous cross-metathesis step (see Scheme 2.12, Equation 1) was investigated. At the time (2009) there were few literature examples[21] of this type of reaction. Generally, after the metathesis steps an additive such as H_2,[21a] NaH,[21c] $NaBH_4$,[21c] MeOH[21b] or ethyl vinyl ether[21c] is introduced. However, application of either MeOH (3 drops), ethyl vinyl ether (5 equiv.) or vinyloxytrimethylsilane[21e] (5 equiv.), each in CH_2Cl_2 at 40 °C, returned only starting material. Pleasingly, the use of vinyloxytrimethylsilane (5 equiv.) in toluene at 110 °C for 16 h gave 40% of the desired product **58** by ^{1}H–NMR data analysis of unpurified reaction mixture (^{1}H δ 7.03, CH=, ^{1}H δ 4.73, CH_2-O). Heating at 110 °C for 7 d slightly improved the ratio (2:1) in favour of butyrolactone **58**. At the same time, 10 mol % of $Pd(OAc)_2$[25] and 10 mol % of $PdCl_2(MeCN)_2$[25] were used in refluxing CH_2Cl_2, but only starting material **54** and a trace of deprotected starting material **59** was recovered. An attempt to use a palladium hydride species by addition of TMSH (3 equiv.) and Et_3N (1 equiv.) with $Pd(OAc)_2$,[26] gave only starting material and a trace amount of desired product **58**. Moreover, during this reaction, possible hydrogenation of the starting material and/or the desired product seems to have occurred (ratio aliphatic proton/methylene proton higher by ^{1}H–NMR data analysis of unpurified reaction mixture). Use of the rhodium hydride catalyst $RhH(CO)(PPh_3)_3$[27] was examined but, again, mainly starting material was recovered. Despite all efforts, only a small amount of desired product **58** was obtained using catalytic amounts of transition metals. To solve the problem, the use of inexpensive metal catalysts which could be used in stoichiometric amounts was considered. $Fe(CO)_5$ has been previously used for the

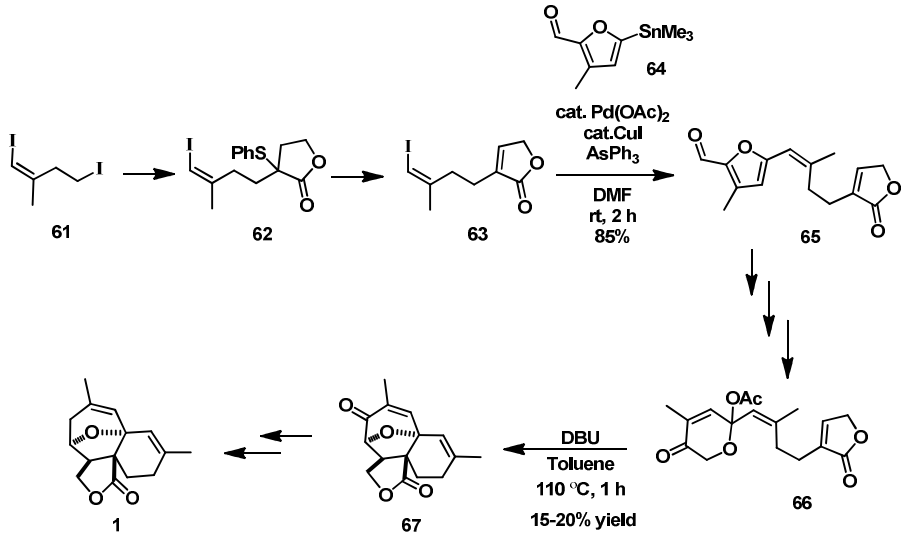
isomerisation of alkenes.[28] Using 10 mol % of this catalyst and heating in refluxing toluene for 14 h generated a small amount of the desired product **58**. A sun lamp was used with the aim of generating the active species, $Fe(CO)_3$, both with and without heating. The best conditions were found to be 2 equiv. of $Fe(CO)_5$ in toluene at 110 °C in the presence of a sun-lamp for 8 h. This gave 65-75% (isolated yield) of the desired product **58** and 20% (by ^{1}H–NMR analysis) of the deprotected (acetal) product **59** (Scheme 2.15).



Scheme 2.15 Isomerisation of **54** using $Fe(CO)_5$.

2.3 First synthesis of anthecularin

While the above isomerisation studies were being undertaken, Pattenden *et al.* published the first total synthesis of anthecularin, in 15 steps (Scheme 2.16).[29] Pattenden's route involves a related oxidopyrylium strategy, and achieved a 15-20% yield for the key-step. Surprisingly, the use of a *Z*-alkene precursor to assist the cycloaddition via a entropic effect was not beneficial in this case.



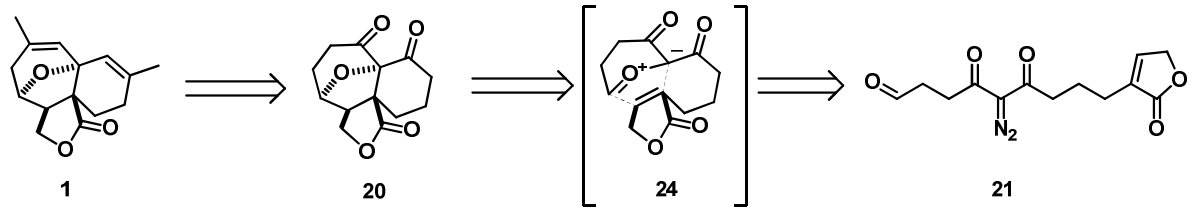
Scheme 2.16 Pattenden's total synthesis of (±)-anthecularin (**1**).[29]

Considering the similarity of our route and Pattenden's route as well as the poor yield of his key step, I decided to abandon the oxidopyrylium route and focused my attention on a diazo strategy (below), in the hope of synthesising anthecularin (**1**) in an asymmetric fashion and better overall yield.

2.4 Second strategy

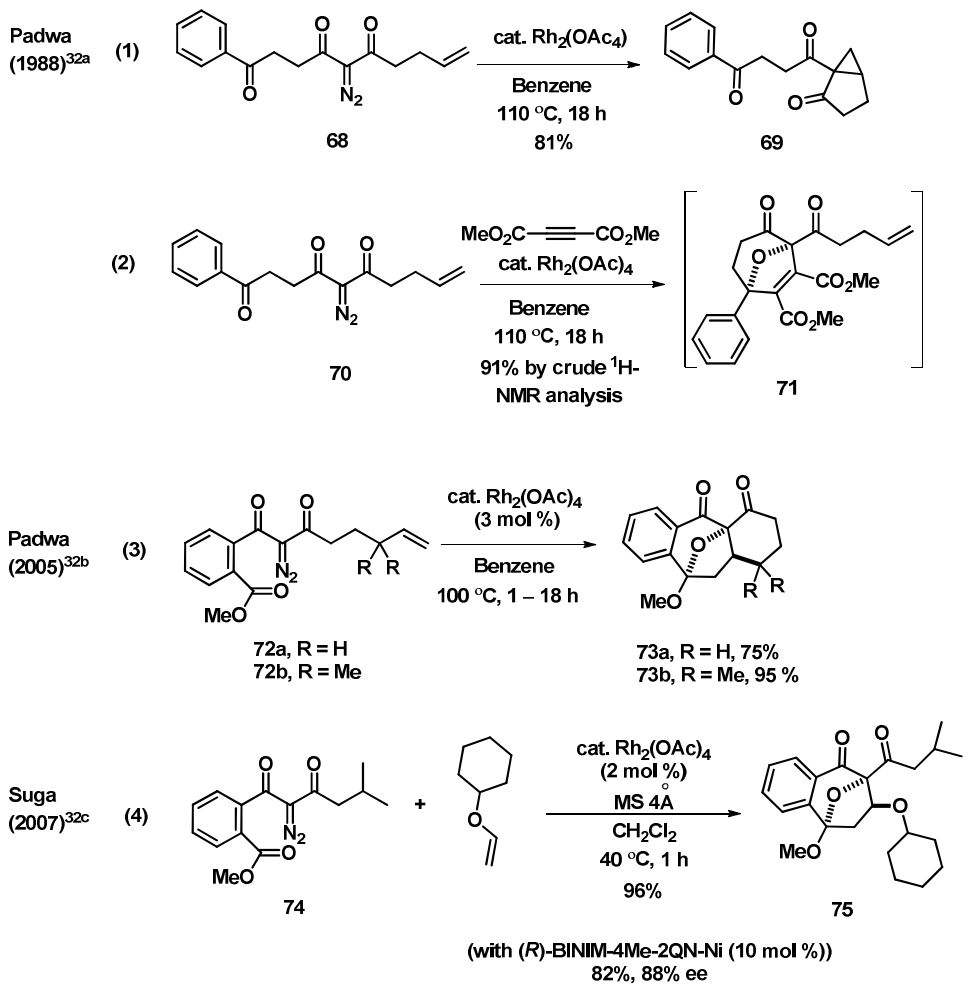
2.4.1 Introduction and retrosynthesis

The basis of this strategy is to use a transition metal complex (ultimately a chiral complex) to catalyse (enantioselective) tandem carbonyl ylide formation–intramolecular cycloaddition from diazodiketone **21** (Scheme 2.17).[30] This diazodiketone is anticipitated to form the ylide **24** which could be trapped with a tethered butenolide to generate **20**.



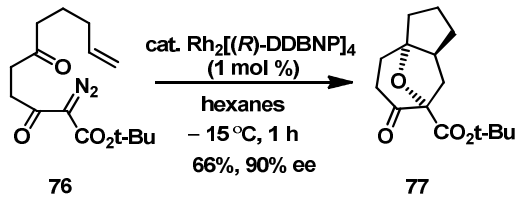
Scheme 2.17 Carbonyl ylide formation–intramolecular cycloaddition.

Carbonyl ylide formation–intramolecular or intermolecular cycloadditions via diazo substrates have been well documented.[31] When we started the project (2008-2009), most examples were using diazo ketoesters or diazo ketoamides in the presence of a ketone or, in a few cases, an ester as the interacting carbonyl group to form the intermediate ylide. To the best of our knowledge, the use of diazodiketones for ylide cycloadditions is rare, only a few examples have been found in the literature (Scheme 2.18).[32]



Scheme 2.18 Examples of carbonyl-ylide formation / cycloadditions with diazodiketones.

Previously in the Hodgson group, a catalytic enantioselective version of the intramolecular cycloaddition of carbonyl ylides has been developed (Scheme 2.19).[33] The asymmetric process is not completely understood but it seems likely that the metal stays close to the ylide, generating the asymmetry.

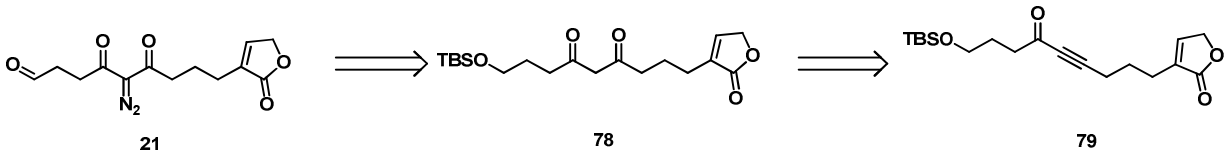


Scheme 2.19 Example of enantioselective carbonyl-ylide formation/intramolecular cycloaddition.

I aimed to use this earlier work in the field of intramolecular cycloadditions of carbonyl ylides as a basis for the synthesis of anthecularin.

2.4.2 Synthesis of 1,3-diketone 78 via an acetylenic ketone

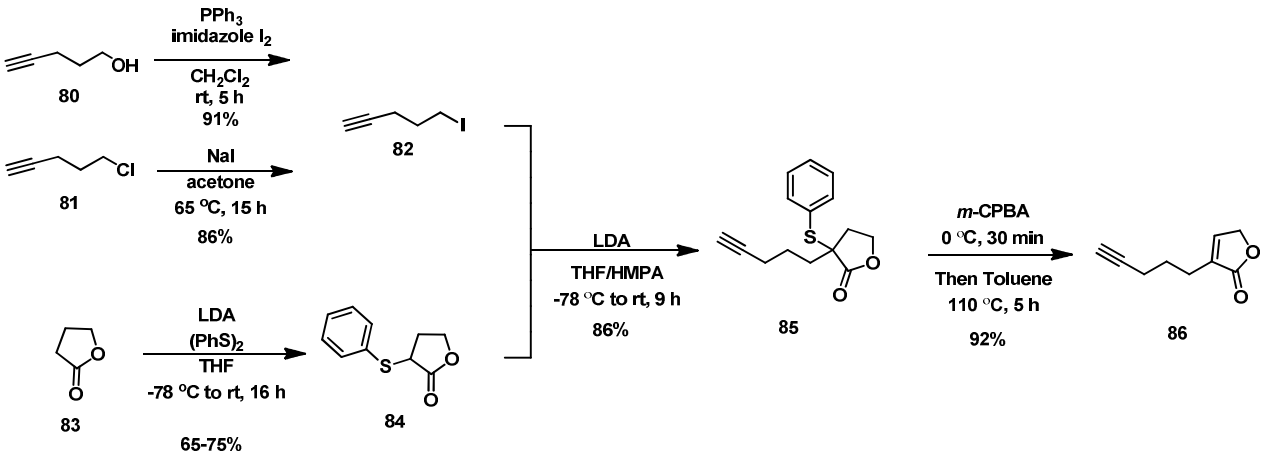
With the aim of synthesising the key precursor **21** (Scheme 2.20), I decided to look for an efficient way to synthesise a 1,3-diketone such as **78**. Considerable research has been conducted on methods for the synthesis of 1,3-diketones.[34] A classic procedure involves acylation of a ketone by an ester in the presence of an alkoxide base.[35] This method has limited substrate scope, gives only modest to good yields and requires elevated temperatures. A current procedure of choice for 1,3-diketone synthesis uses a strong, non-nucleophilic base such as LDA to preform the required enolate, followed by addition of the acylating agent, typically an acid chloride.[36] Yields generally improve under these conditions, but the presence of acidic functionality (such as butenolide core) is an issue. The principal idea behind our synthetic route shown in Scheme 2.20 was to generate the 1,3-diketone via α,β-acetylenic ketones such as **79**.



21 **78** **79**

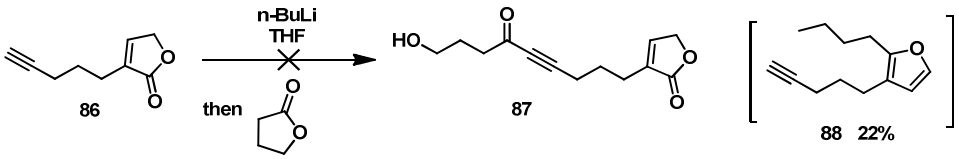
Scheme 2.20 Diazo retrosynthetic scheme.

A few examples of hydrolysis of simple alkynes are present in the literature using transition metals such as Pd, Pt and Au.[37] In addition to metals, organic compounds such as oximes have also been employed with some degree of success.[38] The synthesis starts with the preparation of alkyne **85** from commercially available chloropentyne (**81**) or pentyn-ol (**80**) in three steps. Addition of the known iodoalkyne **82**[39] with the known lithiated lactone **84**[40] in the presence of HMPA gave alkyne **85** in 86% yield.[41] Oxidation with *m*-CPBA and thermal elimination of the sulfoxide intermediate gave the butenolide **86** in 95% yield (Scheme 2.21).



Scheme 2.21 Synthesis of butenolide **86**.

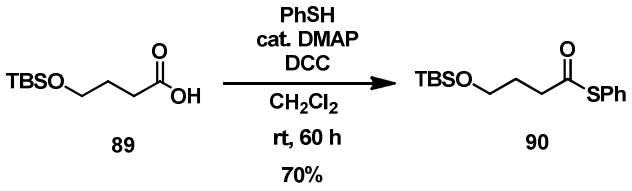
Synthesis of alkynone **87** was first attempted via a classical approach involving alkylation of an alkyne with a lactone.[42] Unfortunately, after examining a range of conditions (parameters varied: temperature (−78 °C, –40°C and 0 °C), base (LDA or BuLi); protection of the lactone via TMSether) only starting material and 2,3-disubstituted furan **88** (40% and 20% respectively) were isolated.



Scheme 2.22 Attempted synthesise of alkynone **87**.

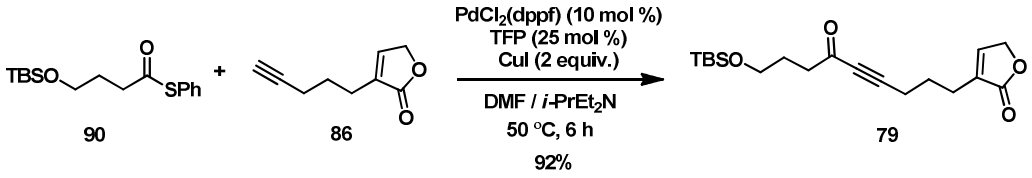
2.4.3 New strategy to alkyne 87

Due to problems with the above strategy, a range of mild alternative conditions were investigated. Fukuyama and co-workers efficently synthesised a range of α,β-acetylenic ketones by Sonogashira cross-coupling of unsaturated thioesters.[43]Therefore, it was decided to synthesise the novel thioester **90** to test this cross-coupling. DCC esterification of the known acid **89**[44] with thiophenol gave the desired thioester **90** in 70 % yield (Scheme 2.23).



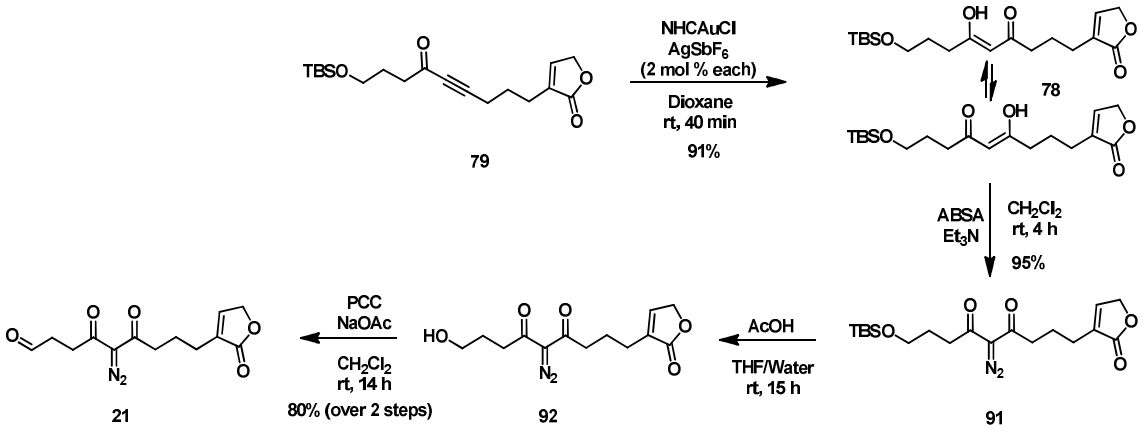
Scheme 2.23 Synthesis of thioester **90**.

Using the modified conditions described by Shair *et al* (methodology used on a more complex substrate than Fukuyama),[45] cross-coupling of alkyne **86** with thioester **90** gave the desired α,β-acetylenic ketone **78** in 85-93% yield with good reproducibility (Scheme 2.24).



Scheme 2.24 Sonogashira cross-coupling.

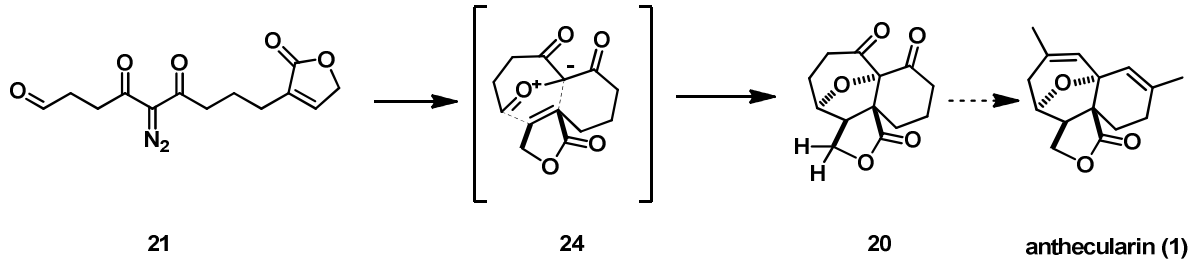
Following the successful synthesis of alkyne **79**, hydration was carried out using 4 mol % of gold/silver catalyst in dioxane/water (5/1 v/v) (Scheme 2.25). After stirring for 40 min at rt, the desired product **78** was isolated in 50% yield. After reducing the amounts of water (2-3 equiv.), catalyst (2 mol %) and changing the work-up (quenching with Et_3N and passing through Celite®), the desired 1,3-diketone **78** was obtained in 90% yield. Diazo transfer of 1,3-diketone **78** using *p*-acetamidobenzenesulfonyl azide (ABSA) in MeCN gave the diazodione **91** in excellent yield (95%).[46] Desilylation in THF/water/AcOH at rt followed by oxidation with PCC in CH_2Cl_2 gave the desired aldehyde **21** in good yield (80% over 2 steps).[47]



Scheme 2.25 Synthesis of the cycloaddition substrate **21**.

2.4.4 Attempted cycloaddition steps

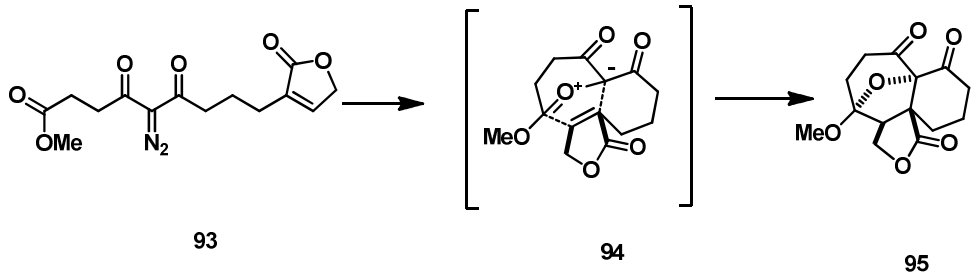
Due to the small amount of diazodiketone **21** synthesised, all of the following reactions discussed were carried out on a 10 mg scale. Initially, I decided to use cat. $Rh_2(OAc)_4$ (2 mol %) in CH_2Cl_2 at rt as a starting point for examining the cycloaddition. If the cycloaddition occurred, it was rationalised that ^{1}H–NMR signals between 4–5 ppm present in anthecularin (**1**) (which could be assigned to protons CH_2-O of the lactone ring) would also be present in cycloadduct **20** (Scheme 2.24).[4]



Scheme 2.24 Formation of cycloadduct **20**.

After addition of the catalyst, gas (nitrogen) was observed evolving over the first 2-3 min. However after 5 h, ^{1}H–NMR analysis of the unpurified reaction mixture revealed the presence of the butenolide functionality (^{1}H δ 7.1 and ^{1}H δ 4.8) with an aldehyde proton (^{1}H δ 10.0), but the absence of starting material **21** . Changing the solvent for toluene, 1,2-dichloroethane or *p*-trifluorotoluene at rt or reflux failed to give the desired product (analogous to previous ^{1}H–NMR data analysis of unpurified reaction mixture). Using a

different catalyst, such as $Rh_2(OCOCF_3)_4$ (5 mol %) was also unrewarding. Due to problems with purification (decomposition using silica, basic/neutral alumina and Fluorisil®) and scale-up, no product has been isolated. LC-MS shows six different products, none of which matched the mass of the desired product **20** (the major peak contains $[M+H]^+$=515). Due to these results, I decided to alter the aldehyde functionality for ester such as **93** (Scheme 2.27), in the hope that modifying the cycloadduct **95** would afford anthecularin (**1**). Previous unpublished work in the group shows the possibilty of generating an ylide using an aliphatic ester.[48]

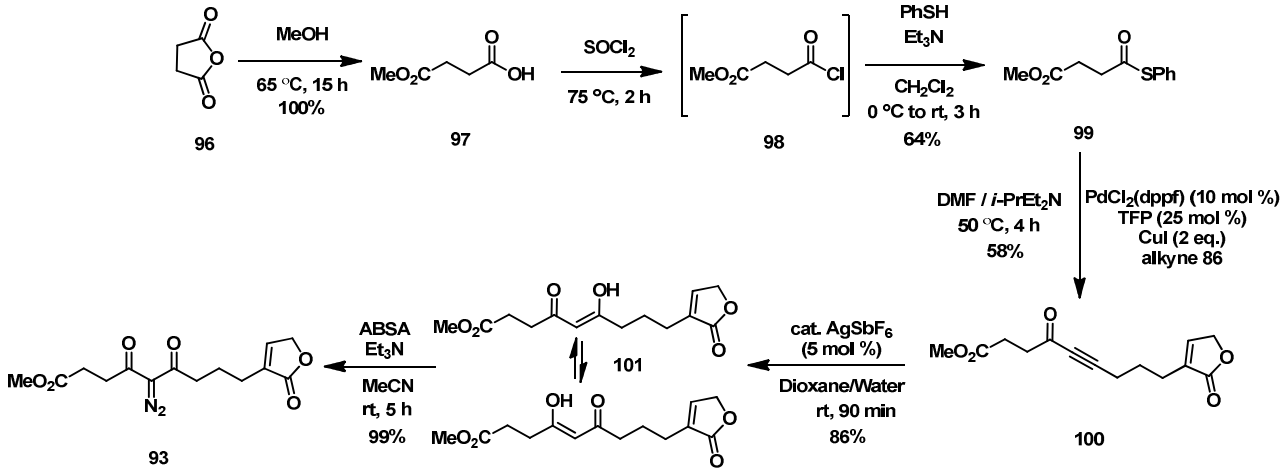


93 94 95

Scheme 2.27 Formation of cycloadduct **95.**

2.4.5 Synthesis of precursor 93: oxidopyrylium strategy using aliphatic ester

The synthesis of the desired ester (Scheme 2.28) was carried out using a similar sequence to our previous strategy.



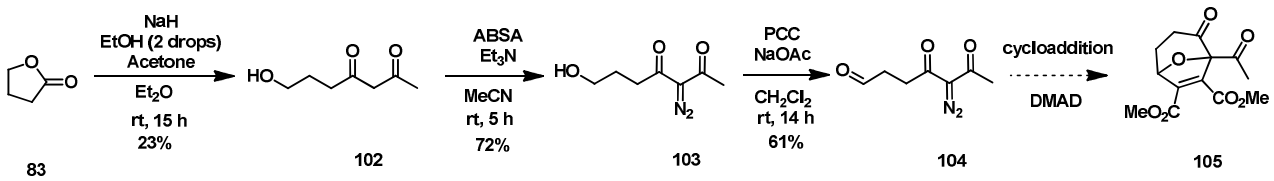
96 97 98 99 100 101 93

Scheme 2.28 Diazoester route.

Ring-opening of succinic anhydride (**96)** in refluxing methanol gave acid **97** in quantitative yield.[49] Formation of the acid chloride **98** followed by thioesterification using thiophenol gave thioester **99** in 64% yield. Subsequent Fukuyama-Sonogashira cross-coupling gave alkyne **100** in 58% yield. During the hydration step, it was discovered that 5 mol % of $AgSbF_6$ alone was sufficient to generate the 1,3-diketone **101** (86%). Finally, diazo transfer with ABSA gave the diazodione **93** in 99% yield. Unfortunately, under cycloaddition conditions previously used (5 mol % $Rh_2(OAc)_4$, or $Rh_2(OCOCF_3)_4$ in CH_2Cl_2 or toluene), ^{1}H–NMR data analysis of unpurified reaction mixture indicated the presence of the butenolide and, for the same reasons (difficult purification and small scale), no cycloadduct was isolated.

2.4.6 Cycloaddition of simple diazoaldehyde with external dipolarophiles

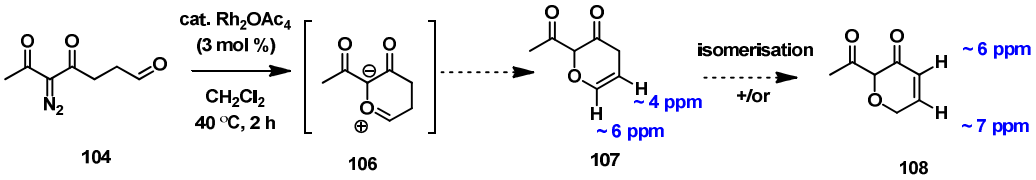
With the aim of understanding the origin for the absence of the desired product in the cycloaddition, simple diazo aldehyde **104** was synthesised and tested for cycloaddition with external dipolarophiles (Scheme 2.29).



Scheme 2.29 Cycloaddition of diazoaldehyde with external dipolarophiles.

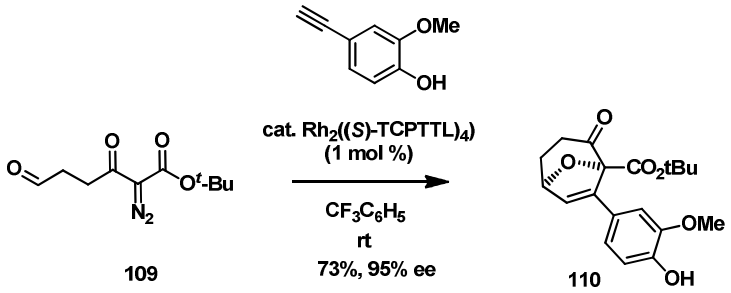
Diketone **102** was synthesised in one step from the commercially available α-butyrolactone (**83)** and acetone using Detty's conditions[50] in 23% yield (lit. 65%). Diazo transfer with ABSA gave diazodione **103** in 72% yield and subsequent PCC oxidation gave aldehyde **104** in 61% yield. 3 mol % of $Rh_2(OAc)_4$ in toluene at 80 °C was used as a starting point for examining the cycloaddition. With DMAD (4 equiv.) as the dipolarophile, after 4 h ^{1}H–NMR data analysis of unpurified reaction mixture showed a trace amount of the desired product

105 (^{1}H δ 5.3, CH-O). Using CH_2Cl_2 at reflux or at rt gave the same results. Believing that the desired product was not stable during purification on silica,[32a] it was decided to use *N*-phenyl maleimide as the reactive dipolarophile. Using the same conditions of refluxing CH_2Cl_2 gave the cycloadduct in poor yield (5%, ^{1}H δ 5.05, CH-O, ^{1}H δ 3.5 and 3.9, CH-CO from *N*-phenyl maleimide).



Scheme 2.30 Possible hydride abstraction following ylide formation.

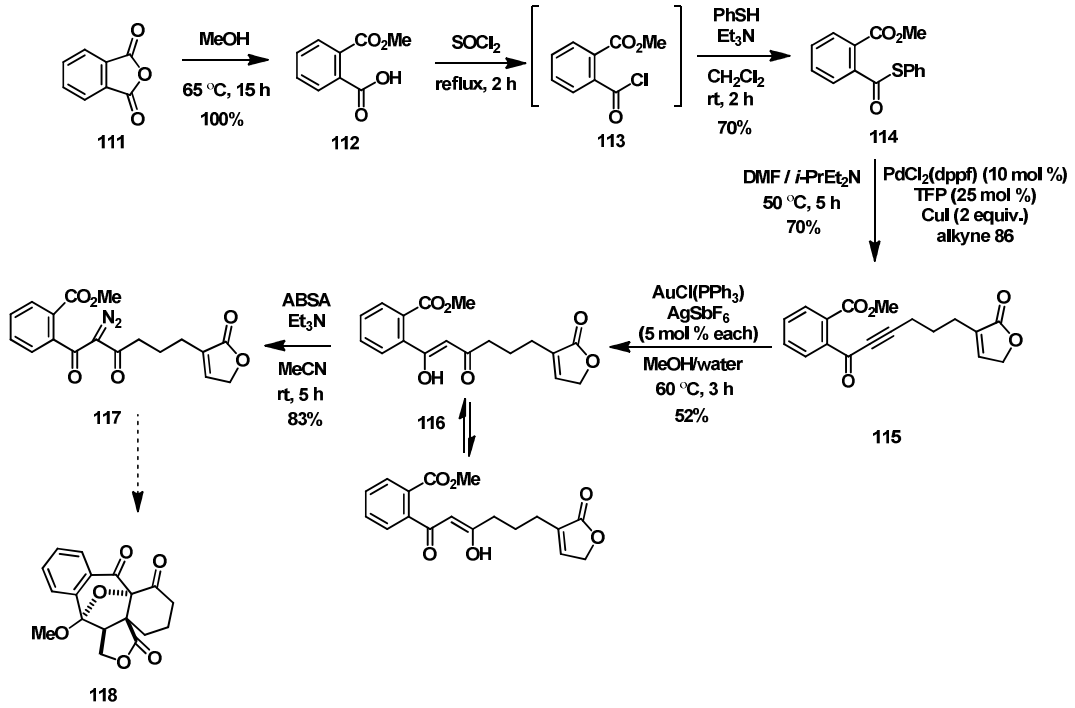
Assuming the ylide forms, it is possible that products resulting from hydrogen-shift are generated (Scheme 2.30).[51] In an effort to confirm this and isolate the by-product, the diazodione **104** was slowly added over 1 h to a solution of catalyst (Rh_2OAc_4) in refluxing CH_2Cl_2 and stirred for 2 h. Unfortunately, ^{1}H-NMR data analysis of unpurified reaction mixture showed no signal between 4 and 6 ppm (predicted value for **107** and **108**, Scheme 2.30). Only one signal between 2-3 ppm appeared. After purification (silica, alumina and Florisil®), no product could be isolated. It is interesting to note that some TLC spots during this experiment were the same as our previous cycloaddition attempts with the diazodione and DMAD or *N*-phenyl maleimide. This suggests that the diazodione decomposes or reacts with itself before reacting with the dipolarophile. Recently (2010), the first intramolecular ylide formation using an aliphatic aldehyde was published[52] (Scheme 2.31). This suggests that the aliphatic aldehyde was not the problem but generating a stable ylide from diazo-1,3-diketones is certainly an issue.



Scheme 2.31 Example of intramolecular ylide formation using aliphatic aldehyde.[52]

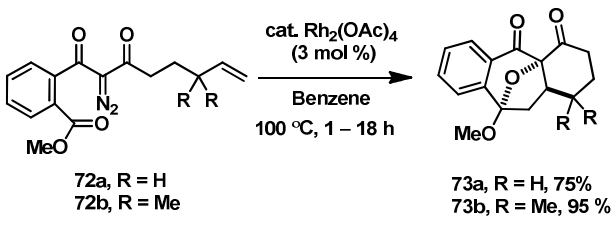
2.4.7 Synthesis of precursor 117: aromatic oxidopyrylium strategy.

We considered that an aromatic oxidopyrylium may help to stablise the ylide, giving it a long enough lifetime to form the cycloadduct. Following the work of Padwa,[32b] I attempted to form the cycloadduct **118** (Scheme 2.32) with the aim of understanding the reactivity of the ylide with the butenolide functionality. The synthesis of **118** would also provide a good opportunity to probe the structure-activity relationships of anthecularin (**1**). The following strategy (Scheme 2.32) used a similar sequence that had been used previously. Ring-opening of phthalic anhydride (**111)** in refluxing MeOH gave 2-(methoxycarbonyl)benzoic acid (**112**)[53] in quantitative yield. Thioesterification with acid chloride and thiophenol gave the thioester **114** in 70% yield. Subsequent Fukuyama-Sonogashira cross-coupling gave the alkyne **115** in 70% yield. During the hydratation step, $AuCl(PPh_3)$ with $AgSbF_6$ was used in MeOH/water at 60 ˚C and gave the desired diketone **116** after acidic work-up[54] in 52% yield. Finally, diazo transfer with ABSA generated the diazodione **117** in 83% yield.



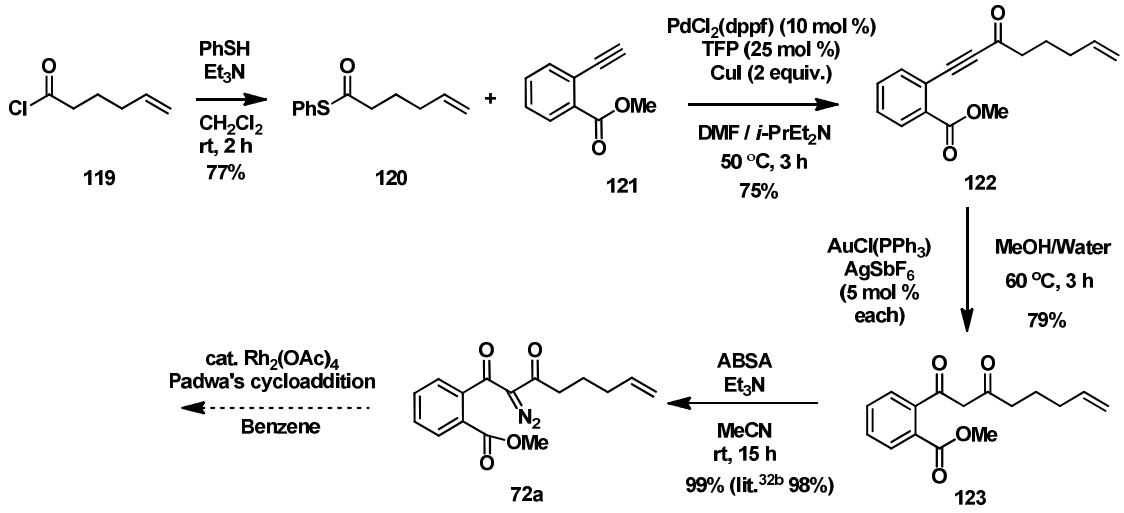
Scheme 2.32 Diazo route for substrate **117**.

Following the procedure of Padwa,[32b] diazodione **117** was heated for 1 h or 18 h at 80 °C in benzene with 3 mol % of $Rh_2(OAc)_4$, but unfortunately no desired product was detected by ^{1}H–NMR data analysis of unpurified reaction mixture from either experiment and the same problem of purification, as previously seen (Section 2.4.6, p. 29), occurred. Using 10 mol % of $EuTf_3$ with 5 mol % of $Rh_2(OAc)_4$ in refluxing CH_2Cl_2, as used by Suga and co-workers[32c] (Scheme 2.18, p. 20), gave similarly unrewarding results as those without a Lewis acid. Careful reading of Padwa's publications indicates that there appear to be numerous errors in the quoted yields of related cycloadditions, notably in the yields for cycloadducts (Scheme 2.33). The quoted yield of 75% in fact calculates to 25%, and the quoted yield of 95% calculates to 33% (see below).



Scheme 2.33 Cycloaddtion of Padwa's intermediate **72a/b**.

With the aim of understanding the reaction and to confirm the yield, the synthesis of **72a** was planned. The cycloaddition precursor **72a** from Padwa's work[32b] was made by a similar route (Scheme 2.34) used for the precursor **117** (Scheme 2.32). Unfortunately, despite several attempts, I never managed to obtain the cycloadduct **73a** in the reported yield. My yields were between 15-24% for cycloadduct **73a**, consistent with what I calculated from Padwa's experimental data.[32b] Correspondance by email[a] with Prof. Padwa has been unsuccessful to solve this problem.



Scheme 2.34 Synthesis of Padwa's intermediate for cycloaddition.

2.5 Summary

During the study of the oxidopyrylium strategy, I have established the viability of using a cross-metathesis with a more complex alkene cross-partner using Grela's catalyst and I have also shown the possibility of using $FeCO_5$ for the isomerisation of α-methylene lactones to butenolides. Using the diazo strategy, I have developed an original, mild approach for the synthesis of 1,3-diketones using Fukuyama-Sonogashira cross-coupling followed by gold-catalysed hydration of alkynones in good overall yield. I have also shown the difficulty of

[a] First correspondance September 2009 then October 2009 at chemap@emory.edu, Prof. Padwa was not able to reach his previous student to clarify the situation.

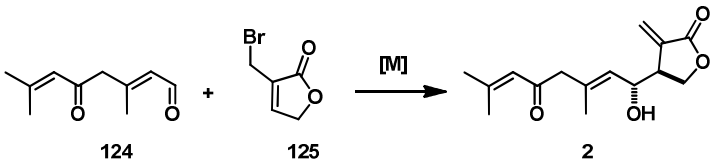
forming cyclic carbonyl ylides from diazo-1,3-diketones. Having arrived at a dead-end for this ylide cycloaddition approach to anthecularin (**1**)**,** I decided to investigate a new but related natural product: (+)-hydroxyanthecotulide (**2**) with the hope of subsequently achieving a biosynthesis (see Section 1.4, p. 5) of anthecularin (**1**) using hydroxyanthecotulide (**2**).[5]

Chapter 3. Towards the synthesis of hydroxyanthecotulide

This chapter details the development of a new methodology for the stereoselective synthesis of β-hydroxymethyl-α-methylene-γ-butyrolactones and its application toward the first synthesis of (±)-hydroxyanthecotulide (**2**).

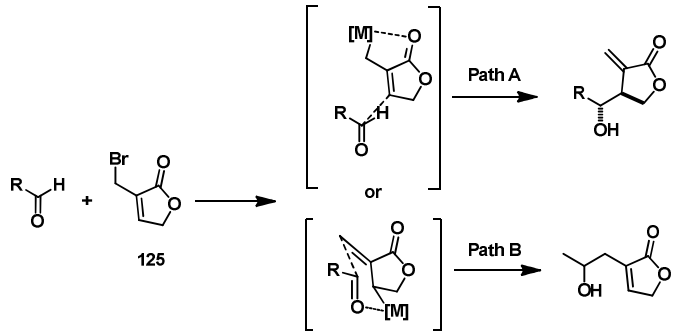
3.1 Introduction and key step

The key step in our projected synthesis of hydroxyanthecotulide was a novel transition metal complex-catalysed (enantioselective) C-C bond-forming step to directly generate the natural product in a single operation from achiral ketoaldehyde **124** and known[55] bromolactone **125** (Scheme 3.1).



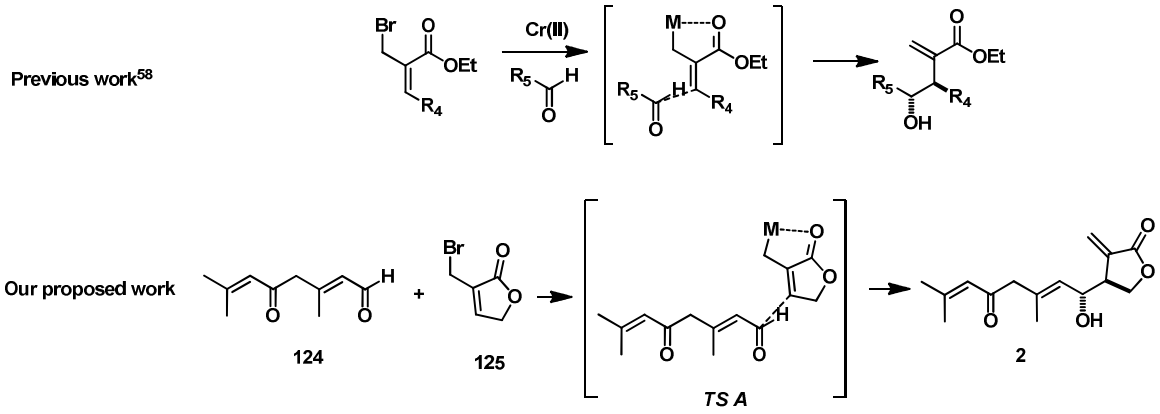
Scheme 3.1 C-C bond-forming towards hydroxyanthecotulide

The first goal was to develop methodology towards such motifs, initially in a racemic fashion, which require that the key allylic organometallic (exchange Br → Met) intermediate reacts regioselectivity at the more substituted position (Path A, Scheme 3.2)



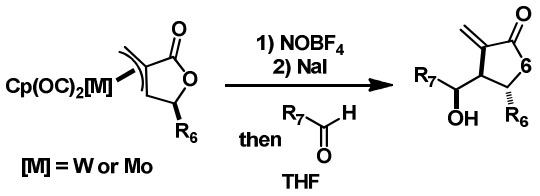
Scheme 3.2 Possible products during allylation using bromolactone **125** and aldehydes.

Taking all of the above requirements into consideration, it was considered that an allylic chromium species would be most suited to address these challenges.[56] Unlike many organometallics, there are examples of organochromiums where potential elimination of β-oxy leaving groups does not occur (i.e. does not compromise successful C-C bond formation).[57] Moreover, due to potential co-ordination between the metal and the lactone carbonyl (see previous work,[58] Scheme 3.3), it was anticipated that the intermediate allylic chromium would show high levels of regioselectivity and diastereoselectivity *via* an acyclic transition state such as TS *A* (Scheme 3.3) in couplings with aldehydes, leading to the relative anti-stereochemistry required for the natural product. Moreover, nonbasic organochromiums typically undergo 1,2- (rather than conjugate) addition and display exquisite chemoselectivity for aldehyde over ketone functionality.[56]



Scheme 3.3 Acyclic transition states based on proposals by Nozaki.[58]

Surprisingly, the general type of allylation outlined in Scheme 3.3 to give systems containing diverse β-hydroxymethyl-substitution (Path A, Scheme 3.2) had not been examined, aside from the work of Liu and co-workers on γ-substituted adducts involving alkyne-derived molybdenum- or tungsten-π-allyl intermediates (Scheme 3.4; M = MoL_n or WL_n, R = alkyl).[59]

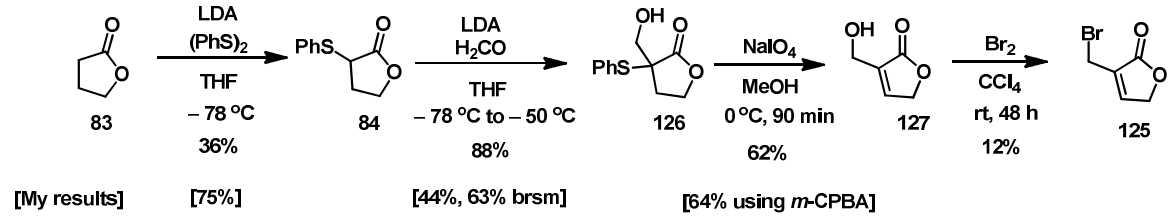


Scheme 3.4 Allylation of Liu.[59]

3.2 New methodology for synthesis of β-(hydroxy)-α-methylene-γ-butyrolactones

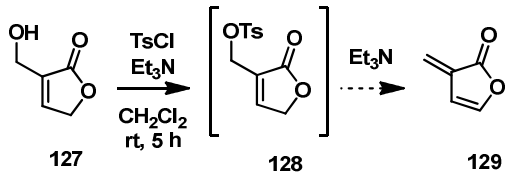
3.2.1 Synthesis of bromolactone 125

At the beginning of our investigation (2010), bromolactone **125** had only been previously made by March *et al.*, (Scheme 3.5) in 4 steps, starting with commercially available γ-butyrolactone (**83**).[55b] Unfortunately, the last step occurred in poor yield.



Scheme 3.5 March's work.[55b]

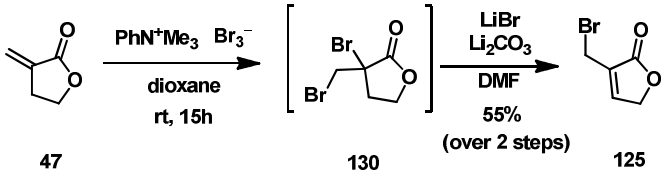
To begin with, we decided to use exactly the same strategy as March, with the hope of finding a way to improve the last step. Having lactone **84** already in hand (See Scheme 2.21, p. 22), a second alkylation with paraformaldehyde gave the alcohol **126** in 44% yield (63% brsm). Oxidation with *m*-CPBA and thermal elimination of the sulfoxide gave the butenolide **127** in 64 % yield. At this stage, it was decided to tosylate the alcohol with the aim of subsequently displacing it *via* a Finkelstein reaction. However, after attempted tosylation no product was recovered and the mass balance of unpurified product was poor. Elimination of the tosylate, with Et_3N, via the mechanism shown in Scheme 3.6, could generate the likely volatile lactone **129** as a possible product.



Scheme 3.6 Possible elimination during tosylation.

With the aim of producing the bromolactone **125** in large quantities, we envisaged a new route. Bromination of commercially available (albeit expensive; 5 mL for £136 : Aldrich®; October 2011) unsaturated lactone **47**[60] followed by selective elimination with LiBr and Li_2CO_3 in DMF[61] gave the more thermodynamically stable alkene **125** in 55% overall yield involving only one chromatographic purification. This elimination has been proposed to pass through a transition state where the base (LiBr) can interact with the α-carbon as well as the β-hydrogen (E2C elimination).[35] Changing the base for an organic one such as DBU, or

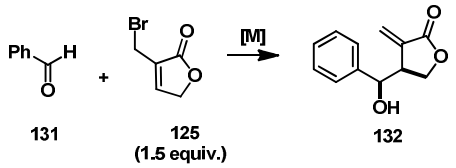
changing the solvent to THF increased the formation of by-products observed by TLC analysis.



Scheme 3.7 Alternative synthesis of **125**.

3.2.2 Allylation using bromolactone 125

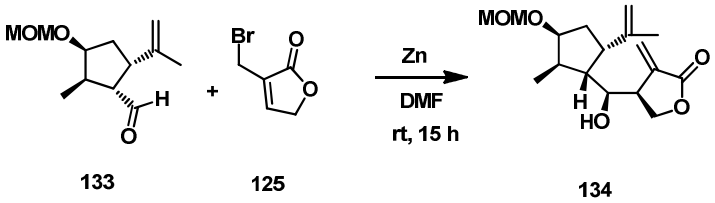
With bromolactone **125** in hand, Barbier-type coupling with benzaldehyde was investigated. As discussed on p. 32-33, allylic chromium[56] (or zinc[62]) intermediates were considered to have the potential to provide high regio- and stereoselectivity in the C–C bond forming step, together with lactone functional group tolerance. In practise, using the chromium(II) sources $CrCl_2$,[63] $CrCl_3/LiAlH_4$,[64] a catalytic chromium process ($CrCl_3$/Mn/TMSCl),[65] zinc with sat. aq NH_4Cl in DMF[66] and indium in the presence of a Lewis acid[67] gave, in all cases, one major diastereoisomer of methylene lactone **132** by ^{1}H–NMR data analysis of unpurified reaction mixture (Table 3.1).



Entry	Conditions	yield of **132**	*dr*
1	$CrCl_2$ in DMF (rt, 15 h)	83%	97:3
2	$CrCl_3/LiAlH_4$ in THF (rt, 15 h)	68%	98:2
3	Cat. $CrCl_3$/Mn/TMSCl/*i*-Pr_2EtN in THF (rt, 15 h)	85%	98:2
4	Zn/trace sat. aq NH_4Cl in DMF (rt, 15 h)	83%	95:5
5	In/$Eu(OTf)_3$ in sat. aq NH_4Cl (rt, 15 h)	67%	97:3

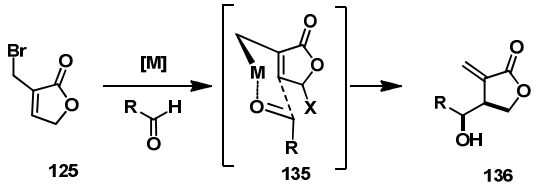
Table 3.1 Metal screening for allylation using bromolactone **125**.

During our preliminary investigation, a Chinese patent[66a] appeared where the same strategy had been used for a different natural product synthesis (Scheme 3.8). *syn*-Diastereoselectivity was obtained with zinc in DMF. In the same patent, the lactone **125** was synthesised via the butyrolactone **127** using PBr_3 in Et_2O in 77% yield.



Scheme 3.8 Chinese Patent.

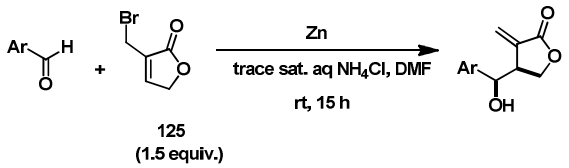
We were initially surprised by the *syn*-diastereoselectivity claimed. Based on our original prediction (p 34), the *anti*- diastereoisomer was expected to be the major product. This observation can be rationalised if, in the transition state, the metal does not chelate to the carbonyl and therefore change the diastereoselectivity via a classic chair transition state (Scheme 3.9).



Scheme 3.9 Transition state hypothesis.

3.2.3 Scope of zinc allylation using aromatic aldehydes

Due to the comparative experimental simplicity of the zinc protocol (Table 3.1, entry 4), it was decided to evaluate the scope of the allylation process with different aromatic aldehydes under the zinc conditions (Table 3.2).



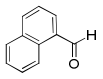
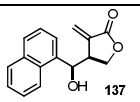
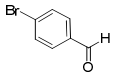
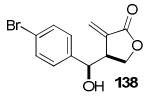
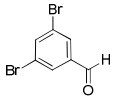
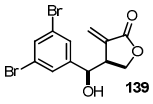
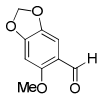
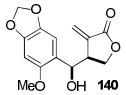
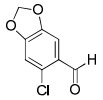
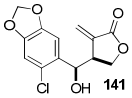
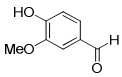
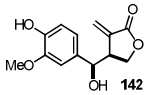
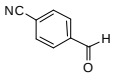
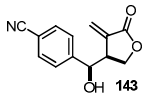
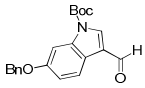
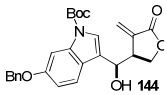
Entry	aldehyde	lactone	yield	*dr*
1			79%	99:1
2			91%	94:6
3			78%	95:5
4			73%	90:10
5			74%	90:10
6			71%	90:10
7			82%	90:10
8			67%	90:10

Table 3.2 Scope of allylation using bromolactone **125** with zinc and aromatic aldehydes.

The chemistry was found to tolerate electron-rich (Table 3.2, entries 4 and 6) and -deficient (Table 3.2, entry 7) aromatic aldehydes, the presence of aryl halide (Table 3.2, entries 2, 3 and 5), hydroxyl (Table 3.2, entry 6), cyano (Table 3.2 entry 7) and carbamate (Table 3.2, entry 8) functionality. The stereochemistry of the major diastereoisomer **137** arising from 1-naphthaldehyde (table 3.2, entry 1) was established by X-ray crystallographic analysis.[a] This work supports the provisional diastereoselectivity observed in the Chinese patent.

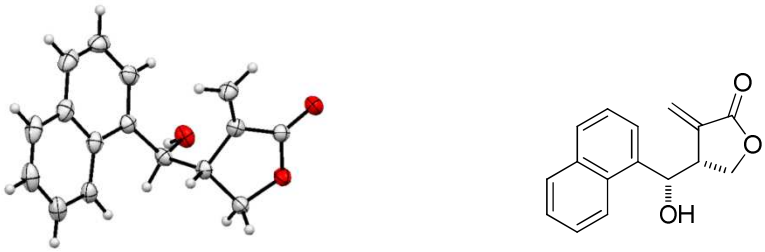
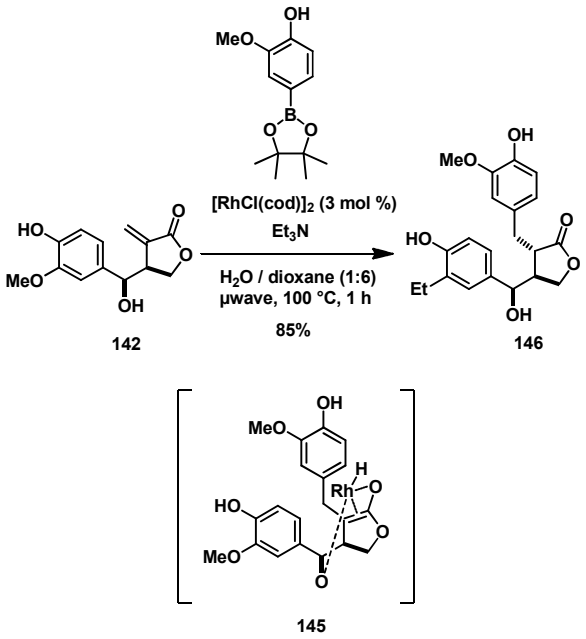


Figure 3.1 X-ray structure of lactone **137**.[b]

3.2.4 Application of zinc allylation

To show the potential of this chemistry, we decided to apply the methodology to a small natural product synthesis. MOM protection of alcohol **140** (Table 3.2, entry 4) gave a MOM ether of established configuration, which has previously been converted into the insecticide phrymarolin II.[68] 1,4-addition[69] of commercially available boronic ester on the vanillin-derived alcohol **142** (Table 3.2, entry 6) resulted in a concise, protecting group-free, synthesis of the lignan hydroxymatairesinol (**146)**[70] (Scheme 3.10). The excellent control in the introduction of the new stereocenter is likely due to chelation of the alcohol to the rhodium **145**.[69b]

[b] The crystal structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 817384, available at http://www.ccdc.cam.ac.uk.



Comparison of ^{13}C NMR data of (±)-hydroxymatairesinol with previous synthesis[70]							
previous	new	previous	new	previous	new	previous	new
179.2	179.3	133.4	133.4	114	114	55.9	55.9
146.8	146.8	129.4	129.5	111.9	111.8	55.8	55.8
146.5	146.5	122.5	122.5	108.2	108.1	45.1	45.1
145.6	145.6	118.8	118.7	75.4	75.3	43.7	43.7
144.4	144.4	114.4	114.4	68.5	68.6	35.1	35.1

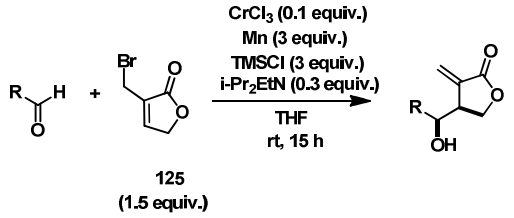
Scheme 3.10 Application of allylation to (±)-hydroxymatairesinol (**146**).

3.2.5 Scope of chromium allylation using unsaturated and aldehydes

Reduction of diastereoselectivity was observed with non-aromatic aldehydes under the zinc allylation conditions: 83:17 *dr* for **147** (79% yield) with the aliphatic aldehyde docecanal, and 55:45 *dr* for **149** (75% yield) with the α,β-unsaturated aldehyde 3-methylbut-2-enal.[c] For such substrates we found that the cat. Cr(II) conditions (Table 3.3, entry 1 and 3) were more effective. Moreover excellent *drs* (98:2 – 99:1) were uniformly observed with different aliphatic aldehydes (Table 3.3), aside from an α,β-unsaturated aldehyde (Table 3.3, entry 3). The mild allylation conditions are indicated by the functional group tolerance of cyano,

[c] After the publication of this work, we decided to reinvestigate the choice of solvent for the zinc allylation and found that using THF with trace of sat aq. NH_4Cl (procedure A', see experimentale section) was as effective as DMF(Procedure A) for unsaturated and aliphatic aldehydes (same diastereoselectivity and yield as seen with DMF)

alkenyl iodide and ketone functionality (Table 3.3, entries 5-7), and the viability of a β,γ-unsaturated aldehydes (Table 3.3, entry 6).



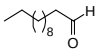
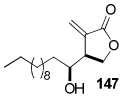
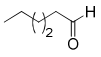
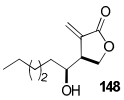
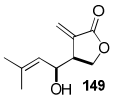
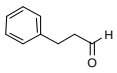
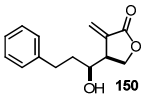
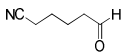
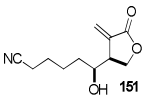
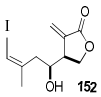
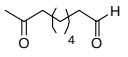
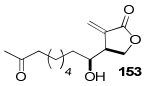
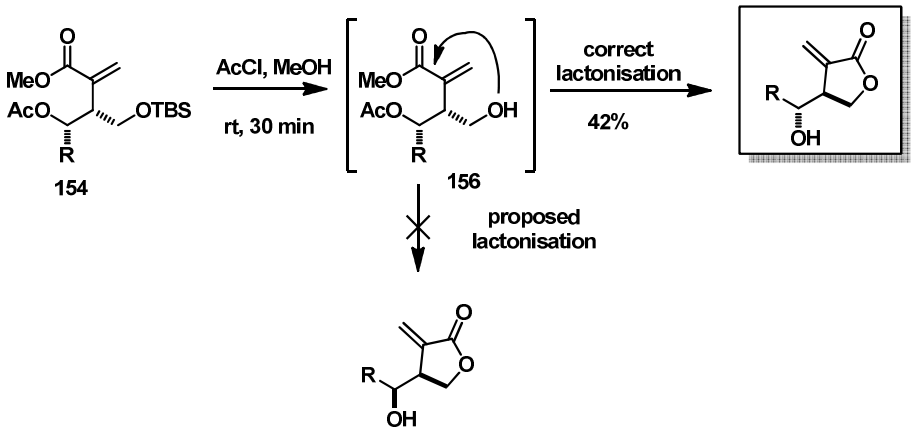
entry	aldehyde	lactone	yield	*dr*
1		 147	94%	99:1
2		 148	93%	99:1
3		 149	55%	88:12
4		 150	75%	99:1
5		 151	65%	99:1
6		 152	56%	98:2
7		 153	70%	99:1

Table 3.3 Scope of the allylation of aliphatic aldehydes using cat. Cr(II) conditions.

To confirm the diastereoselectivity with aliphatic aldehydes, we decided to compare methylene lactone **147** (Table 3.3, entry 1) with the lit.[71] However, the ^{1}H and the ^{13}C NMR data of the lactone **147** were not in accordance with the literature data. Using zinc in DMF afforded the compound as a mixture of diastereoisomers (83:17 *dr*) and surprisingly the minor diastereoisomer was in concordance with the compound previously described in the literature[71] (see experimentale section p. 133). Looking more carefully at the publication, we found that during the lactonisation step they drew the wrong product (Scheme 3.11). These

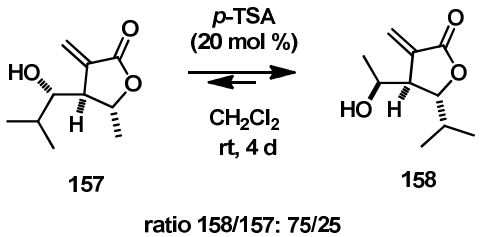
results confirm our diastereoselectivity which is the same as found with the aromatic examples earlier.



Scheme 3.11 Correction of stereochemistry during the lactonisation proposed by Chen.[71]

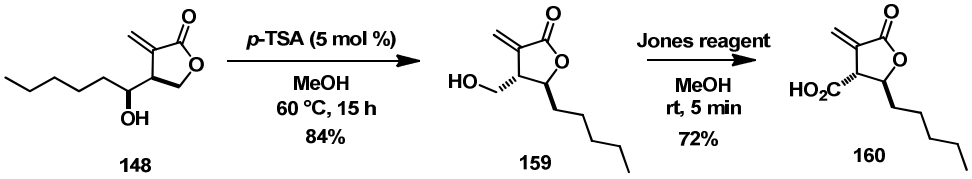
3.2.6 Translactonisation and synthesis of (±)-methylenolactocin (160)

We also examined acid-catalysed translactonisation as a process to isomerise the β-hydroxymethylene products generated in the above chemistry to *trans* β,γ-disubstituted α-methylenebutyrolactones (e.g. **159**, Scheme 3.13). The latter substitution pattern is found in many natural products (see Figure 1.3, p. 3).[72] Although the generation of primary alcohols from secondary alcohols by this approach has not been previously reported, it is known in a related *trans* [β,γ]-disubstituted α-methylenebutyrolactone that a less-hindered (Me-substituted) free secondary alcohol is favored (80:20 – 75:25) over a more hindered (*i*-Pr-substituted) free secondary alcohol at equilibrium (Scheme 3.12).[59a, 59b]



Scheme 3.12 Equilibrium of *trans* β,γ-disubstitued α-methylenebutyrolactone in acidic conditions.

Secondary alcohol **148** (Table 3.3, entry 2) was recovered unchanged using the reported conditions (*p*-TSA, CH_2Cl_2, rt, 15 h) for the secondary alcohol equilibration. However, reaction with 5% *p*-TSA in MeOH (60 °C, 15 h) led smoothly to a 4:96 mixture in favour of the known[73] primary alcohol **159** (Scheme 3.13), which was cleanly isolated in 84% yield. The origin of the thermodynamic preference for primary alcohol **159** may lie in reduction of destabilising *gauche* interactions present in conformations of the secondary alcohol **148**.[74] Jones oxidation[73] of primary alcohol **159** completed a short synthesis of the naturally occurring antibacterial and antitumour agent (±)-methylenolactocin (**160**).[73]



Comparison of ^{13}C NMR data of (±)-methylenolactocin (**160**) with previous synthesis[73]							
previous	new	previous	new	previous	new	previous	new
174.4	173.5	126.1	125.8	35.8	35.7	22.6,	22.4
168.4	168.1	79.1	78.8	31.5	31.3	14	13.9
132.6	132.4	49.7	49.4	24.6	24.4		

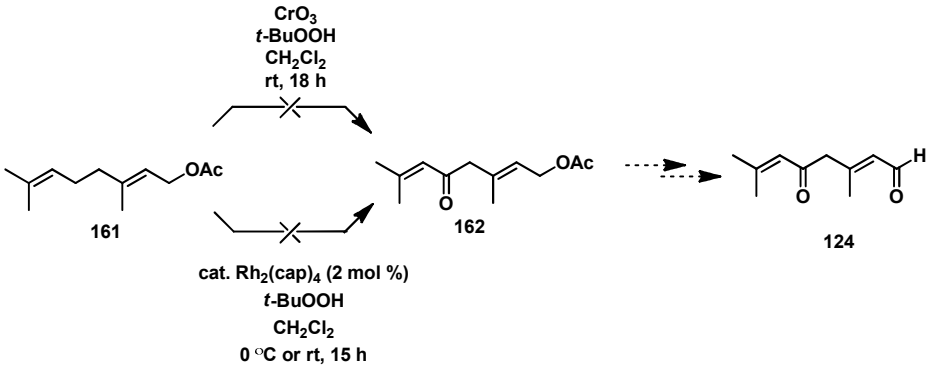
Scheme 3.13 (±)-methylenolactocin (**160**) by translactonisation.

3.3 Synthesis of (±)-hydroxyanthecotulide (2): First strategy

3.3.1 Synthesis of the ketoaldehyde by allylic oxidation

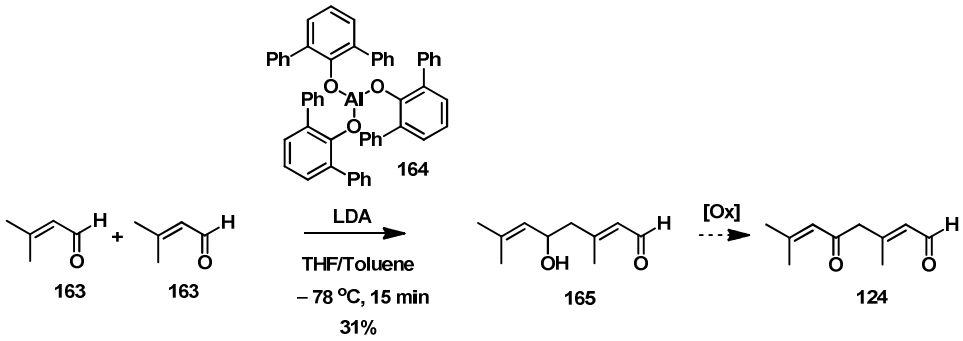
Despite the *syn*-diastereoselectivity obtained from our methodology, we still hoped to use this methodology to access hydroxyanthecotulide and clarify the relative stereochemistry (see Section 1.3, p. 4) of this natural product. Access to required ketoaldehyde **126** (Scheme 3.1, p. 32) was initially planned *via* chromate-mediated allylic oxidation of geranyl acetate (**161**) to give ketone **162** (Scheme 3.14).[75] Although the latter is reported to be very low yielding (~5%), it is direct and the starting material is commercially available and inexpensive. Unfortunately, after attempting the reaction, many products were observed by TLC analysis.

After chromatography, ^{1}H–NMR analysis of different fractions showed no trace of ketone **162**. The use of dirhodium(II) caprolactamate, recently reported to catalyse allylic oxidation of cycloalkenes,[76] also proved unsuccessful. TLC and ^{1}H–NMR data analysis of unpurified reaction mixture, again indicated many by-products, which could not be identified (Scheme 3.14).



Scheme 3.14 Attempted allylic oxidation of geranyl acetate (**161)**.

Another strategy subsequently envisaged was by way of a vinylogous self aldol reaction of 3-methylbut-2-enal (**163)** (Scheme 3.15).[77]



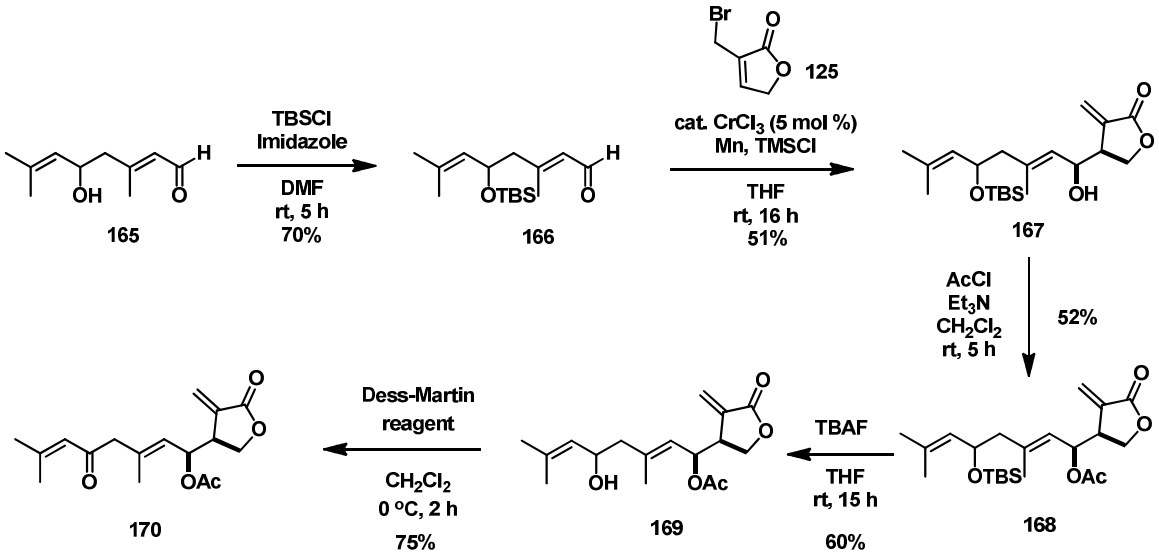
Scheme 3.15 Vinylogous aldol reaction.

3.3.2 Synthesis of the ketoaldehyde by vinylogous aldol reaction

The vinylogous aldol reaction developed by Yamamoto[77b] was used to access ketoaldehyde **124**. Treatment of aldehyde **163** (2.0 equiv.) with a solution of bulky aluminum tris(2,6-diphenylphenoxide) (ATPH **164**) (2.2 equiv.) in toluene at −78 °C under argon was followed by deprotonation using a THF solution of LDA (1.2 equiv.). The reaction mixture was stirred

for 15 min, then quenched with aqueous NH_4Cl to give, after chromatography on silica gel, homoallylic alcohol **165** in ~30 % yield. Changing the temperature (to −30 °C and 0 °C), the reaction time (5 min and 60 min) and solvent ratio (2/1 or 1/2 of THF/Toluene) did not improve the chemical yield. Unfortunately, attempted oxidation of alcohol **165** (using PCC, PDC, Dess-Martin, TPAP/NMO, MnO_2, Pfitzner–Moffatt or Swern) gave a mixture of *E*/*Z* isomers of **124** (determined by ^{1}H–NMR data analysis of unpurified reaction mixture; ratio *E*/*Z* = 4/1; aldehyde proton for *E*-isomer: 9.91 ppm and aldehyde proton for *Z*-isomer: 9.76 ppm) and other by-products. Purification of the unpurified product from these attempted oxidations on silica, Fluorosil® or alumina led to decomposition and using the unpurified mixture for the next step in our proposed synthesis (catalytic chromium allylation) gave no product (by ^{1}H–NMR data analysis of unpurified reaction mixture). Due to the instability of aldehyde **124**, I decided to protect the alcohol **165** and carry this forward in the synthesis (See Scheme 3.16, below).

3.3.3 Synthesis of acetoxyanthecotulide



Scheme 3.16 New strategy via protection and deprotection steps.

The sequence shown in Scheme 3.16 was carried out with only 100 mg of **165** without optimisation. Protection of alcohol **165** with TBSCl, followed by catalytic chromium

allylation (5 mol %) gave the desired lactone **167** as one diastereoisomer (assumed to be *syn;* see Section 3.2.5 p. 40*).* It has been observed by Kishi[78] that catalytic Cr-mediated coupling in the presence of TMSCl does not proceed to completion for enolisable aldehydes because of silyl enol ether formation. Therefore, in an attempt to improve the yield of **167**, we decided to use $Zr(Cp)_2Cl_2$ which has been found to be a more effective dissociating agent than TMSCl. Unfortunately, in our case, only 20% of the desired lactone was obtained along with several unknown by-products. Acylation of lactone **167** followed by deprotection with TBAF afforded the acetate **169**. Mild oxidation with Dess-Martin reagent gave synthetic *syn*-acetoxyanthecutolide (**170**) in 75% yield. There appeared to be some differences in the ^{13}C and ^{1}H NMR chemical shifts between synthetic acetoxyanthecutolide and the data reported in the isolation paper[5] (Figure 3.2). To confirm the structure, we attempted to compare our synthetic material (see Appendix, p. 204-205) with the original ^{1}H and ^{13}C NMR spectra. Unfortunately, after contacting Dr Skaltsa in Greece, only a copy of the ^{1}H–NMR spectrum was received (she was not able to locate the original ^{13}C NMR spectrum); however it proved difficult to draw conclusive results from this data due to the clarity of the spectrum (see Appendix,p. 210).

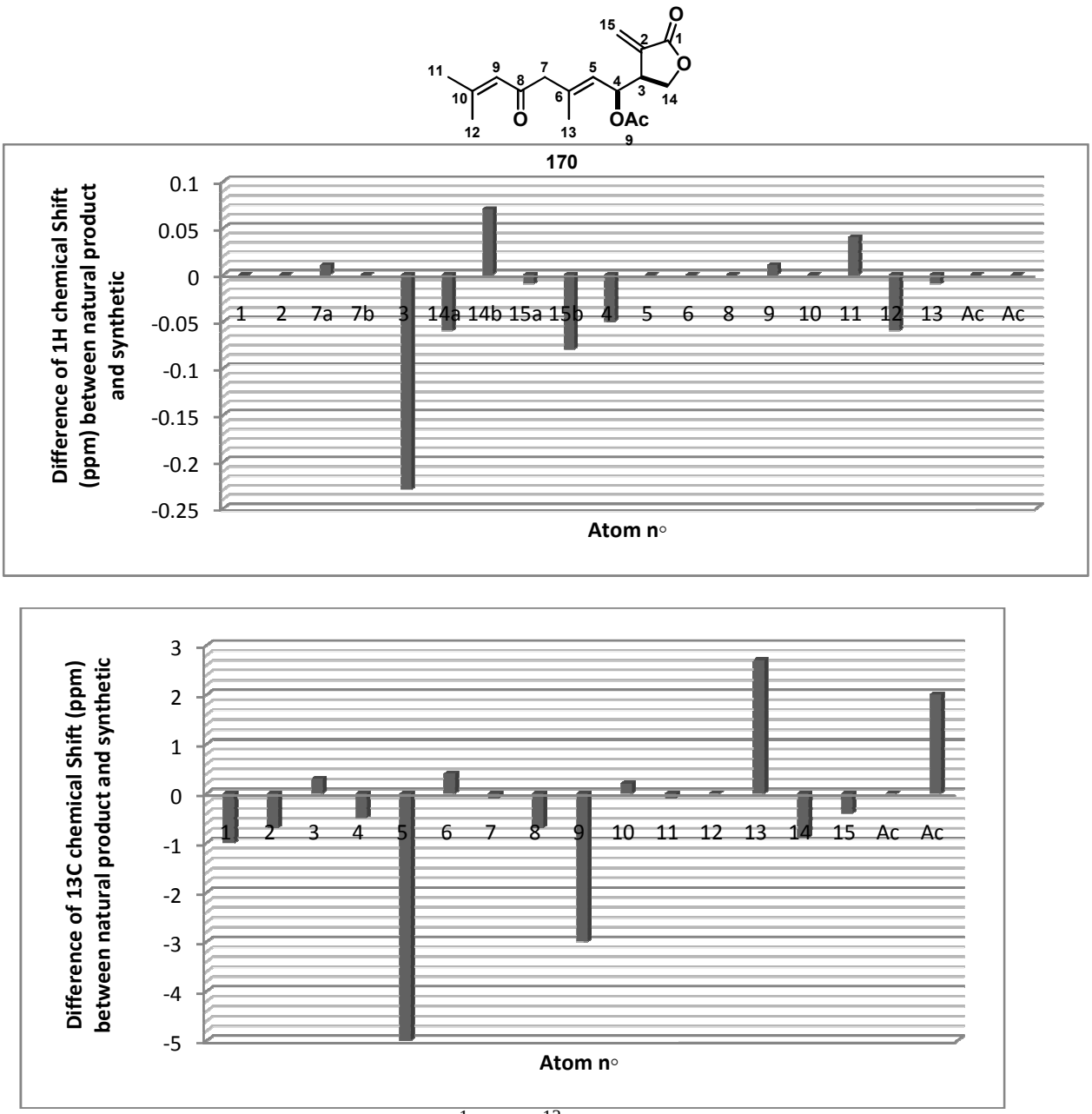
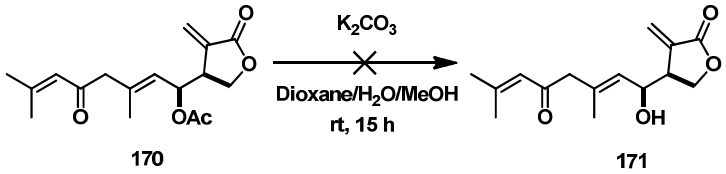


Figure 3.2 Comparison between ^{1}H and ^{13}C–NMR spectra of synthetic *syn*-acetoxyanthecotulide (**170**) and natural product.

Dr. Skaltsa also sent us the ^{13}C and ^{1}H NMR spectra for anthecotulide and hydroxyanthecotulide. We therefore decided to attempt hydrolytic removal of the acetoxy group from synthetic acetoxyanthecutolide (**170**). However, acetoxyanthecutolide is very base sensitive due to the presence of the lactone and the two acidic α-protons of the β,γ-unsaturated ketone. We decided to attempt deacylation using K_2CO_3[79] in dioxane/water

(Scheme 3.17). After 6 h, no product was observed by TLC analysis; only starting material remained intact. MeOH was added and the reaction mixture was checked after further 3 h (no sign of decomposition), then left overnight. Decomposition was observed by TLC analysis and only a trace of starting material was observed with unknown by-products by ^{1}H–NMR data analysis of unpurified reaction mixture.



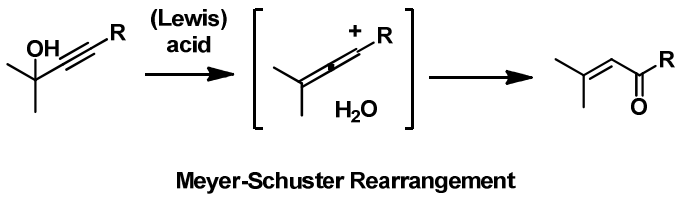
Scheme 3.17 Attempted deacylation of *syn*-acetoxyanthecotulide (**170**).

The main drawback in this retrosynthetic approch is the number of protection and deprotection steps. Moreover, the first step of this synthesis is low yielding and difficult to scale up (ratio ATPH/aldehyde high). In light of this, we decided to investigate other strategies.

3.4 Synthesis of (±)-hydroxyanthecotulide (2): Second strategy

3.4.1 Retrosynthesis using Meyer-Schuster rearrangement

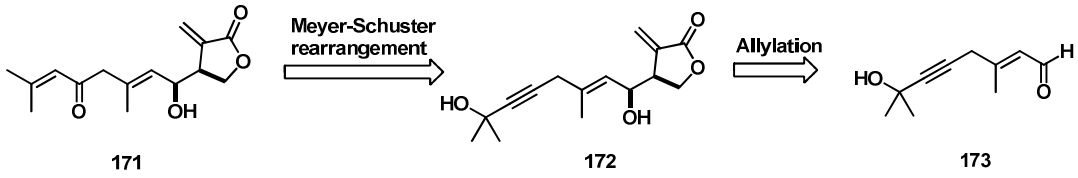
The major problem we encountered during the synthesis of hydroxyanthecotulide (**2**) is the deconjugated labile ketone. Looking at mild ways of generating this ketone, we postulated that using a Meyer-Schuster rearrangement of an alkynol (Scheme 3.18) would be a suitable replacement of our deconjugated ketone.



Scheme 3.18 Meyer-Schuster Rearrangement.

The classic conditions for Meyer-Schuster rearrangements are strongly acidic,[80a] but recently mild methods for the conversion of propargyl alcohols into α,β-unsaturated

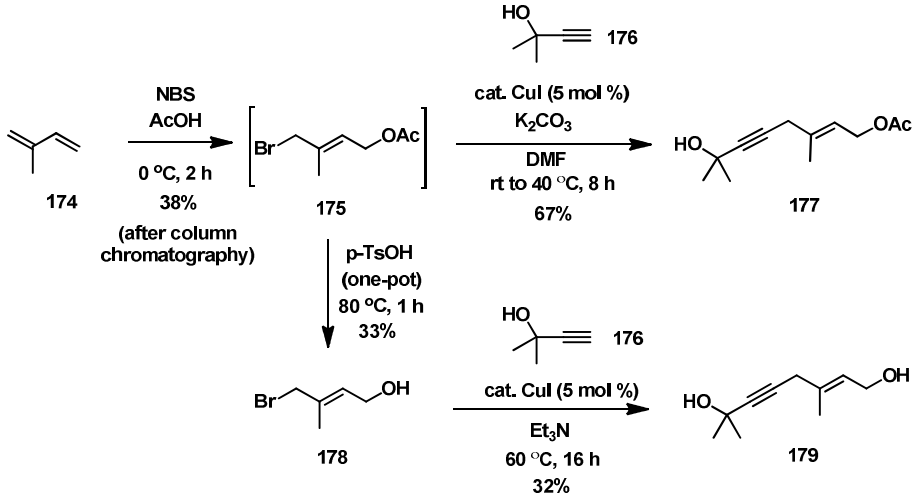
ketones (Meyer-Schuster rearrangements) have been developed.[80b] We decided to investigate the following synthesis (Scheme 3.19)



Scheme 3.19 New synthesis via a Meyer-Schuster rearrangement.

3.4.2 Atempted synthesis of aldehyde 173

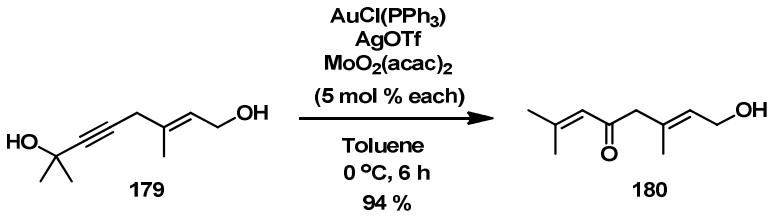
The sequence started with the synthesis of the trisubstitued alkene **175**, easily achieved via bromination of isoprene (**174**) in 33% yield for the free alcohol **178,** and in 38% yield for the acetate **175**.[81] Coupling using Et_3N and cat. CuI (5 mol %) with commercially available and inexpensive alkyne **176** gave 32% of the diol **179**.[82] Using Martin's condition (CuI (5 mol %) and K_2CO_3 (1.2 equiv.)[83]) for the acetate **175**, in the hope of improving the yield, gave alkyne **177** in 67% yield (Scheme 3.20).



Scheme 3.20 Synthesis of precursor **177** and **179.**

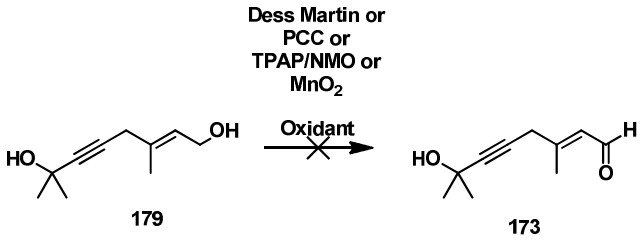
For the Meyer-Schuster rearrangement, Akai *et al.*[84] had reported an effective catalytic combination of $MoO_2(acac)_2$ with $AuCl(PPh_3)$-AgOTf, where rearrangement is considered to proceed by [3,3]-sigmatropic rearrangement of an intermediate molybdate which is facilitated by alkyne coordination to an *in situ* generated cationic gold catalyst.[80b] As a test

for the synthesis of hydroxyanthecotulide (**2**), the Meyer-Schutser rearrangement was performed on the substrate **179** (Scheme 3.21). Using 5 mol % each of triphenylphosphine gold chloride ($AuCl(PPh_3)$), silver triflate (AgOTf) and $MoO_2(acac)_2$ at 0 ^oC for 6 h gave the desired enone **180** in excellent yield (94%). Some impurities were found by TLC analysis, when running the reaction at rt.



Scheme 3.21 Meyer-Schutser Rearrangement on **179**.

Returning to the original synthesis, we tried to selectively oxidise the diol **179**, but all the conditions attempted (Dess-Martin reagent, PCC, TPAP/NMO or MnO_2) led to considerable decomposition. The presence of the desired product **173** (aldehyde proton by ^1H–NMR: 9.92 ppm) was observed by ^1H–NMR data analysis of unpurified reaction mixture but purification on silica, alumina or Fluorisil® proved unfeasible due to the instability of aldehyde **173**.

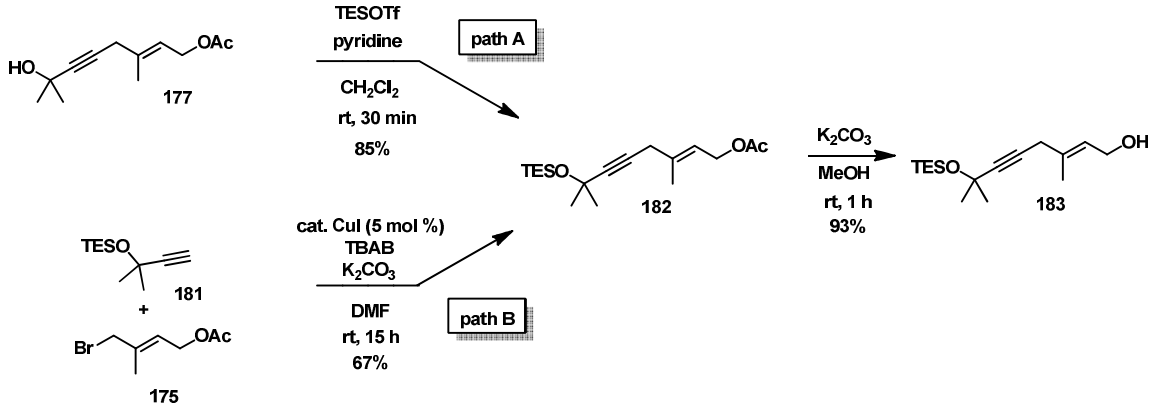


Scheme 3.22 Attempted oxidation of **179**.

3.4.3 Synthesis and stereochemical assignment of hydroxyanthecotulide

We decided to protect the tertiary alcohol (to avoid any problems during the oxidation step) using triethylsilyl triflate (85%), followed by deprotection of the acetate using K_2CO_3 in MeOH (93%) which gave alcohol **183** (Path A, Scheme 3.23). Alternatively, displacement

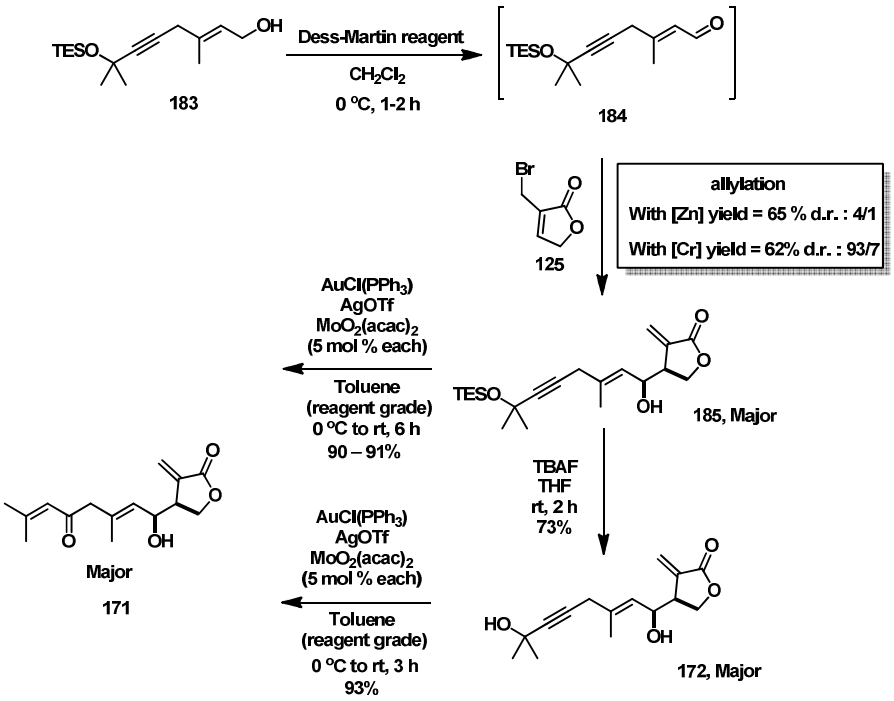
of the allylic bromide **175** with known alkyne **181**[85] gave allylic **182** (67%), followed by the same deprotection, also gave allylic alcohol **183** (Path B, Scheme 3.23).



Scheme 3.23 Synthesis of allylic alcohol **183**.

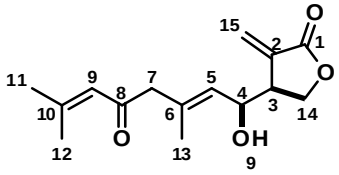
This time, clean oxidation of **183** with Dess-Martin reagent led to the desired aldehyde **184** (Scheme 3.24) without isomerisation of the double bond (determined by ^{1}H–NMR data analysis of unpurified reaction mixture), but aldehyde **184** was still unstable to chromatography. The next reaction was performed without further purification of the aldehyde. For this allylation, we decided to initially use the zinc procedure (see Section 3.2.2, p. 36) which is less sensitive to moisture and impurities than the catalytic chromium chemistry. We were pleased to generate the coupled lactone **185** in 65% yield (4:1 *dr*, Scheme 3.24). With this result in hand, we decided to carry out the rest of the synthesis with a mixture of diastereoisomers, in the hope of confirming the relative stereochemistry of the natural product (see Section 1.3, p. 4). At the same time, we attempted to improve the diastereoselectivity by using catalytic chromium (see Section 3.2.5, p. 40). Achieving the coupling with catalytic chromium was more problematic as the reaction proved to be very sensitive to the quality of the TMSCl. Successful results (yield > 40%) were obtained only when the TMSCl was freshly distilled (stored over polyvinylpyridine) and passed through basic alumina before use. Optimised results were obtained by following the reaction carefully. After 4 h, usual work-up gave the desired alcohol **185**, together with the corresponding TMS ether (ratio 4/1). Using one drop of 1 M HCl in THF at 0 °C and

stirring for 30 min afforded the desired lactone **185** in 62% yield (*dr* : 93/7) after column chromatography. In both cases (lactone **185** from zinc or chromium chemistry), using 1 equiv. of TBAF, followed by the Meyer-Schuster rearrangement conditions, gave synthetic *syn*-hydroxyanthecotulide **171** in 78% yield (over 2 steps). During the process, we discovered that the Meyer-Schuster conditions were acidic enough to facilitate desilylation and gave, directly, synthetic hydroxyanthecotulide **171** from **185** in one step, in 90-91% yield.



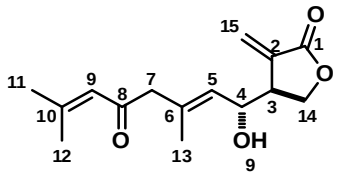
Scheme 3.24 Zinc and chromium induced allylation of aldehyde **184**.

Differentiation of diastereosiomers by ^{1}H–NMR analysis was difficult, which is why only ^{13}C NMR data of the major and minor diastereoisomer from the zinc chemistry were compared to the natural product (Figure 3.3).



Major (*syn*)

171



Minor (*anti*)

2

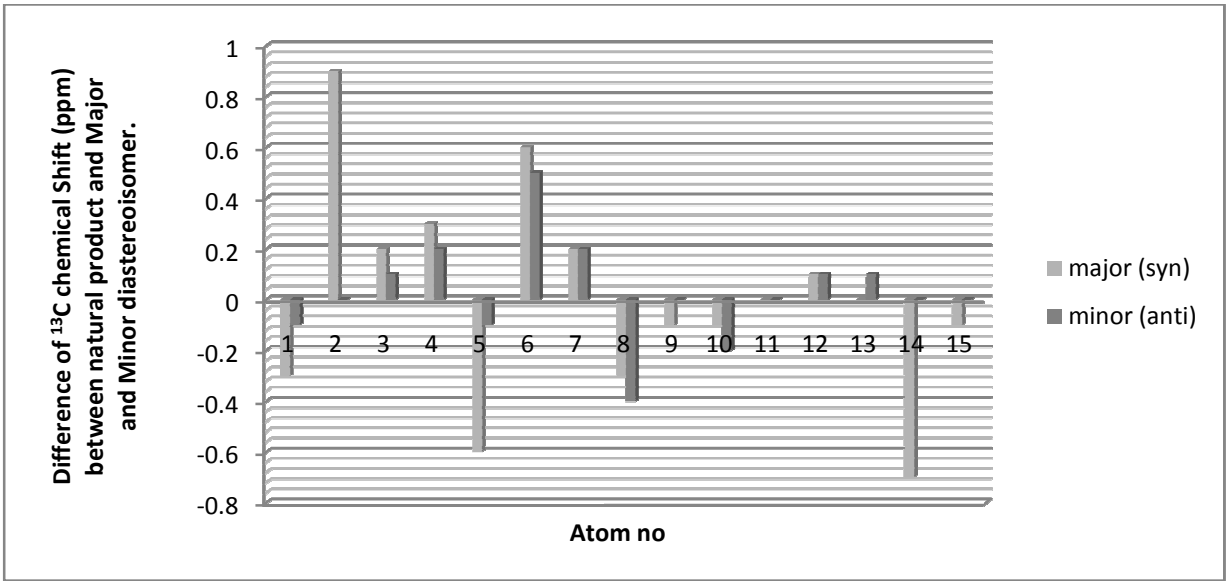
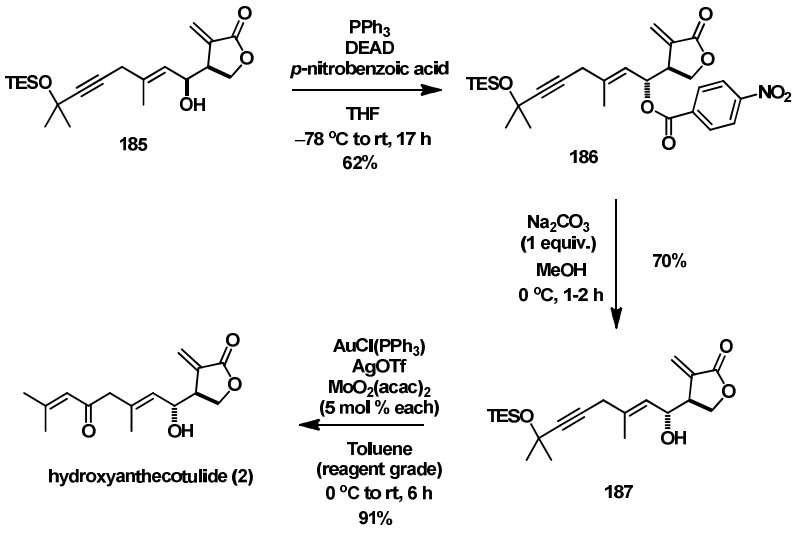


Figure 3.3 Comparison of Natural[5] and Synthetic ^{13}C–NMR data of hydroxyanthecotulide (**2**) and (**171**) derived from zinc chemistry.

Comparison of ^{13}C–NMR spectral data (Figure 3.3) indicates that the minor diastereoisomer (black bars closer to baseline) possesses the same relative configuration as the natural product. We therefore decided to invert the secondary alcohol via a Mitsunobu reaction.



Scheme 3.25 Synthesis of hydroxyanthecotulide (**2**).

We were not able to apply the Mitsunobu reaction using *p*-nitrobenzoic acid and DEAD on our final substrate **171** due to the sensitivity of the molecule, only degradation was observed by ^{1}H–NMR data analysis of unpurified reaction mixture. Pleasingly, using *p*-nitrobenzoic acid and DEAD with **185** gave the lactone ester **186** in 62% yield. Different bases and solvents were examined for the ester hydrolysis of **186** such as LiOH, K_2CO_3 or Na_2CO_3 in MeOH, THF or water. We finally found that using 1 equiv. of Na_2CO_3 in MeOH, and carefully following the reaction at 0 °C for 1-2 h gave, after work-up, the inverted alcohol **187** which was converted to hydroxyanthecotulide (**2**) under the standard Meyer-Schuster conditions. Small differences appeared in the chemical shifts between the mixture of diastereoisomers (from zinc chemistry) and the diastereomerically pure synthetic hydroxyanthecotulide (from chromium chemistry), most likely due to chemical interaction between the diastereoisomers. Comparing ^{13}C–NMR chemical shifts of both diastereoisomers with the natural product was inconclusive (Figure 3.4 (b); only C2 and C14 seem to support that natural product is the *anti*-diastereoisomer (**2**)). On the other hand, comparison of the ^{1}H–NMR chemical shifts of *syn*-hydroxyanthecotulide (**171**) and *anti*-hydroxyanthecotulide (**2**), strongly indicate the concordance of *anti*-

hydroxyanthecotulide (**2**) with the natural product (Figure 3.4 (a), + 0.05 ppm difference for every ^{1}H–NMR signal except for proton **7a** which seems to be a typographical error by looking the original spectrum; see Appendix p.209). Moreover, comparison of our synthetic (**2**) with original ^{1}H–NMR spectrum of the natural product received from Dr. Skaltsa showed them to superposable (see Appendix p. 203 and 209).

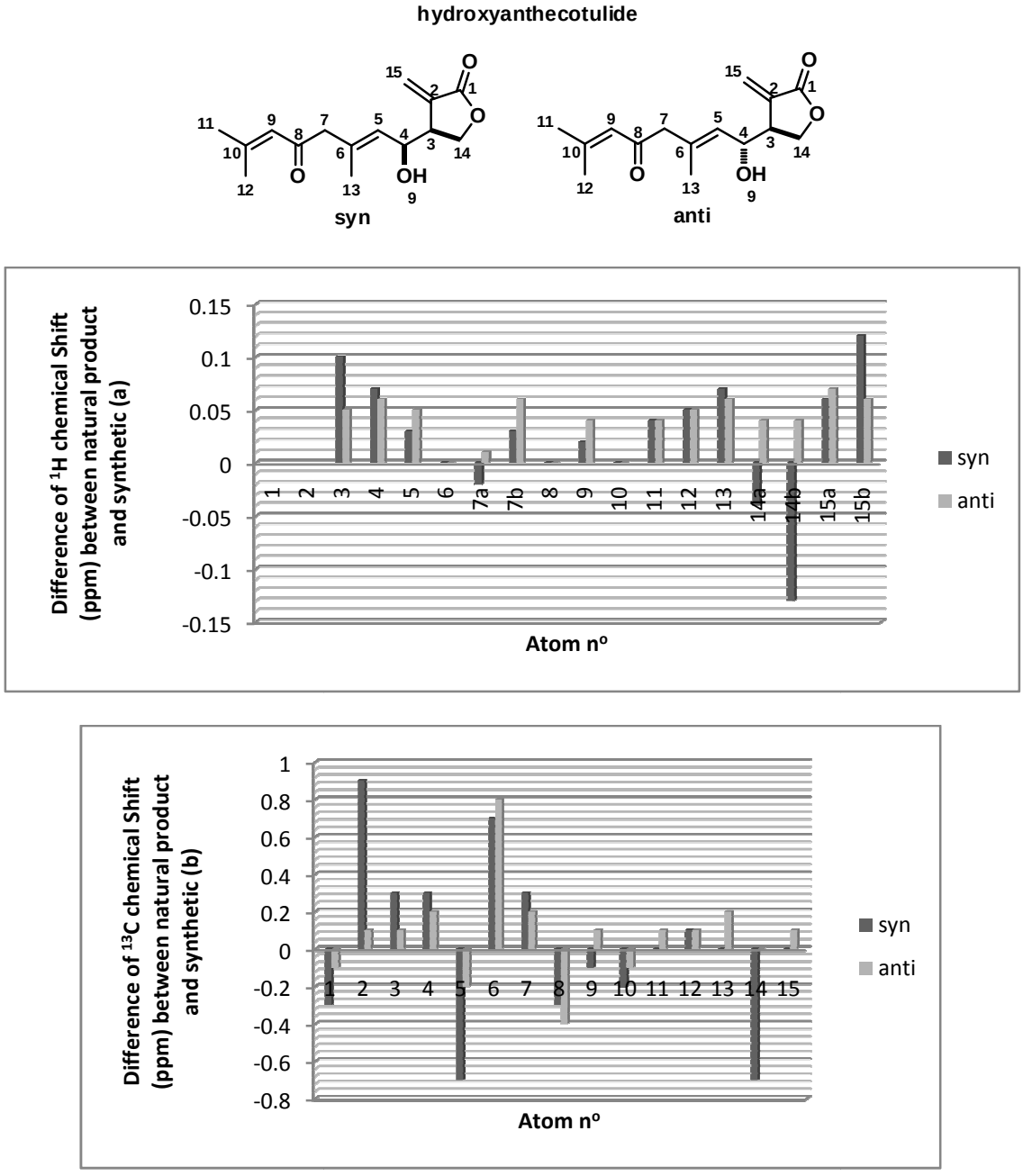


Figure 3.4 Comparison of natural[5] and synthetic NMR data of hydroxyanthecotulide (**2**) and (**171**) derived from chromium chemistry.

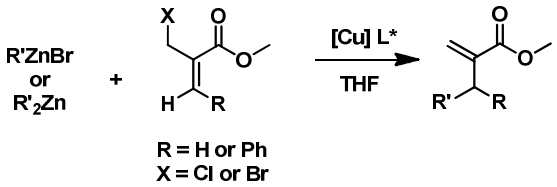
3.5 Biosynthesis of anthecularin

Having a small quantity of the material in hand, we tried to achieve the proposed biosynthesis of anthecularin (**1**) discussed earlier (see Section 1.4, p. 5). Heating *anti*-hydroxyanthecotulide **(2)** in the presence of a UV lamp in benzene at 65 °C afforded no trace of the desired product. Only small impurties was observed by ^{1}H–NMR data analysis of unpurified reaction mixture. Heating at 110 °C in benzene in a microwave reactor was no more successful.

3.6 New application of bromolactone 125

3.6.1 Introduction

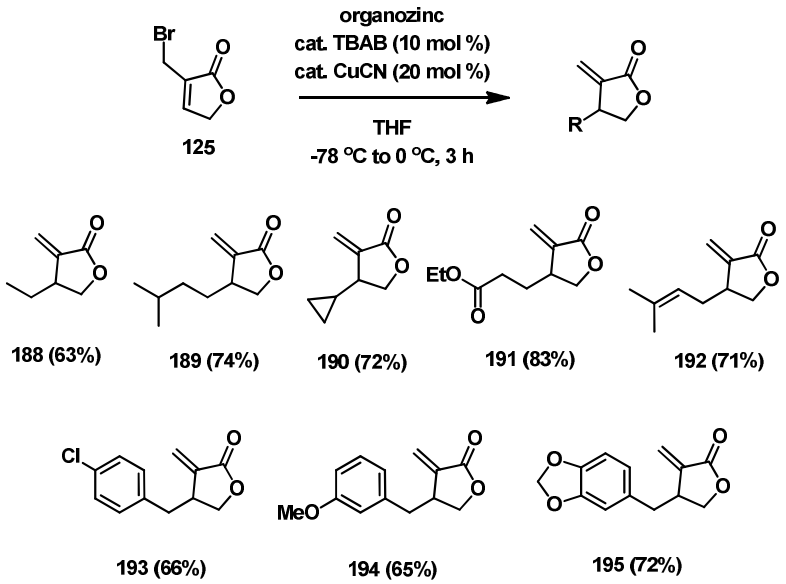
We showed previously that bromomethylfuran-2(5*H*)-one (**125**) could be used as a nucleophile, following conversion to an intermediate allylic chromium or zinc.[2] With the aim of furnishing new applications of bromomethylfuran-2(5*H*)-one (**125**), we decided to see if it was possible to turn the reactivity around and use the bromolactone **125** as an electrophile. We considered that if viable and regioselective, this would be a quick entry to β-(methylvinyl) α-methylene γ-butyrolactones and, ultimately, for the synthesis of anthecotulide (**4**). Woodward and co-workers demonstrated the addition of mono and dialkylorganozinc to bromo/chloro methylacrylate or bromo/chloro phenyl methylacrylate in high yield (high enantiomeric excess for chloroacrylate) (Scheme 3.26).[86]



Scheme 3.26 1,4-addition of organozincs.

3.6.2 Scope of the reaction

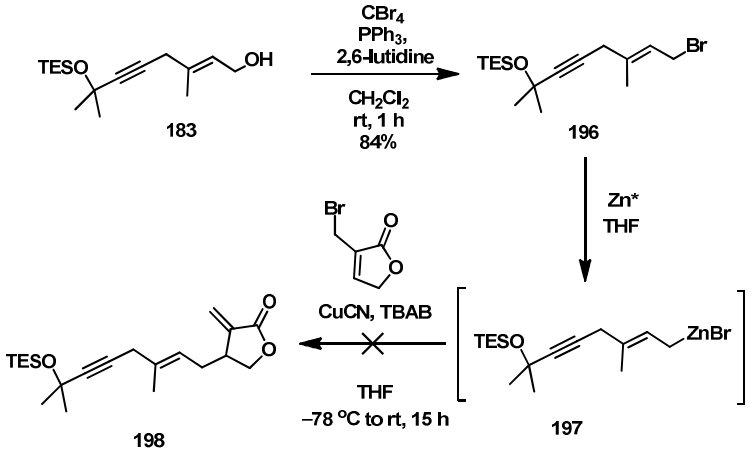
Starting with Woodward's conditions (CuCN and TBAB in THF),[86a] we subjected our lactone to different organozincs. Pleasingly, using diethylzinc, alkyl, benzyl and allyliczinc bromide,[87] the desired products (see below) were obtained in moderate to good yields. Only S_N2' addition was observed (Scheme 3.27).



Scheme 3.27 1,4-addition of organozincs to lactone **125**.

3.6.3 Toward the synthesis of anthecotulide

Following this success, the methodology was applied to anthecotulide (**4**) following the synthetic scheme below (Scheme 3.28).



Scheme 3.28 Attempted synthesis of anthecotulide (**4**).

We decided to use one of our precursors **183** from the previous synthesis (Scheme 3.23, p. 51) to synthesis the allylic bromide **196**. Bromination using the classic Appel reaction (CBr_4/PPh_3) failed to afford the desired compound. However, using a sterically hindered base such as 2,6-lutidine to quench the HBr formed during the bromination[88] gave the desired allylic bromide **196** in 76% yield. Activated zinc (1,2-dibromoethane and TMSCl)[89] was used to form the organozinc **197**, which was used directly in the next step. Unfortunately, after a few attempts (changing the temperature to form the organozinc from – 78 °C, – 40 °C, 0 °C and rt), no desired product was obtained. Complete decomposition of the substrate was observed by ^{1}H–NMR data analysis of unpurified reaction mixture. Our substrate **196** is more sensitive than the previous dimethylallylorganozinc (used to synthesise **192**), due to the presence of the acidic proton between the alkyne and the alkene.

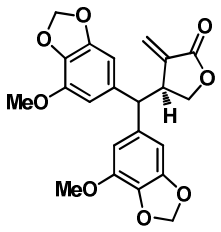
3.6.4 Arylzincs

We decided to look in more detail at the use of aromatic arylzincs. Interestingly, the use of aromatic organozincs has never been report by Woodward.[88] Using commercially available phenylzinc or pyridylzinc bromide under the standard conditions (CuCN and TBAB) gave only recovery of starting material. Raising the temperature to 0 ºC then 25 ºC was no more successful. Using phenyllithium, transmetallated with copper iodide, was also unsuccessful

and gave only recovery of starting material. Using phenylmagnesium bromide alone or in the presence of copper iodide also led to partial recovery of starting material and decomposition. No trace of the characteristic methylene protons (around 6–7 ppm) were observed by ^{1}H–NMR data analysis of unpurified reaction mixture. The poor reactivity of arylzincs is possibly due to steric hindrance.

3.6.5 Application: peperomin C (199)

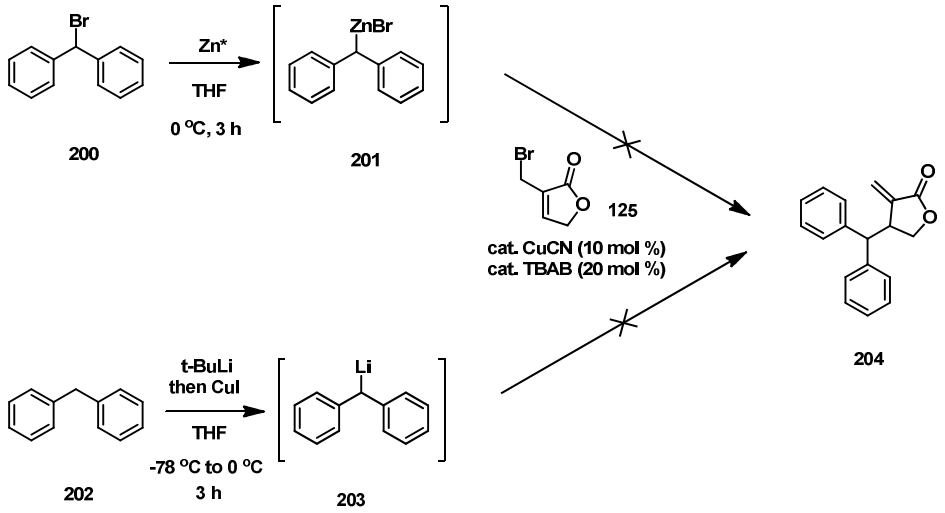
We decided to apply this methodology to the synthesis of natural products. Peperomins are a family of natural products[90] with anti-inflammatory activity.[91] We decided to look at the synthesis of peperomin C (Figure 3.5).[92]



199

Figure 3.5 peperomin C (**199**).

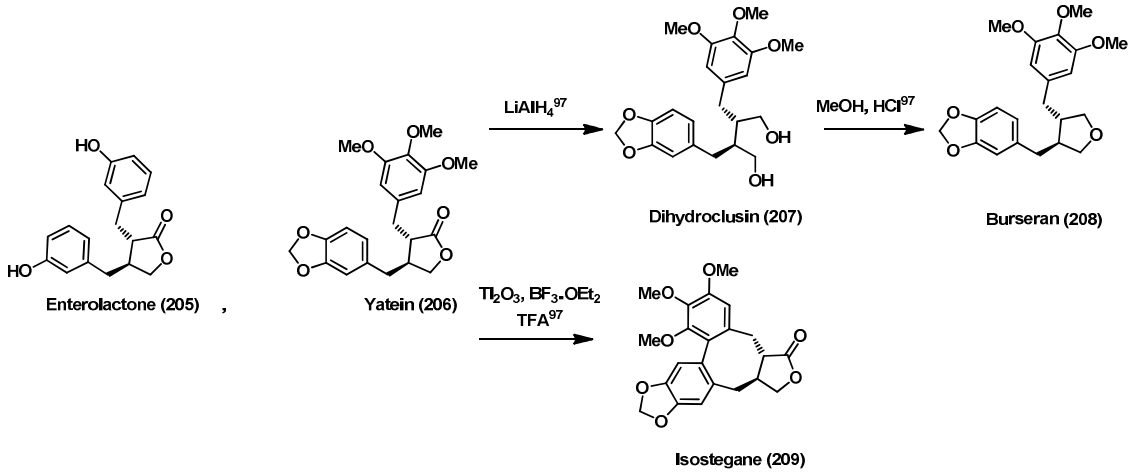
As a model substrate, we decided to use dibenzylorganozincs. To begin with, we needed to prepare the organozinc **201**. A solution of **200** was added to a solution of activated zinc[89] and after 3 h complete consumption of the starting material was observed by TLC analysis. The organozinc was used as previously described and again no product was found, only starting material **125**. Raising the temperature or using Knochel's conditions was also found to be unsuccessful.[93] Trying to transmetallate the lithium salt **203** with copper iodide was no more rewarding (Scheme 3.29).[94]



Scheme 3.29 Model study for peperomin C (**199**).

3.6.6 Application: Enterolactone (205) and Yatein (206)

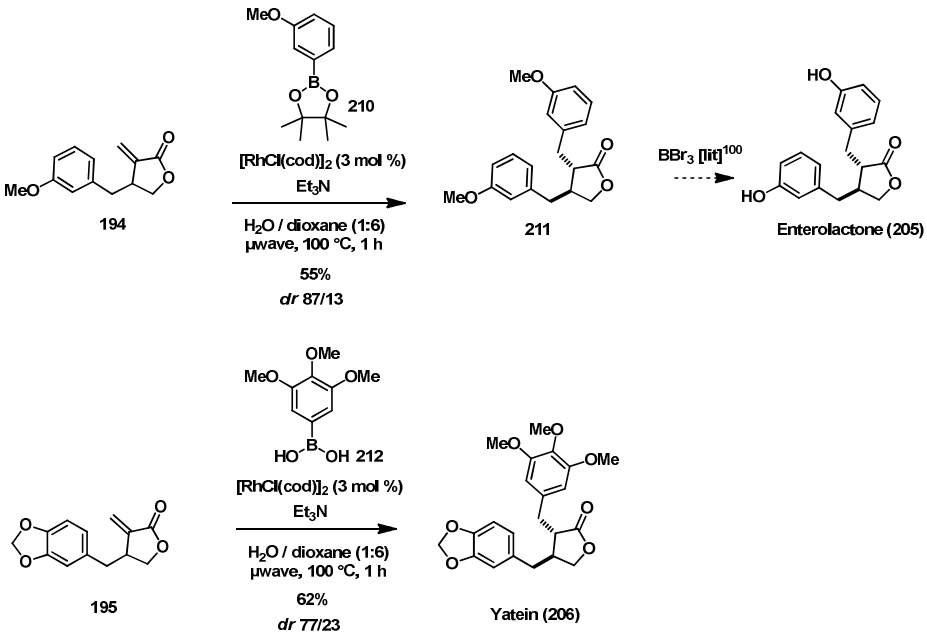
Still with the aim of demonstrating the potential of this methodology, we decided to apply the strategy to other targets. Enterolactone (**205**) and yatein (**206**) are two natural lignans (Scheme 3.30). Enterolactone (**205**) acts as a phytoestrogen[95] while yatein (**206**) shows some antiherpes activity,[96] and is a formal precursor of a range of other lignans such as dihydroclusin (**207**), burseran (**208**) and isostegane (**209**).[97]



Scheme 3.30 Enterolactone (**205**) and yatein (**206**).

Both syntheses are fairly similar. 1,4 - addition of boronic ester **210** and acid **212** with the corresponding methylene lactones **194** and **195**, catalysed by $[Rh(cod)Cl]_2$[69a] gave the desired products **211** and **206** (Scheme 3.31). These conjugate additions occurred in

moderate yield compared to the previous example with a hydroxyl group (where possible chelation of the α hydroxyl group with rhodium could be invoked; see Section 3.2.4 p. 39). In the present case, the *trans*-diastereoisomer **211** was the major but not exclusive product (by comparison of **211** with the literature).[98] Surprisingly, Hall *et al.*, recently published a combinatorial study of methylene lactones, where the *cis*-diastereoisomer formed preferentially during 1,4-addition of boronic acid catalysed by rhodium to the methylene lactone (β,γ-disubstitution).[99] Compared to our work, Hall and coworkers used acidic conditions: $B(OH)_3$ is the proton source whereas in our case water plays the role of proton source. Believing that during basic conditions[100] the *cis*-diastereoisomer isomerises to the thermodynamically more favored *trans*-diastereoisomer, we decided to add 1 equiv. of Et_3N to **211** after the rhodium-catalysed reaction in an attempt to achieve isomerisation. However, no change of *dr* was observed after heating for 2 h in a microwave at 100 °C. Due to resources and time, Hall's conditions were not examined for the conjugate addition.



Scheme 3.31 Syntheses of enterolactone (**205**) and yatein (**206**).

At the end of this work, we questioned the use of TBAB in the Zn additions. Woodward *et al.* used TBAB in the presence of allylic chlorides. We repeated the reaction using 2-methoxybenzylzinc chloride both in the presence of and in the absence of TBAB, and a similar yield of 70% of **194** (Scheme 3.27, p 57) was obtained in both cases.

3.7 Summary

During this chapter, we discovered a new methodology for the stereoselective synthesis of β-hydroxymethyl-α-methylene-γ-butyrolactones and applied this chemistry for the first synthesis of (±)-hydroxyanthecotulide (**2**) via gold-catalysed Meyer-Schuster rearrangement. During the synthesis we also confirmed and assigned the stereochemistry of **2**. We have also shown the possibility of reversing the reactivity of bromolactone **125** using organozinc chemistry to synthesise β-methyl-α-methylene γ-butyrolactones.

Chapter 4. Towards asymmetric synthesis of anthecotulides

This chapter details different approaches for an asymmetric synthesis of β-(hydroxy)-α-methylene-γ-butyrolactones using asymmetric chromium chemistry or Rh(I)-catalysed asymmetric enyne rearrangement followed by α-oxygenation of the aldehyde. This chapter culminates in the first asymmetric synthesis of (+)-anthecotulide (**4**).

4.1 Enantioselective allylation with organochromium chemistry

Several ligands (Scheme 4.1) have been used for asymmetric allylation with chromium salts, but only simple allylic bromides, such as crotyl bromide or allyl bromide, have been tested.[101] We decided to start with two ligands that appeared easier to access, those reported by Sigman (**213**)[102] and by Kishi (**214**).[103]

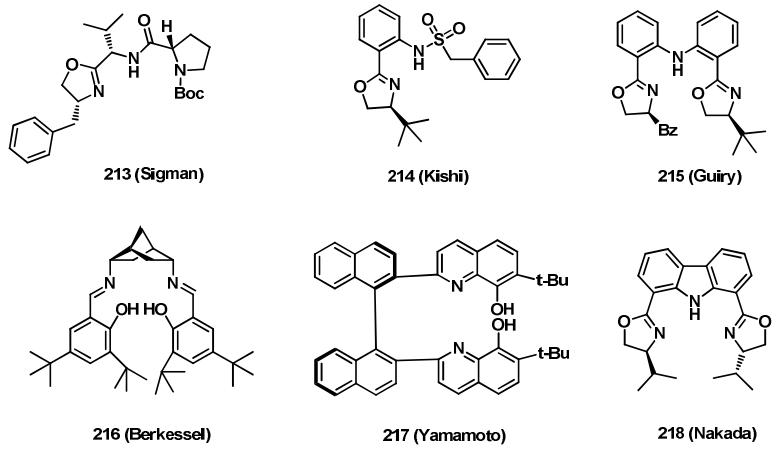
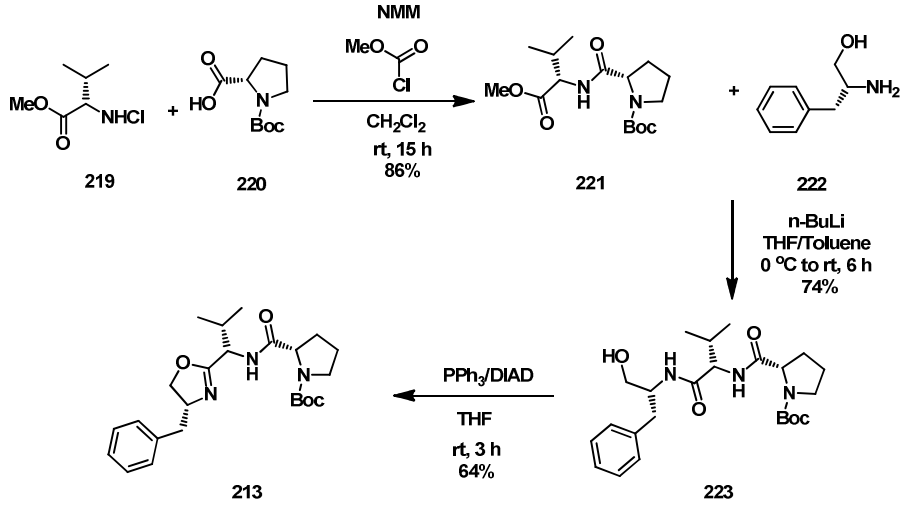


Figure 4.1 Chiral ligands for asymmetric allylation with chromium.

4.1.1 Sigman's ligand

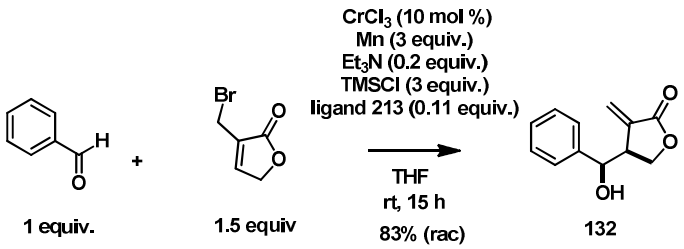
The first ligand synthesised was Sigman's ligand **213**, reported in 2005 as exhibiting good asymmetric induction with aryl aldehydes and unsaturated aldehydes.[102] A recent publication

proposed the synthesis of this ligand in three steps, without column chromatography (Scheme 4.1).[104]



Scheme 4.1 Synthesis of Sigman's ligand.[104]

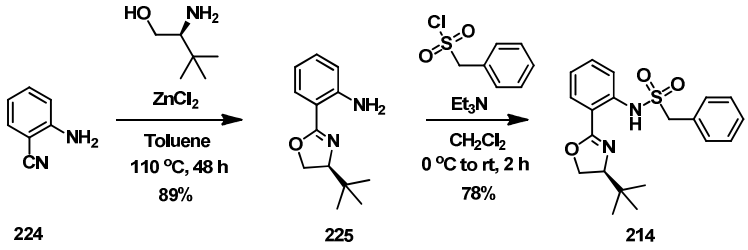
The synthesis starts with the coupling of *(S)*-valine methyl ester **219** (commercially available or easily accessible from the inexpensive acid with $SOCl_2$ in MeOH)[105] and Boc-proline **220** using *N*-methylmorpholine (NMM) and methyl chloroformate in 86% yield. Unfortunately, it was not possible to crystallise **221** and column chromatography was necessary to achieve good purity for the next step. Acyl transfer with n-BuLi in THF and toluene gave alcohol **223** in 74% yield. The oxazoline core was generated in moderate yield (64%) using Mitsunobu reaction conditions (PPh_3/DIAD). Again, no crystallisation was achieved, and column chromatography was required to purify the ligand. Variable temperature NMR data matched with the experimental data but our ligand **213** was not crystalline, as claimed in the publication.[104] Allylation using bromolactone **125** with benzaldehyde gave the lactone **132** in good yield (83%) but as a racemate (Scheme 4.2) (CHIRALPAK IB, 1.25 mL/min, 2% IPA/Hexane) t_R: 11.42 min and 14.12 min.



Scheme 4.2 Allylation with Sigman's ligand.

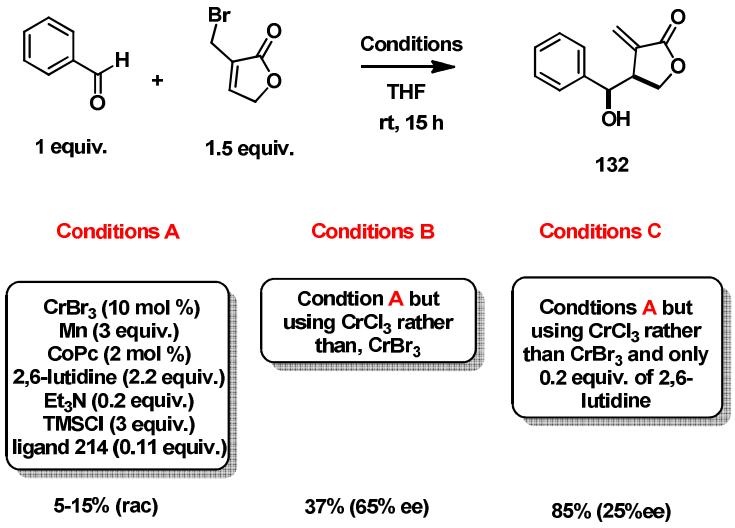
4.1.2 Kishi's ligand

The synthesis of the ligand **214** was achieved in two steps starting from commercially available aniline **224** in good yield (Scheme 4.13).[103]



Scheme 4.3 Synthesis of Kishi's ligand.

The ligand was tested under the following experimental conditions (Scheme 4.4):



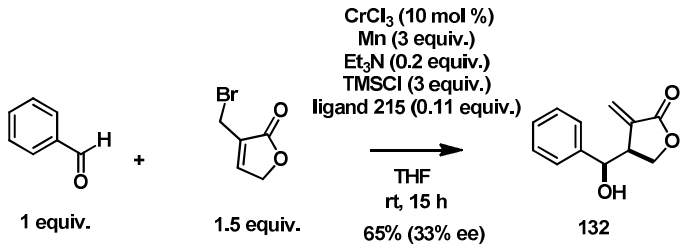
Scheme 4.4 Results with Kishi's ligand.

Kishi's conditions (Scheme 4.4, Conditions A) gave the desired lactone **132** in low yield as a racemate. We believe this result reflects the quality of the anhydrous $CrBr_3$ (old bottle found in the laboratory, salts activated by flame-drying under vaccum). Unfortunately, dry $CrBr_3$ is

not commercially available. Using the previous conditions with $CrCl_3$ instead (Scheme 4.4, Conditions B) resulted in 65% *ee* and 37% yield. The benefiting effect of 2,6-lutidine on enantioselectivity was discovered by Kishi[106] but no explanation has been given on its mechanism of action. Believing that a possible negative effect of 2,6-lutidine on bromolactone **125**, we decided to decrease the amounts of 2,6-lutidine (Scheme 4.4, Conditions C). Interestingly, the yield was increased to 85% but *ee* decreased to 25%.

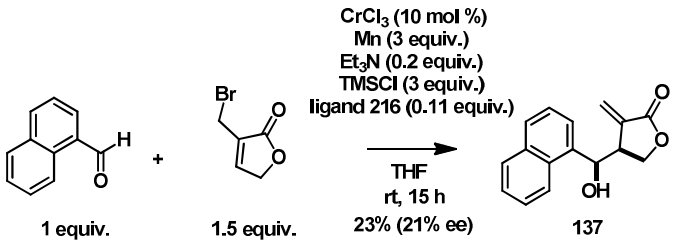
4.1.3 Guiry's and Berkessel's ligands

During our investigation we also contacted Guiry who kindly offered us a small amount of his ligand **215**.[107] Using Guiry's ligand, I managed to form the desired lactone **132** in 65% yield and 33% ee (Scheme 4.5).



Scheme 4.5 Allylation with Guiry's ligand.

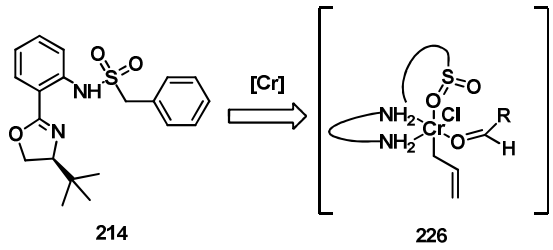
At this stage of the screening, we decided to use 1-naphthaldehyde to evaluate ligand efficiency due to an easy separation of each enantiomer by chiral HPLC (CHIRALPAK IB), 1.3 mL/min, 5% IPA/hexane) t_R: 26.86 min and 37.86 min.). Commercially available (TCI) Berkessel's ligand[108] **216** gave the desired lactone which was isolated in 23% yield and 21% ee (Scheme 4.6).



Scheme 4.6 Allylation with Berkessel's ligand.

4.1.4 New ligands

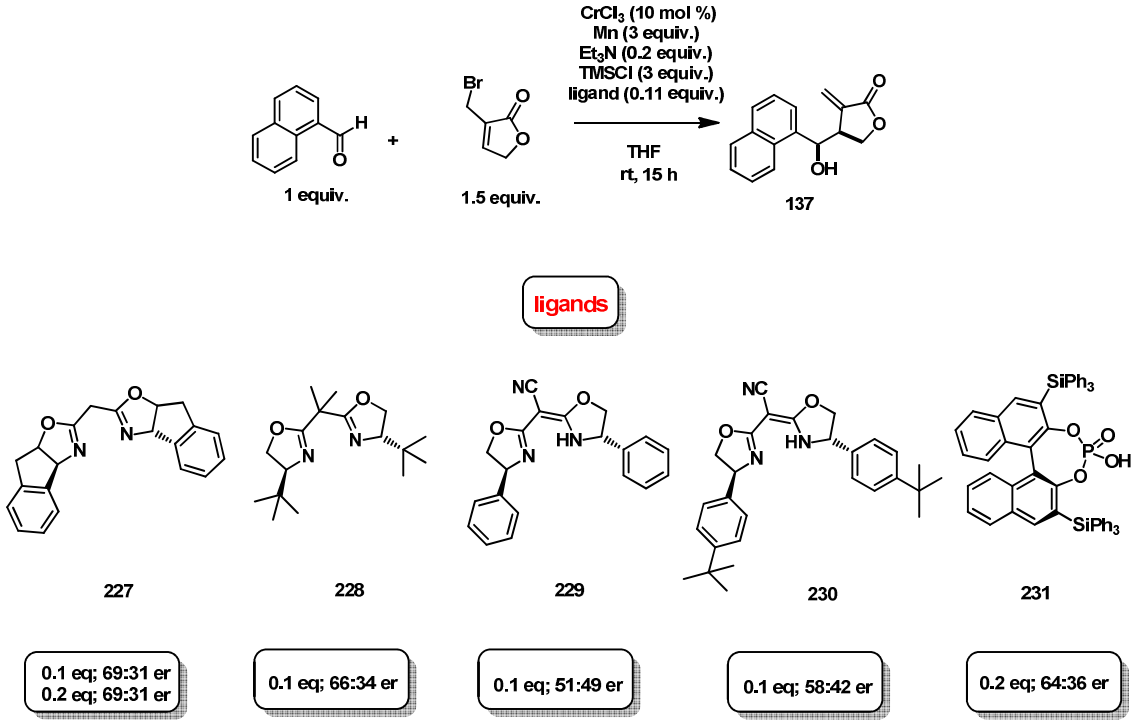
Kishi has proposed a model for his ligand where 4 of 6 coordination sites of the hexadentate chromium were used by the ligand and the other two were used for the aldehyde and the allyl fragment (Scheme 4.7).[109]



Scheme 4.7 Proposed active species for the allylation with Kishi's ligand.

With bromolactone **125**, an extra coordination site is possible with the carbonyl group. Based on this hypothesis, we decided to screen some bidentate ligands where an extra-coordination site is possible. Moreover, in an early report by Kishi,[110] a bidentate bisoxazoline ligand was used and showed moderate levels of enantioselectivity (30% ee). The major problem of a bidentate ligand is the reversibility of the ligand binding to the chromium and the possibility that two ligands can be attached to the chromium. To extend our studies with different ligands (Scheme 4.8), we also decided to use phosphoric acid **231** (kindly offered by the Dixon group) which has been used in both organocatalysis and, more recently, with Mn in asymmetric epoxidation.[111] During the screening, yields were poor by ^{1}H–NMR data analysis

of unpurified reaction mixture (< 40% conversion), leaving us unable to purify properly **137.** At this stage, only er's were obtained (Scheme 4.8).



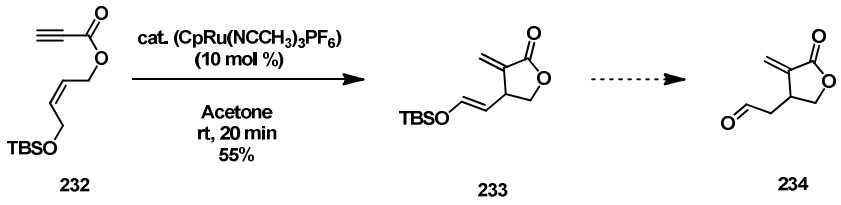
Scheme 4.8 Results with new ligands **227**, **228**, **229**, **230** and **231**.

Most ligands showed only moderate levels of enantioselectivity. Interestingly, the presence of cyano or dimethyl functionality does not seem to influence asymmetric induction. We also varied the stoichiometry of the ligand to study the coordination on the chromium. With ligand **227**, no change of enantioselectivity was observed with 2 equiv., which may imply that the active catalyst has one ligand. We were pleased to see moderate asymmetric induction with 2 equiv. of phosphoric acid **231** which has never been used before for this kind of transformation. Unfortunately we were not able to generate high ee using this different ligand. Kishi's ligand **214** gave us the best results but, due to resources and time, we decided to focus on another strategy to achieve an asymmetric synthesis of the anthecotulides.

4.2 Enantioselective synthesis of methylene lactone *via* enyne chemistry

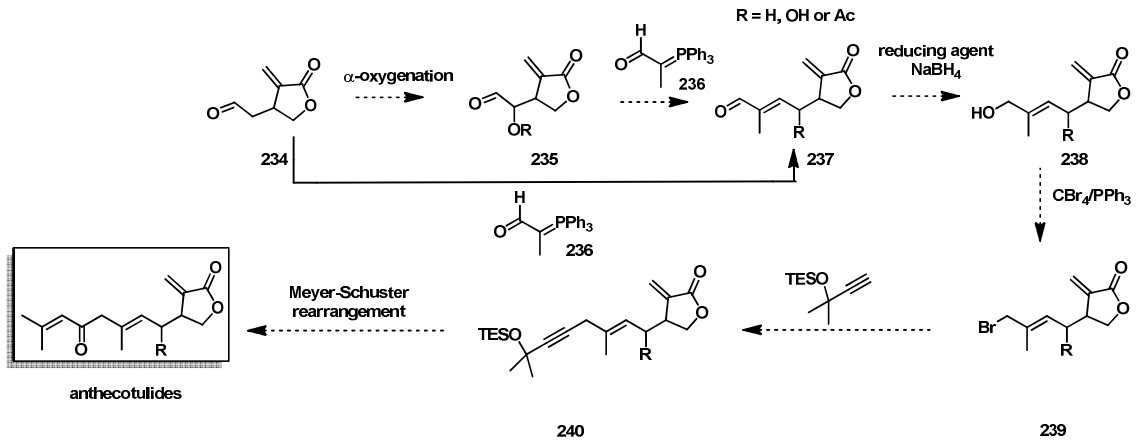
4.2.1 Introduction

Still aiming to find a way to synthesis the anthecotulides in an asymmetric fashion, I went back to the literature and was interested by metal-catalysed formation of 5-membered rings generated from 1,6-enynes. Although metal catalysed Alder-ene reactions of 1,6-enynes have been well-studied,[112] to the best of our knowledge only a single isolated example to form an α-methylene-γ-butyrolactone[113] has been reported using an achiral ruthenium(I) catalyst ($CpRu(NCCH_3)_3PF_6$) (Scheme 4.9).



Scheme 4.9 α-methylene-γ-butyrolactone synthesis by Trost.[112]

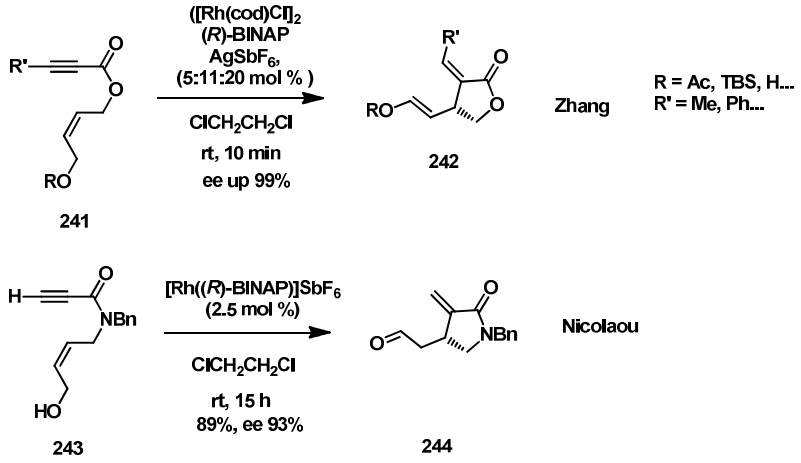
Deprotection of silyl enol ether **233** would furnish aldehyde **234**, which hopefully could be a common precursor for synthesising all three anthecotulides, via the following synthesis strategy (Scheme 4.16).



Scheme 4.10 Proposed synthesis of anthecotulides.

Considering the prospects for asymmetric catalysis, we decided at the beginning to investigate the synthesis of the α-methylene-γ-butyrolactone core under asymmetric

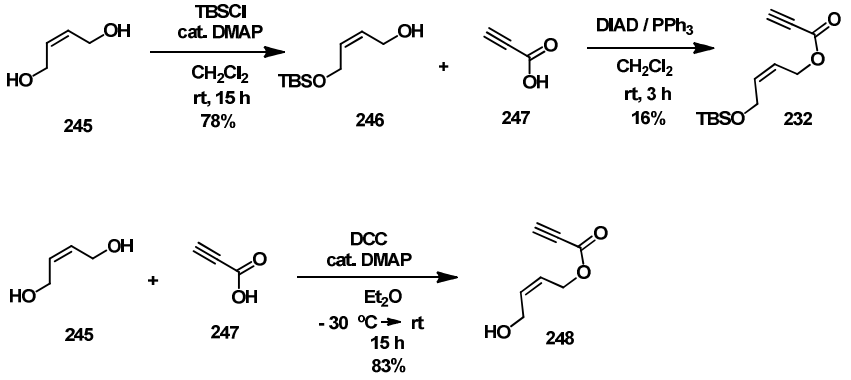
rhodium(I) catalysis, which was originally developed by Zhang[114] (2002) and co-workers with internal alkynes and later-on (2009) revisited by Nicolaou[115] for the synthesis of α-methylene-γ-butyrolactams (Scheme 4.11).



Scheme 4.11 α-methylene-γ-butyrolactone/lactam cores from Zhang[114] and Nicolaou.[115]

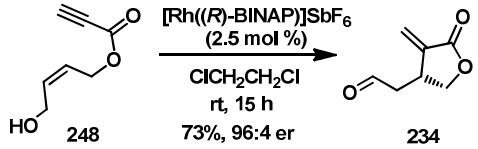
4.2.2 Synthesis and cycloaddition of enyne 248

Following Trost's procedure (Scheme 4.12), enyne **232** was synthesised in two steps using DIAD and PPh_3 in 16% yield (lit.[113] 22%). Propiolic acid (**247**) is sensitive and easily polymerises which may explain the low yield. Enyne **248** was prepared by DCC coupling of commercially available (*Z*)-but-2-ene-1,4-diol (**245**) with propiolic acid (**247)** in 83% yield (Scheme 4.12) using the procedure developed by Ballas.[116] We found that slow addition of propiolic acid with DCC at – 30 °C is absolutely crucial to achieve high yield.



Scheme 4.12 Synthesis of the precursor for the enyne chemistry.

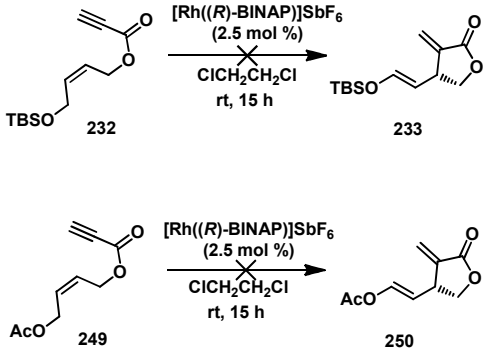
Using Zhang's conditions ([Rh(cod)Cl]$_2$/*rac*-BINAP/AgSbF$_6$, (0.025:0.05:0.05), ClCH$_2$CH$_2$Cl, rt, 15 h), enyne **248** gave the desired aldehyde **234**, albeit in low yields (20-30%) which were difficult to reproduce. During our investigation, we found that an inert atmosphere was crucial for the reactivity (solvent and flask degassed with argon). On the basis that polymerisation might be a competitive side reaction, we lowered the reaction concentration from 0.2 M to 0.1 M and 0.05 M, but these experiments also gave low yields (23% and 15%, respectively). However, modifying the conditions to those used by Nicolaou and co-workers, where pre-forming the catalyst [Rh(*rac)*-BINAP)]SbF$_6$ was found optimal for the synthesis of α-methylene-γ-butyrolactams,[115] gave aldehyde **234** in much improved yield (72%). Finally, using [Rh((*R*)-BINAP)]SbF$_6$ gave (+)-aldehyde **234** in 73% yield (Scheme 4.13) and 96:4 er by chiral HPLC (see Appendix, p. 211).



Scheme 4.13 Synthesis of the enyne precursor chemistry.

We also tried to use these conditions (cat. [Rh(*rac)*-BINAP)]SbF$_6$; 5 mol %) on the substituted known alcohol **232**[113] and **249**[117] but we were not able to isolate the desired lactone (Scheme 4.14). Only decomposition and trace of starting material were observed by ^{1}H–NMR data analysis of unpurified reaction mixture. Using Zhang's conditions

(([Rh(cod)Cl]$_2$/*rac*-BINAP/$AgSbF_6$, (0.025:0.05:0.05), $ClCH_2CH_2Cl$, rt, 15 h) gave the same results as Rh(*rac)*-BINAP)]SbF_6. It is possible that extra coordination from the alcohol plays an important role in the chemistry.



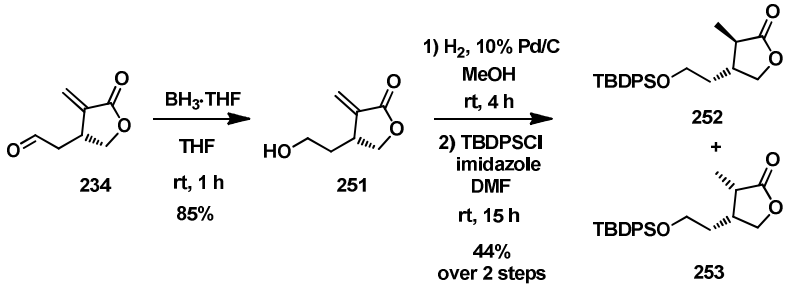
Scheme 4.14 Synthesis of the precursor for the enyne chemistry.

Using other metal catalysts such as AuCl, $PtCl_2$, $AgSBF_6$/AuCl(PPh_3) and $AuCl_3$ in $CDCl_3$ (5 mol % each) which have been extensively used in enyne isomerisation chemistry,[118] were unsuccessful with substrates **232** and **248**. In each case, starting material was recovered with some minor impurities.

4.2.3 Sense of induction of cycloaddition

To confirm the sense of asymmetric induction in the cycloisomerisation using (*R*)-BINAP, we decided to convert (+)-aldehyde **234** to the *trans*-lactone **252**[119] of previously established absolute configuration and compare the specific rotation values (Scheme 4.15). Chemoselective reduction of aldehyde **234** using BH_3,[120] (attempt to reduce with 1.1 eq. of $NaBH_4$ gave a mixture of undesired products) followed by hydrogenation of the α-methylene group in hydroxylactone **251** and silylation of the resulting saturated primary alcohol gave a *cis*-*trans* mixture of lactones **252**/**253** from which *trans*-lactone **252** could be obtained by careful chromatography. This correlation established that the *R*-configured aldehyde **234** was obtained from enyne **248** when using (*R*)-BINAP, and this corresponds

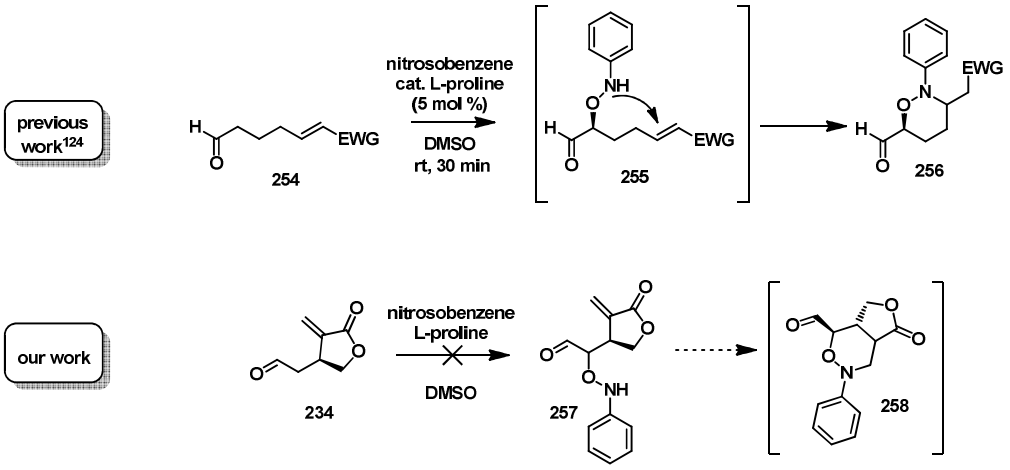
to the same sense of asymmetric induction observed in Zhang's[114] and Nicolaou's studies.[115]



Scheme 4.15 Configuration of aldehyde (+)-**234** by conversion to *trans*-lactone (+)-**252**.

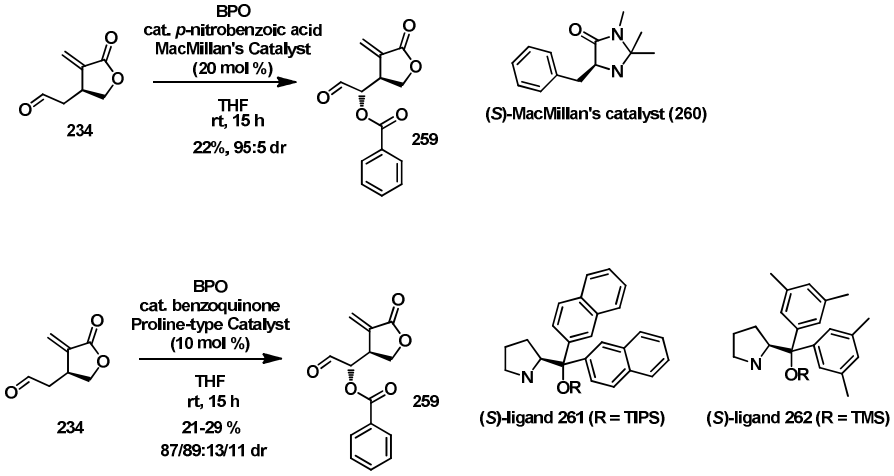
4.2.3 α-Hydroxylation of aldehyde: organocatalysis

Having one of the two stereocenters controlled for hydroxyanthecotulide, we started to look at how to install the second stereocenter (Scheme 4.10, p 69). Trying to minimise the number of operations on aldehyde **234**, we decided to look at the α-oxygenation of aldehydes. The enantioselective introduction of an oxygen moiety at the α-position of carbonyl groups continues to be an intensely investigated field.[121] In this context, enamine catalysis recently became a powerful approach for the direct asymmetric α -oxygenation of aldehydes, in particular, the α-oxygenation of aldehydes with nitrosobenzene[122] or benzoyl peroxide[123] (BPO), the latter being readily available and inexpensive. Most of this chemistry has been carried out on simple aldehydes; in our case a potentially very reactive unsaturated ester is present. Both methodologies were tested on our substrate (Scheme 4.16). In the case of nitrosobenzene, after 5 min no more starting material was observed by TLC analysis. ^{1}H–NMR data analysis of unpurified reaction mixture showed the disappearance of the methylene proton. It is possible that the hydroxylamine generated attacked our unsaturated ester, as seen previously with unsaturated nitro/ester groups (Scheme 4.16).[124]



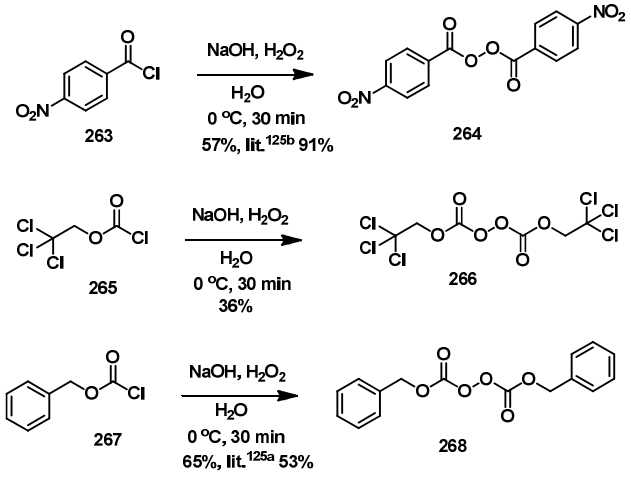
Scheme 4.16 α - oxygenation using nitrosobenzene.

In the case of BPO (1.3 equiv.) and using (*S*)-lactone **234** (Scheme 4.17), the desired α-benzoyloxyaldehyde **259** (^{1}H δ 9.73, CHO, major diastereoisomer and ^{1}H δ 9.67, CHO, minor diastereoisomer) was observed with excellent diastereoselectivity (95:5 *dr*) using (*S*)-Macmillan's catalyst (**260**) (20 mol %) or (*S*)-prolinol-type catalysts (10 mol %; ligand **261** = 89:11 *dr* and ligand **262** = 87:13 *dr*) by ^{1}H–NMR data analysis of unpurified reaction mixture. In this present Scheme 4.17, we assume that catalyst **260**, **261** and **262** gave the α-(*S*)-benzoyloxyaldehyde functionality as seen with previous simple aldehydes[123, 124] and therefore the *syn*-diastereoisomer **259**. Isolation of aldehyde **259** was difficult, due to its instability by chromatography (^{1}H Major δ 9.73 CHO; 6.47 and 5.88 CH_2=, 5.61 CH-OBz, 4.58 – 4.39 CH_2-O, 3.90 CH).



Scheme 4.17 Oxybenzylation of aldehyde **234**.

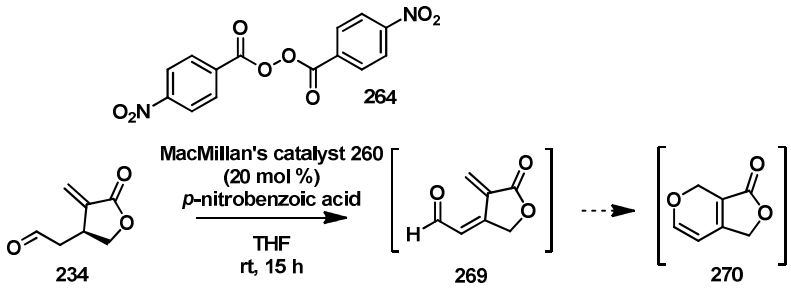
The use of BPO seemed to be a good starting point for this chemistry. Unfortunately we know from previous work (see Section 3.3.2, p. 49) that having a benzoate or acetate at this position will be problematic. We therefore decided to modify the peroxide used. Three peroxides were synthesised following previous experimental work in this field (Scheme 4.18).[125]



Scheme 4.18 Synthesis of peroxide **264**, **266** and **268**.

To begin with, we synthesised the known[125b] peroxide **264**. We knew from previous research with hydroxyanthecotulide (see Section 3.4.3, Scheme 3.25, p. 56), that the *p*-nitrobenzoate group can be removed. Having the peroxide **264** in hand, 20 mol % of (*S*)-MacMillan catalyst **260** with (*S*)-lactone **234** was used with it, and after 15 h at rt,

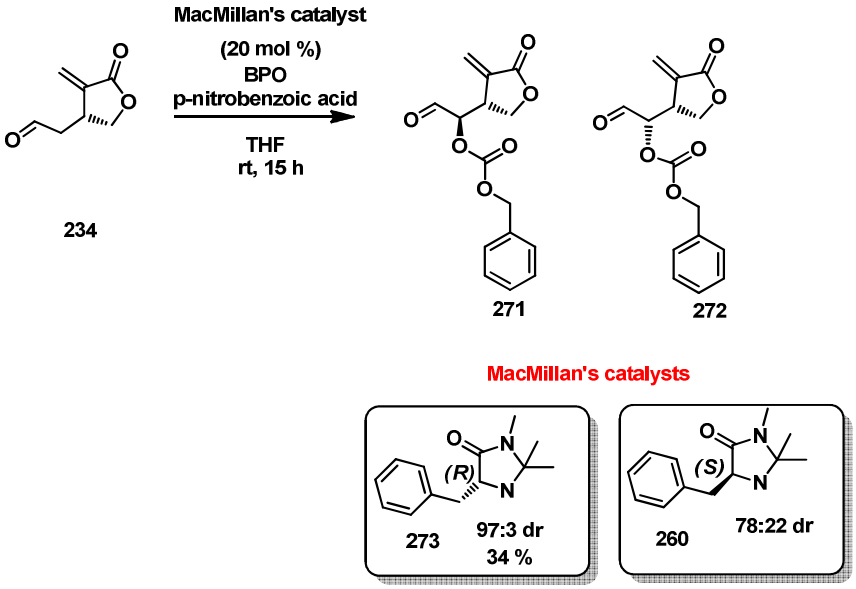
^{1}H–NMR data analysis of unpurified reaction mixture showed the presence of the starting material (20%) with the desired α-benzoyloxyaldehyde (~ 20%; ^{1}H δ 9.72, CHO, major diastereoisomer and ^{1}H δ 9.68, CHO, minor diastereoisomer; chemical shift of the aldehyde similar to α -benzoyloxyaldehyde **259**) and a new aldehyde product with a lower chemical shift (~ 50%, ^{1}H δ 9.61, CHO). Changing the temperature (0 ^{o}C) and catalyst loading (5 mol %) did not improve the ratio in favor of our desired product (large excess of starting material). Trying to isolate this aldehyde was unsuccessful (Scheme 4.19); it may be the elimination product **269** which can undergo a variety of side reactions such as **270**. Interestingly, using the proline-type catalyst such as **261** and **262**, starting material was recovered. The reactive peroxide **264** may react with the catalyst **260**.



Scheme 4.19 Attempted oxybenzylation of aldehyde **234** with peroxide **264**.

Looking more carefully in the literature, we became aware of the use of peroxycarbonate in stoichiometric enamine chemistry, which seemed to give better results than BPO.[126] Following this precedent and having in mind that a carbonate protecting group can be removed under neutral conditions,[19] I synthesised the peroxidicarbonates **266** and **268**. To begin with, we investigated Trocperoxide **266**. This new peroxide would allow us to generate the Troc protecting group which can be easily removed with Zn in NH_4Cl/THF[19] (conditions used in our allylation chemistry in the first synthesis of hydroxyanthecotulide (**2**), see Section 3.24, p. 54). Unfortunately, no desired product was obtained with catalyst **260**, **261** and **262**, only starting material was recovered. Switching to peroxidicarbonate **268,**[125a] we isolated 34% of the desired lactone **271** (100% conversion after 15 h, ^{1}H δ 9.66,

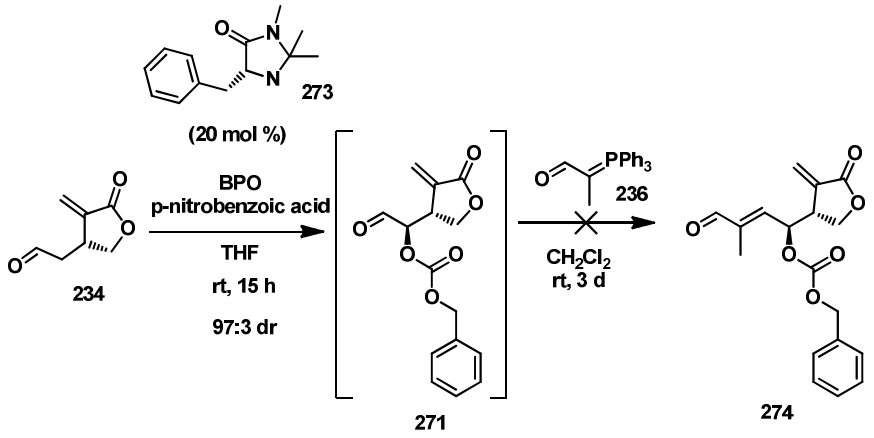
CHO, major diastereoisomer and ^{1}H δ 9.65, CHO, minor diastereoisomer) starting with (*R*)-lactone **234**, with excellent diastereoselectivity (97:3 *dr*) using (*R*)-MacMillan's catalyst **273**. As seen previously, no product was isolated using (*S*)-prolinol-type catalysts. We believe that favourable interactions exist between our peroxidicarbonate and MacMillan-catalyst such as π-stacking. We also observed a match and mismatch effect, using (*S*)-catalyst **260** gave the desired compound **272** in 78:22 *dr* (60 % conversion after 15 h, ^{1}H δ 9.65, CHO, major diastereoisomer and ^{1}H δ 9.66, CHO, minor diastereoisomer) (Scheme 4.20).



Scheme 4.20 α - oxygenation of aldehyde (**234**).

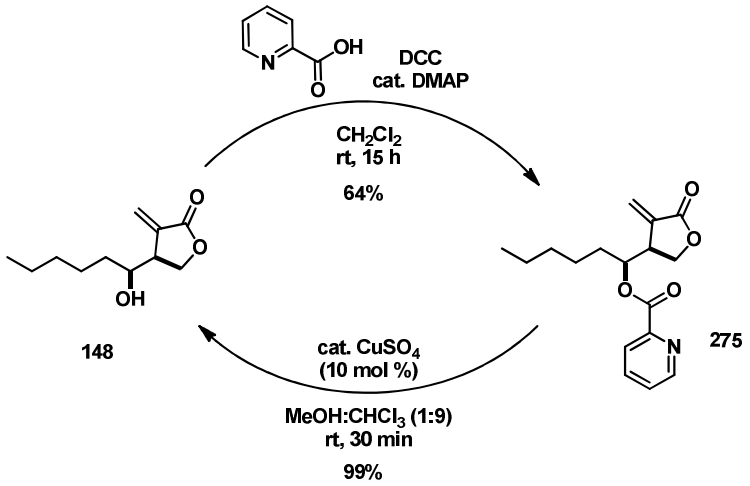
After several attempts, I was never able to isolate more than 30% of α-oxygenated aldehyde **271** after column chromatography. Aldehyde **271** is not very stable and the reactions are not high yielding due to the sensitive nature of the unsaturated lactone. Previous work[122b] showed the possibility of carrying out a Wittig olefination in one-pot synthesis after oxybenzylation step using proline-type catalysts. In the hope of improving our overall yield, we used 1.5 equiv. of ylide **236**[127] after the organocatalysis step (Scheme 4.21). Unfortunately, after 3 days, no desired product was recovered. Degradation seems to occur; a large quantity of benzylic alcohol was recovered after column chromatography (70

% based on starting peroxide). By an unknown mechanism, decarbonylation of our CBz protecting group seems to occur. In this case, the unstable α-hydroxyaldehyde[128] certainly decomposed.



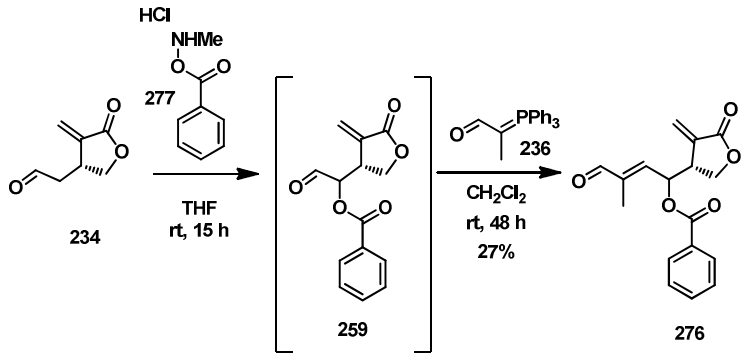
Scheme 4.21 Attempted α - oxygenation of aldehyde **234** followed by Wittig reaction.

The real difficulty at this stage of the project was to find a protecting group which would be able to survive the Wittig olefination (see Scheme 4.10, p. 69) but also easily deprotect under mild conditions. Looking carefully in the literature, we found that deprotection of picolinic esters can be achieved under mild conditions using zinc acetate or copper acetate in MeOH/$CHCl_3$.[129] To test the viability of this protecting group, we decided to protect one of our previous lactones and test the deprotection step (Scheme 4.22). Pleasingly, the desired lactone **275** was isolated after DCC coupling in 64% yield. Furthermore, using 10 mol % of $CuSO_4$ in a mixture of methanol and chloroform returned, cleanly, the original lactone **148**.



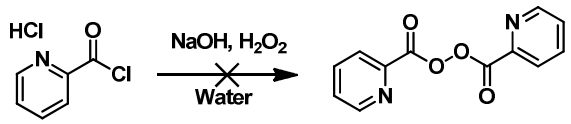
Scheme 4.22 Esterification of lactone **148** and hydrolysis.

We decided also to perform the Wittig olefination (Scheme 4.23) on a similar substrate such as α - benzoate aldehyde **259**. (prepared using Tomkinson's reagent, see Section 4.2.4, p. 80) to check the stability of a benzoate group to the Wittig reaction.



Scheme 4.23 α - oxybenzylation of aldehyde **234** followed by Wittig reaction.

Pleasingly, using ylide **236** (1.5 equiv.), the desired product **276** was isolated in 27% after 48 h (E alkene only observed). Having established the viability of such protecting group, we attempted to synthesise peroxide **279**. Unfortunately, despite all the conditions we tried (changing the equiv. of NaOH and different work-up), peroxide **279** was never isolated (Scheme 4.24).

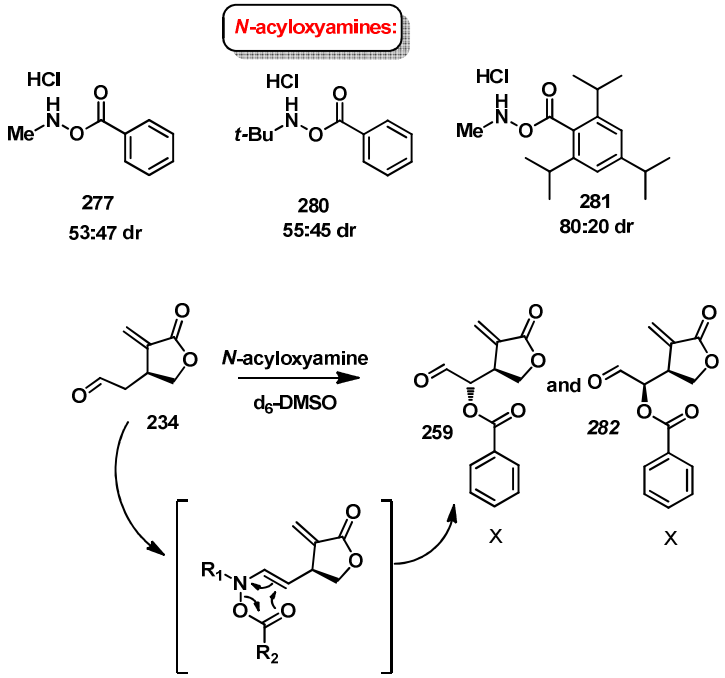


278 279

Scheme 4.24 Attempted synthesis of peroxide **279**.

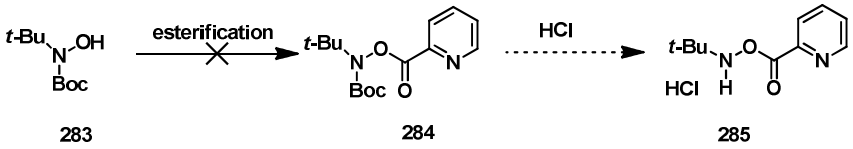
4.2.4 α-Hydroxylation of aldehyde: Tomkinson's methdology

Due to the problems of generating this new stereocenter using organocatalysis, we started to investigate other strategies. Tomkinson recently published a series of studies on α - oxygenation of aldehydes and ketones using *N*-acyloxyamine.[130] This chemistry proceeds via a pericyclic rearrangement (Scheme 4.25). To begin with, we used the simple *N-methyl-O*-benzoylhydroxylamine hydrochloride **277** to establish the chemistry (Scheme 4.25). Having one stereocenter already in place, we hoped this would be enough to induce diastereoselectivity. Using 1.2 equiv. of *N*-acyloxyamine **277** with (*S*)-lactone **234** afforded cleanly, after 15 h, the desired lactone **259**/**282** as mixture of diasteroisomers (53:47 *dr* in favour of **259**) by ^{1}H–NMR data analysis of unpurified reaction mixture. To study the influence of the *N*-acyloxyamine on the diasteroselectivity, I switched the methyl amine for the *tert*-butyl amine and modified the benzoate group. Changing for the *tert*-butyl amine did not influence the diastereoselectivity significantly (55:45 *dr* in favour of **259**). In contrast to the benzoate functionality, where after 3 days, formation of the desired α-benzoyloxyaldehyde **259**/**282** was observed by ^{1}H–NMR data analysis of unpurified reaction mixture with 80:20 *dr* (75% conversion, d_6-DMSO ^{1}H δ 9.75, CHO, major diastereoisomer and ^{1}H δ 9.79, CHO, minor diastereoisomer) with *N*-acyloxyamine **281**.



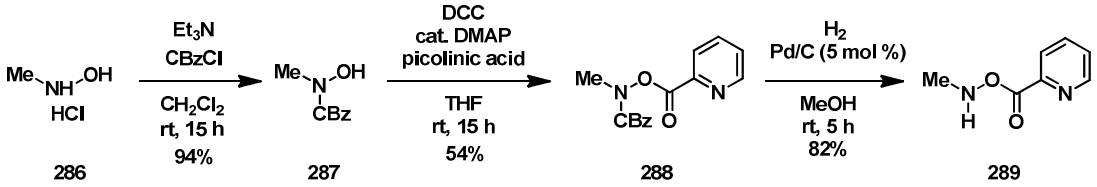
Scheme 4.25 α - oxygenation of aldehydes using *N*-acyloxyamines.

With this information in hand, we decided to synthesis the simple picolinyloxyamine **285** to establish the chemistry (Scheme 4.26). The synthesis was more problematic than previously observed with the simple benzoate.[130] Esterification using picolinic chloride,[131] picolinic anhydride[132] or CDI [133] all failed. A small amount (~ 10 %) of desired product was isolated after DCC coupling[134] (^{1}H $CDCl_3$ δ 8.85 – 8.73 (m, 1 H), 8.17 – 8.13 (m, 1 H), 7.93 – 7.81(m, 1 H), 7.58 – 7.49 (m, 1 H), 1.49 (s, 9 H), 1.44 (s, 9 H)), but did not survive during the deprotection with HCl, possibly due to the presence of the pyridine ring.



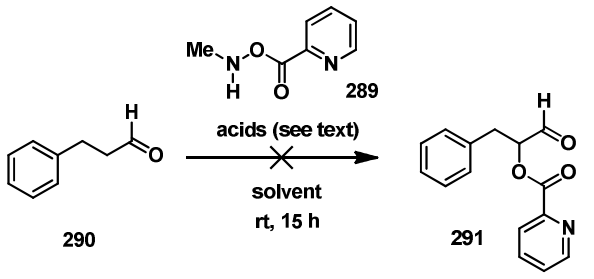
Scheme 4.26 Attempted synthesis of **285.**

Believing that steric hindrance of the Boc protecting group and the *tert*-butyl group during the esterification process may be causing problems, we decided to change our strategy and used a CBz protecting group in the chemistry, which would offer the advantage of a milder deprotection (scheme 4.27).[19]



Scheme 4.27 Synthesis of acyloxyamine **289**.

The desired compound **289** was synthesised in 3 steps starting from commercially available acyloxyamine **286**. Pleasingly, DCC coupling gave acyloxyamine **288** in 54% yield and hydrogenation afforded, cleanly, the chromatographically unstable (by TLC) acetyloxyamine **289**. As a test substrate, we used 3-phenylpropanal (**290**) (Scheme 4.28). Using acetyloxyamine **289** (1.1 equiv.) in DMSO gave back the starting aldehyde **290** untouched. A co-acid appeared to be necessary to perform the enamine chemistry.[129] Acids, including HCl, *p*-TSA, sulfonic acid and *p*-nitrobenzoic acid (1 equiv.), were tested in different solvents such as DMSO, $CDCl_3$, CH_2Cl_2, THF and toluene. In each case, no desired product was observed by ^{1}H–NMR data analysis of unpurified reaction mixture. Unfortunately, cleavage of the acyloxyamine seems to be the main pathway (only picolinic acid and starting aldehyde **290** were observed by ^{1}H–NMR data analysis of unpurified reaction mixture).

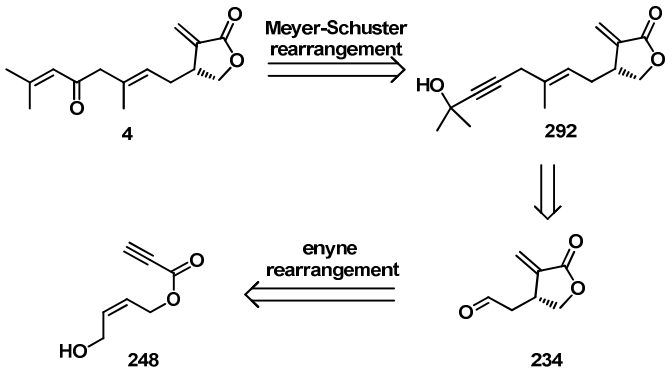


Scheme 4.28 Attempted synthesis of aldehyde **291**.

Unfortunately, we never managed to install the hydroxyl group in an asymmetric fashion, but having one stereocenter in place we decided to finish the synthesis of anthecotulide (**4**). I aimed to establish the absolute stereochemistry of this natural product and then propose the absolute configurations for the rest of the family.

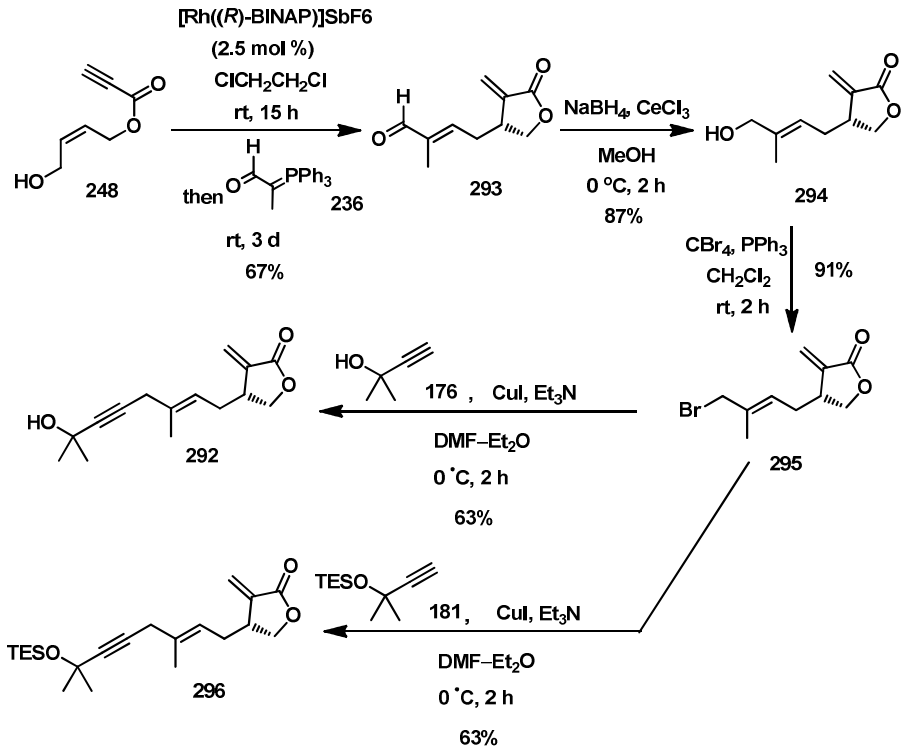
4.3 Asymmetric synthesis of (+)-anthecotulide (4)

With a catalytic and highly enantioselective synthesis of aldehyde **234** established (see Section 4.2.2, p. 70), we examined its conversion to the propargylic alcohol **292** for the projected Meyer-Schuster rearrangement (Scheme 4.29).



Scheme 4.29 Retrosynthetic strategy to anthecotulide (**4**).

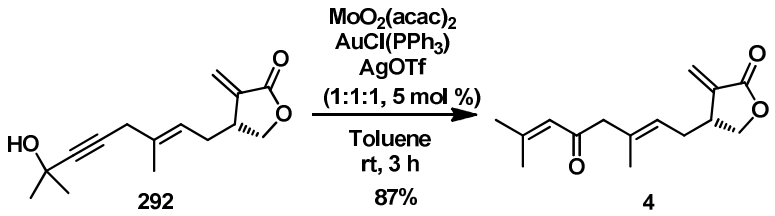
Structurally related (internal alkynes) have been recently shown to undergo one-pot cycloisomerisation–Wittig reaction.[135] In the present case, addition of ylide **236**[127] (1.3 equiv.) following the Alder-ene reaction gave the *E*-α,β-unsaturated aldehyde **293** (67% from enyne **248**, Scheme 4.30).



Scheme 4.30 Synthesis of Propargylic Alcohol **292** and **296.**

1,2 - Reduction of aldehyde **293** with Luche's conditions,[136] followed by an Appel reaction[137] on the resulting allylic alcohol **294** using PPh_3 and CBr_4 gave allylic bromide **295** (79% yield from **293**). At the beginning of our investigation, we decided to use the alkynol **181** to displace the allylic bromide **295**. Of the various procedures examined for the displacement of the allylic bromide **295** by terminal alkynes,[138] conditions developed by White and co-workers were found to work best. [139]. The lactone **296** was obtained by addition of the allylic bromide **295** at 0 °C to the alkynylcopper species from alkynol **181**, prepared by mixing with stoichiometric CuI and Et_3N in a 2:1 mixture of Et_2O and DMF in 72% yield. Looking for a protecting group free synthesis, and therefore using the propargylic alcohol **176** instead, gave the desired lactone **292** in 63% yield. Using previous Meyer-Schuster conditions (see Section 3.4.1, p. 50) on propargylic alcohol **292** gave (+)-anthecotulide (**4**) in excellent yield (87%) (Scheme 4.31). No isomerisation of the β,γ-trisubstituted alkene into conjugation with the ketone was observed. The spectroscopic data were in full agreement with those in the literature,[66] and the specific rotation of synthetic anthecotulide $[\alpha]^{23}_D$ +81.1 (*c* 0.15, $CHCl_3$)

is of comparable magnitude to that reported for the natural product $[\alpha]^{22}_{D}$ +76.9 (*c* 0.032, $CHCl_3$).[140]



Scheme 4.31 Anthecotulide (**4**) by Meyer-Schuster rearrangement

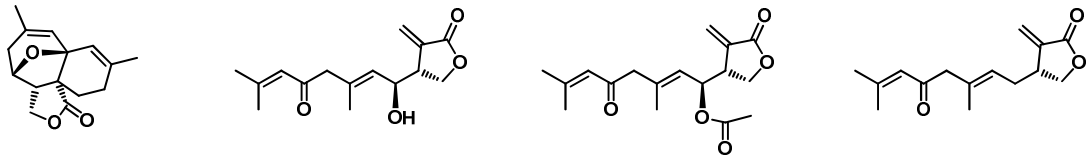
To confirm our synthesis, we contacted Prof. Imming from Martin-Luther-Universität Halle-Wittenberg, who kindly sent us specta and an authentic sample of (**4)**. HPLC (ZORBAX RX-SIL, 5% IPA/Hexane) was run using Imming's sample against our synthetic material and, pleasingly, our synthectic sample matched with the natural product (see Appendix, p. 212).

4.4 Conclusion

During this last part I have demonstrated asymmetric induction using classic, bidentate bisoxazolines (or even phosphoric ligands) in the catalytic chromium allylation using bromolactone **125**. I also showed the use of a chiral rhodium catalyst in a novel enantioselective enyne cycloisomerization to an α-methylene-γ-butyrolactone. The latter was used for the first asymmetric synthesis of (+)-anthecotulide (**4**) in six steps. I also investigated the use of peroxodicarbonate for α-oxygenation of aldehydes.

During the synthesis of anthecotulide (**4**), I established the absolute configuration of the natural product as 3*R*-. This result conflicts with the absolute configuration of the biosynthetically related hydroxanthecotulide (**2**), which was originally assigned using Mosher's method (see Section 1.3, p. 4). The use of this Mosher's method for acyclic structures if found in a few examples,[141] although it is principally used for rigid structures.[9] To determine absolute configuration, this method is based on positive or negative differences

in chemical shifts between the (*R*)-Mosher ester and (*S*)-Mosher ester. In the case of hydroxyanthecotulide, these absolute differences are very small (0.007–0.035 ppm).[5] Moreover, during the preparation of the Mosher ester, configurational assignment switches when Mosher's acid chloride is used ((*R*)-MTPA chloride gives (*S*)-Mosher ester), and therefore confusion is possible.[142] We are currently in contact with Dr. Skaltsa to try and resolve this issue. Strongly believing in the biosynthetic relationship between anthecularin (**1**) and anthecotulides and our assignment of anthecotulide (**4**) (see Section 4.3, p. 83), we propose the following absolute configurations for the family.



(1) anthecularin

(2) hydroxyanthecotulide (3*R*, 4*S*)

(3) acetoxyanthecotulide (3*R*, 4*S*)

(4) anthecotulide

Future work:

With the aim of expanding the methodology, future work is needed on the synthesis of new asymmetric ligands such as cage-ligand 217 developed by Yamamoto. The synthesis of additional stereocenters on the lactone and it's application to new target synthesises is currently being evaluated in our laboratory. Due to the small amounts of hydroxyanthecotulide synthesised, the biosynthesis has not been completely evaluated. A scale-up will be needed in order to understand, and hopefully complete, the biosynthesis of anthecularin.

Chapter 5. Experimental

5.1 General Details

All reactions requiring anhydrous conditions were carried out under an atmosphere of argon in flame-dried glassware. Syringes, needles and cannula were oven-dried.

Materials: Et_2O, CH_2Cl_2, Toluene, MeOH, and THF were degassed and dried over alumina under argon.a Acetone was degassed and dried over 4Å molecular sieves under argon. (i-Pr)$_2$NEt was distilled from CaH_2. Zinc dust <10μm was purchased from Aldrich; Dry 1,2-dichloroethane (99.8%) and dry DMF were obtained from Aldrich Chemical Co. *n*-Buli was titrated using a solution of 2-Propanol (1.0 M) in toluene with 0.2% of 1,10-phenanthroline. Other starting materials were obtained commercially and used without further purification, unless stated otherwise.

Chromatography: Thin layer chromatography (TLC) was preformed on aluminium-backed plates pre-coated with silica (Merck 60 F_{254}). The plates were visualised by irradiation with UV light (254 nm) and by immersion in phosphomolybdic acid or $KMnO_4$ solutions, followed by heating. Purification of reaction products was carried out by flash chromatography using silica gel (35-70 μM) or neutral alumina. HPLC was carried out on an Agilent 1200 series running in normal phase under UV detection using a ZORBAX RX-SIL (150 mm x 4.6 mm ID) as the analytical column. Chiral analysis was carried out using a DAICEL CHIRALPAK-IA or IB (250 mm x 4.6 mm ID).

1. [a] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518−1520.

Optical rotations were recorded on a Perkin-Elmer 241 polarimeter, with a path length of 10 cm in $CHCl_3$. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Concentrations (*c*) are given in grams per 100 cm^3.

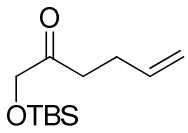
IR spectra were recorded as thin films on NaCl plates using a Perkin-Elmer Paragon Fourier Transform spectrometer; abbre*via*tions br, s, m, and w refer to broad, strong, medium and weak, respectively.

NMR: ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ using a Brücker AVC500 spectrometer. Chemical shifts are reported in ppm and referenced to residual $CHCl_3$ at δ 7.27 for ^1H NMR spectra (apart from anthecotulide (**4**), acetoxyanthecotulide (**3**) and hydroxyanthecotulide (**171**) and (**2**) referred to Me_4Si), and to the central line of $CDCl_3$ triplet at 77.0 for ^{13}C NMR spectra. Coupling constants (*J*) are given in Hz. The ^{13}C NMR peaks were assigned by standard methods using HSQC or DEPT experiments. The diastereoselectvity was determined by crude ^1H-NMR analysis of the methylene protons.

Mass Spectra: High resolution mass spectra were obtained by field ionisation (FI; Micromass GCT) or by electrospray ionization (ESI; LCT Premier reflectron TOF and Bruker MicroTOF) using tetraoctylammonium bromide or sodium dodecyl sulfate as lock mass; values are quoted as ratio of mass to charge in Daltons, and relative intensities of assignable peaks observed are quoted as a percentage value.

5.2 Data for Chapter 2

1-(*tert*-Butyldimethylsilanyloxy)-hex-5-en-2-one (**42**):



A solution of TPAP (183 mg, 0.35 mmol) in CH_2Cl_2 (5 mL) was added to a solution of crude alcohol **41**[18] (1.0 g) with finely crushed NMO (1.42 g, 12.15 mmol) and dry molecular sieves powder 4Å (1.6 g) in CH_2Cl_2 (90 mL) The reaction mixture was stirred at rt for 14 h and then concentrated under reduced pressure and purified by column chromatography (5% EtOAc in petrol) to give ketone **42**[142] (1.59 g, 83% over 2 steps) as a clear oil.

- ***R*$_f$**: 0.4 (5% EtOAc in petrol).
- **IR** (neat): 2930m, 2858m, 1721s, 1642m, 1256m, 1110br.
- **^{1}H NMR** (400 MHz, $CDCl_3$): 5.82 – 5.76 (m, 1 H, C*H*=CH_2), 5.05 (dd, *J* = 1.5, 17 Hz, 1H, =C*H*$_2$), 4.98 (dd, *J* = 1.5, 11 Hz, 1 H, =C*H*$_2$), 4.12 (s, 2 H, C*H*$_2$O), 2.64 – 5.56 (m, 2H, CH_2C*H*$_2$CO), 2.32 (t, *J* = 7 Hz, 2H, CH_2C*H*$_2$CH=CH_2), 0.90 (s, 9 H, C(C*H*$_3$)$_3$), 0.08 (s, 6 H, Si-C*H*$_3$).
- **^{13}C NMR** (100 MHz, $CDCl_3$): 210.2 (*C*=O), 137.0 (*C*H=CH_2), 114.2 (CH=*C*H$_2$), 69.3 (*C*H$_2$-OSi), 37.4 (*C*H$_2$C=O), 27.2 (*C*H$_2$CH=CH_2), 25.8 (*C*H$_3$), 18.3 (*C*(CH$_3$)$_3$), –5.5 (*C*H$_3$Si).
- **HRMS** (FI): (M + H$^+$) –^{t}Bu found 171.0779; $C_8H_{15}O_2Si$ requires 171.0841.

tert-Butyl-(2,2-dimethoxyhex-5-enyloxy)dimethyl silane (**43**):

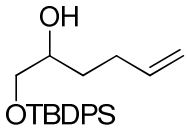
43 **36**

Trimethyl orthoformate (0.76 mL, 7.0 mmol), then *p*-toluenesulfonic acid (16.1 mg, 0.085 mmol) were added to a solution of ketone **42** (0.4 g, 1.75 mmol) in MeOH (30 mL). The reaction mixture was stirred at rt for 7 h, then quenched with sat. aq. $NaHCO_3$ (50 mL). The aq. layer was extracted with EtOAc (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography (10% → 50% EtOAc in petrol) to give:

- First eluted: ketal **43** (134 mg, 26%) as a yellow oil.
    - ***R**_f*: 0.45 (10% EtOAc in petrol).
    - **IR** (neat): 2930m, 2858br, 1642m, 1463m, 1256m, 1125s.
    - **^{1}H NMR** (400 MHz, $CDCl_3$): 5.84 – 5.74 (m, 1 H, C*H*=CH_2), 5.03 (dd, *J* = 1.5, 17 Hz, 1 H, =C*H*$_2$), 4.93 (dd, *J* = 1.5, 11 Hz, 1 H, =C*H*$_2$), 3.52 (s, 2 H, C*H*$_2$O), 3.18 (s, 6 H, OC*H*$_3$), 2.05 – 1.99 (m, 2 H, CH_2C*H*$_2$CH=CH_2), 1.78 – 1.73 (m, 2 H, CH_2C*H*$_2$C$(OCH_3)_2$), 0.88 (s, 9 H, C(C*H*$_3$)$_3$), 0.08 (s, 6 H, Si-C*H*$_3$).
    - **^{13}C NMR** (100 MHz, $CDCl_3$): 138.3 (*C*H=CH_2), 114.2 (CH=*C*H_2), 102.3 (*C*$(OCH_3)_2$), 60.5 (*C*H_2-OSi), 47.8 (O*C*H_3), 30.4 (*C*H_2C$(OCH_3)_2$), 27.8 (*C*H_2CH=CH_2), 25.8 (CH_3), 18.1 (*C*$(CH_3)_3$), –5.5 (*C*H_3Si).
    - **LRMS** (ESI): 149 (40), 281 (55), 367 (100); **HRMS** (EI): (M + H^+) – ^{t}Bu found 217.1267, $C_{10}H_{21}O_3Si$ requires 217.1260.
- Second eluted: alcohol **36** (165 mg, 59%) as a yellow oil.
    - ***R**_f*: 0.52 (30% EtOAc in petrol).

- **IR** (neat): 3345m, 2957s, 1453m, 1642w, 1273m, 1147m, 1084s.
- **^{1}H NMR** (400 MHz, $CDCl_3$): 5.84 – 5.76 (m, 1 H, C*H*=CH_2), 5.01 (dd, *J* = 1.5, 17 Hz, 1 H, =C*H*$_2$), 4.95 – 4.91 (dd, *J* = 1.5, 11 Hz, 1 H, =C*H*$_2$), 3.52 (s, 2 H, C*H*$_2$OH), 3.18 (s, 6 H, OCH_3), 2.18 (br, 1 H, OH), 2.05 – 1.98 (m, 2 H, CH_2CH_2CH=CH_2), 1.75 – 1.71 (m, 2 H, $CH_2CH_2C(OCH_3)_2$).
- **^{13}C NMR** (100 MHz, $CDCl_3$): 138.0 (*C*H=CH_2), 114.5 (CH=*C*H_2), 101.9 (*C*$(OCH_3)_2$) 60.9 (CH_2-OH), 48.1 (OCH_3), 30.7 (*C*$H_2C(OCH_3)_2$), 27.8 (*C*H_2CH=CH_2).
- **LRMS** (ESI): 312 (100), 425 (100); **HRMS** (EI): M + H^+ found 161.1192, $C_8H_{16}O_3$ requires 160.1099.

1-(*tert*-Butyldiphenylsilanyloxy)-hex-5-en-2-ol (**44**):

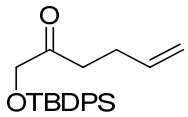


TBDPSCl (1.23 mL, 4.73 mmol) was added to a solution of diol **40**[19] (0.50 g, .4.30 mmol), Et_3N (0.77 mL, 5.59 mmol) and DMAP (52.0 mg, 0.43 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred at rt for 4 h, then quenched with sat. aq. NH_4Cl (20 mL) and the aq. layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography (5% EtOAc in petrol) to give the alcohol **44**[143] (1.58 g (crude), ≈ 100%) as a light yellow oil.

- R_f: 0.26 (5% EtOAc in petrol).
- **IR** (neat): 2931m, 2139s, 1720m, 1428m, 1112s.

- **^{1}H NMR** (400 MHz, $CDCl_3$): 7.72 – 1.65 (m, 4 H, C-H_{Ar}), 7.42 – 7.35 (m, 6 H, C-H_{Ar}), 5.84 – 5.79 (m, 1 H, C*H*=CH_2), 4.98 (dd, *J* = 1.5, 17 Hz, 1 H, =C*H*$_2$), 4.92 (dd, *J* = 1.5, 11 Hz, 1 H, =C*H*$_2$), 3.75 – 3.69 (m, 2 H, C*H*$_2$OSi), 3.53 – 3.49 (m, 1 H, C*H*OH), 2.16 – 2.13 (m, 2 H, CH_2CH_2CH=CH_2), 1.54 – 1.49 (m, 2 H, CH_2CH_2CHOH), 1.08 (s, 9 H, CH_3).
- **^{13}C NMR** (100 MHz, $CDCl_3$): 138.3 (*C*H=CH_2), 135.5 (C_{Ar}), 134.8 (C_{Ar}), 129.7 (C_{Ar}), 127.7 (C_{Ar}), 114.7 (CH=*C*H_2), 71.3 (CHOH), 67.9 (CH_2-OSi), 31.9 (*C*H_2CHOH), 29.7 (*C*H_2CH=CH_2), 26.8 (CH_3), 19.2 (*C*(CH_3)$_3$).
- **LRMS** (ESI-): 353 (100, M - H^+).

1-(*tert*-Butyldiphenylsilanyloxy)-hex-5-en-2-one (**45**):

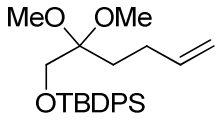


A solution of TPAP (217 mg, 0.62 mmol) in CH_2Cl_2 (5 mL) was added to a solution of crude alcohol **44** (5.55 g), finely crushed NMO (2.56 g, 21.9 mmol) and dry molecular sieves powder 4Å (2.85 g) in CH_2Cl_2 (150 mL). The reaction mixture was stirred at rt for 16 h, then concentrated under reduced pressure and purified by column chromatography (10% EtOAc in petrol) to give ketone **45** [144] (3.51 g, 73% over 2 steps) as a light yellow oil.

- ***R*$_f$**: 0.5 (10% EtOAc in petrol).
- **IR** (neat): 2931m, 1720s, 1428s, 1112m.
- **^{1}H NMR** (400 MHz, $CDCl_3$): 7.69 – 7.65 (m, 4 H, C-H_{Ar}), 7.43 – 7.38 (m, 6 H, C-H_{Ar}), 5.83 – 5.78 (m, 1 H, C*H*=CH_2), 5.02 (dd, *J* = 1.5, 17 Hz, 1 H, =C*H*$_2$), 4.98 (dd, *J* = 1.5, 11 Hz, 1 H, =C*H*$_2$), 4.18 (s, 2 H, C*H*$_2$OSi), 2.66 – 2.63 (m, 2 H, CH_2CH_2CO), 2.34 – 2.29 (m, 2 H, CH_2CH_2CH=CH_2), 1.10 (s, 9 H, CH_3).

- **^{13}C NMR** (100 MHz, $CDCl_3$): 209.6 (CO), 137.0 (*C*H=CH_2), 135.5 (C_{Ar}), 132.6 (C_{Ar}), 129.9 (C_{Ar}), 127.8 (C_{Ar}), 115.2 (CH=*C*H_2), 69.7 (*C*H_2-OSi), 37.7 (*C*H_2CO), 27.1 (*C*H_2CH=CH_2), 26.7 (CH_3), 19.2 (*C*(CH_3)$_3$).
- **LRMS** (ESI): 351 (45, M + H^+), 367 (100).

tert-Butyl-(2,2-dimethoxyhex-5-enyloxy)-diphenyl-silane (**46**):

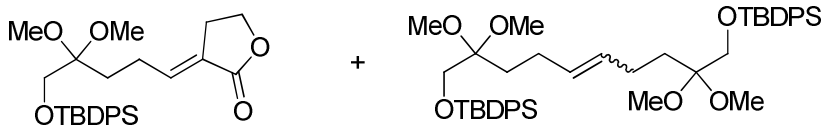


Trimethyl orthoformate (1.24 mL, 11.4 mmol) was added to a solution of ketone **45** (1.00 g, 2.80 mmol), and *p*-toluenesulfonic acid (27.0 mg, 0.14 mmol) in MeOH (50 mL). The reaction mixture was stirred at rt for 24 h, then quenched with sat. aq. $NaHCO_3$ (50 mL). The aq. layer was extracted with EtOAc (3 × 100 mL), then the combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure and purified by column chromatography (5% EtOAc in petrol) to give ketal **46** (850 mg, 76%) as a yellow gum.

- ***R*$_f$**: 0.46 (5% EtOAc in petrol).
- **IR** (neat): 2930m, 1724s, 1427w, 1112s.
- **^{1}H NMR** (400 MHz, $CDCl_3$): 7.68 – 7.66 (m, 4 H, C-H_{Ar}), 7.43 – 7.39 (m, 6 H, C-H_{Ar}), 5.83 – 5.78 (m, 1 H, C*H*=CH_2), 5.02 (dd, *J* = 1.5, 17 Hz, 1 H, =C*H*$_2$), 4.98 (dd, *J* = 1.5, 11 Hz, 1 H, =C*H*$_2$), 3.57 (s, 2 H, C*H*$_2$O), 3.11 (s, 6 H, O-CH_3), 1.93 – 1.78 (m, 4 H, CH_2C*H*$_2$$C_q$ and CH_2C*H*$_2$CH=CH_2), 1.11 (s, 9 H, CH_3).
- **^{13}C NMR** (100 MHz, $CDCl_3$): 138.3 (*C*H=CH_2), 135.6 (C_{Ar}), 133.3 (C_{Ar}), 129.9 (C_{Ar}), 127.8 (C_{Ar}), 114.2 (CH=*C*H_2), 102.45 (*C*(OCH_3)$_2$), 61.1 (OCH_2C_q), 47.9 (OCH_3), 30.5 (*C*H_2C(OCH_3)$_2$), 27.8 (*C*H_2CH=CH_2), 26.9 (CH_3), 19.2 (*C*(CH_3)$_3$).

- **LRMS** (ESI^+): 391 (45), 803 (100), 811 (95); HRMS (ESI^+): M $-^{t}$Bu found 341.1595, $C_{15}H_{25}O_3Si$ requires 315.1573.

3-[5-(*tert*-Butyldiphenylsilanyloxy)-4,4-dimethoxypentylidene(*E*)]-dihydrofuran-2-one (**54**):



54 **55**

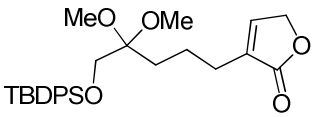
Grela's catalyst[22] (16.1 mg, 0.025 mmol) was added to a solution of ketal **46** (199 mg, 0.5 mmol), 3-methylene-dihydro-furan-2-one (0.065 mL, 0.75 mmol) and 2,6-dichloro[1,4]benzoquinone (8.8 mg, 0.05 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was heated under reflux for 32 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure and purified by column chromatography (10% → 40% EtOAc in cyclohexanes) to give:

- First eluted: Starting material **46** (10 mg, 5%).
- Second eluted: Dimer **55** (70 mg, E/Z: 9/1, 18%) as a clear oil.
    - $\boldsymbol{R_f}$ = 0.85 (40% EtOAc in cyclohexanes).
    - **IR** (neat): 2932m, 1758m, 1135m.
    - **^{1}H NMR** (400 MHz, $CDCl_3$): 7.69 – 7.65 (m, 8 H, C-H_{Ar}), 7.42 – 7.37 (m, 12 H, C-H_{Ar}), 5.45 – 5.40 (m, 2 H, C*H*=C), 3.57 (s, 4 H, CH_2-O), 3.11 (s, 12 H, O-CH_3), 1.95 – 1.86 (m, 8 H, $CH_2CH_2C_q$ and $CH_2CH_2CH{=}CH_2$), 1.11 (s, 18 H, CH_3).
    - **^{13}C NMR** (100 MHz, $CDCl_3$): 135.7 (C_{Ar}), 133.3 (C_{Ar}), 130 (C_{Ar}), 127.8 (C_{Ar}), 102.5 ($C(OCH_3)_2$), 61.1 (OCH_2C_q), 48.0 (O-CH_3), 30.5 ($CH_2C(OCH_3)_2$), 26.9 (CH_3), 26.3 (CH_2), 19.3 ($C(CH_3)_3$).

- **HRMS** (ESI): M+Na^+ found 791.4145 $C_{46}H_{64}NaO_6Si_2$ requires 791.4134.

- Third eluted: lactone **54** (153 mg, 65%) as a clear oil.
  - R_f: 0.60 (40% EtOAc in cyclohexanes).
  - **IR** (neat): 2932m, 1758s, 1113m.
  - **^{1}H NMR** (400 MHz, $CDCl_3$): 7.69 – 7.65 (m, 4 H, C-H_{Ar}), 7.42 – 7.38 (m, 6 H, C-H_{Ar}), 6.69 – 6.65 (m, J = 7, 3 Hz, 1 H, C*H*=C_q), 4.32 (t, *J* = 7, 2 H, CH_2O-CO), 3.57 (s, 2 H, CH_2OSi), 3.14 (s, 6 H, O-CH_3), 2.79 – 2.75 (m, 2 H, CH_2C_q), 2.10 – 2.07 (m, 2 H, $CH_2CH_2CH=CH_2$), 1.97 – 1.94 (m, 2 H, $CH_2C(OCH_3)_2$) 1.08 (s, 9 H, CH_3).
  - **^{13}C NMR** (100 MHz, $CDCl_3$): 171.2 (CO), 140.1 (*C*H=Cq), 135.5 (C_{Ar}), 133.1 (C_q), 129.9 (C_{Ar}), 127.7 (C_{Ar}), 125.3 (C_{Ar}), 102.0 ($C(OCH_3)_2$), 65.3 (CH_2O-CO), 61.1 (SiO-CH_2), 47.9 (O-CH_3), 30.5 ($CH_2CH_2C(OCH_3)_2$), 29.8 ($OCH_2CH_2CH=C_q$), 26.9 (CH_3), 24.9 ($CqCH_2CH_2CH=C_q$), 19.3 ($C(CH_3)_3$).
  - **LRMS** (ESI$^+$): 491 (30, M+Na^+), 959 (100, 2 M+Na^+); **HRMS** (ESI$^+$): M + Na^+ found 491.2200, $C_{27}H_{36}NaO_5Si$ requires 491.2224.

3-[5-(*tert*-Butyldiphenylsilanyloxy)-4,4-dimethoxypentyl]-5*H*-furan-2-one (**58**):

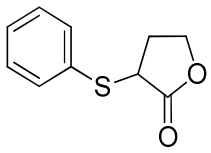


$FeCO_5$ (0.091 mL, 0.68 mmol) was added to a solution of lactone **54** (155 mg, 0.34 mmol) in toluene (6 mL). The reaction mixture was allowed to stir at 110 °C under sun lamp for 8 h, during which time a black precipitate formed. The mixture was then concentrated under

reduced pressure and purified by column chromatography (30% EtOAc in cyclohexanes) to give butenolide **58** (110 mg, 71%) as a clear oil.

- ***R*$_f$**: 0.22 (30% EtOAc in cyclohexanes).
- **IR** (neat): 2933w, 1757s, 1428w, 1113s.
- **^{1}H NMR** (400 MHz, $CDCl_3$): 7.73 – 7.62 (m, 4 H, C-H_{Ar}), 7.47 – 7.34 (m, 6 H, C-H_{Ar}), 7.06 – 7.00 (m, 1 H, CH=C_q), 4.78 – 4.67 (m, 2 H, CH_2-O-CO), 3.65 – 3.54 (m, 2 H, CH_2-OSi), 3.16 (s, 6 H, O-CH_3), 2.32 – 2.20 (m, 2 H, CH_2-Cq), 1.88 –1.75 (m, 2 H, CH_2-CH_2-CH=CH_2), 1.48 – 1.36 (m, 2 H, CH_2-C$(OCH_3)_2$) 1.14 – 1.02 (s, 9 H, CH_3).
- **^{13}C NMR** (100 MHz, $CDCl_3$): 174.2 (CO), 144.3 (CH=C_q), 135.7 (C_{Ar}), 133.9 (C_{Ar}), 133.2 (C_q), 129.7 (C_{Ar}), 127.7 (C_{Ar}), 102.3 (C$(OCH_3)_2$), 70.1 (CH_2-O-CO), 61.2 (SiO-CH_2), 47.9 (O-CH_3), 31.1 (CH_2-*C*H_2-C$(OCH_3)_2$), 26.8 (CH_3), 25.4 (CH_2-C_q=), 21.2 (*C*H_2-*C*H_2-C$(OCH_3)_2$), 19.3 (*C*$(CH_3)_3$).
- **HRMS** (ESI+): M + Na^+ found 491.2233, $C_{27}H_{36}NaO_5Si$ requires 491.2224.

3-Phenylsulfanyldihydrofuran-2-one (**84**):

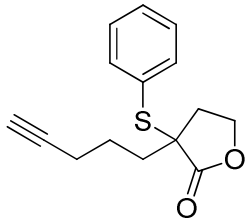


n-BuLi (8.0 mL, 1.6 M in hexanes, 12.8 mmol) was added to a solution of (*i*-Pr)$_2$NH (0.9 mL, 12.8 mmol) in THF (50 mL) at -78 °C. The reaction mixture was stirred 30 min at -78 °C, then the lactone **83** (500 mg, 5.8 mmol) was added. The reaction mixture was stirred at -78 °C for 30 min, then a solution of $(PhS)_2$ (1.26 g, 5.8 mmol) in THF (5 mL) was added and the reaction mixture was stirred at -78 °C for 3 h, then 2 h at 0 °C and finally 11 h at rt. The reaction was quenched with sat. aq. NH_4Cl (20 mL) at -78 °C. The aq. layer was extracted

with Et_2O (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography (30% EtOAc in cyclohexanes) to give lactone **84**[40] (844 mg, 75%) as a clear oil.

- ***R*$_f$**: 0.31 (30% EtOAc in cyclohexanes).
- **IR** (neat): 2913w, 1772s, 1479w, 1439s, 1373s, 1157s, 1024s.
- **^{1}H NMR** (400 MHz, $CDCl_3$): 7.62 – 7.47 (m, 2 H, C-H_{Ar}), 7.43 – 7-30 (m, 3 H, C-H_{Ar}), 4.32 – 4.19 (m, 2 H, C*H*$_2$-CH_2-O), 3.87 (dd, *J* = 6, 9 Hz, 1 H, C*H*-CO), 2.75 – 2.63 (m, 1 H, C*H*$_2$-O), 2.36 – 2.24 (m, 1 H, C*H*$_2$-O).
- **^{13}C NMR** (100 MHz, $CDCl_3$): 174.9 (CO), 133.6 (C_{Ar}), 131.9 (C_{Ar}), 129.3 (C_{Ar}), 128.7 (C_{Ar}), 66.5 (*C*H_2-O), 44.4 (*C*H-S), 30.0 (C*H*$_2$-CH_2-O).
- **LRMS** (ESI): 193.1 (100, M-H^+).

3-(Pentynyl)-3-(phenylthio)dihydrofuran-2(3*H*)-one (**85**):

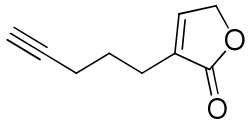


n-BuLi (14.2 mL, 1.6 M in hexanes, 22.7 mmol) was added to a solution of (*i*-Pr)$_2$NH (3.2 mL, 22.7 mmol) in THF (35 mL) at -78 °C. The reaction mixture was stirred at this temperature for 45 min, then a solution of 3-(phenylthio)dihydrofuran-2(3*H*)-one **84** (4.40 g, 22.7 mmol) in THF (5 mL) was added and the reaction stirred 1 h at -78 °C. After a further 1 h, a solution of dry HMPA (11 mL) and 1-iodopent-4-yne **82**[39] (4.00 g, 20.7 mmol) is added, and the reaction mixture is stirred for 3 h at -78°C, then 1 h at 0 °C and finally 4 h at rt. The mixture was then quenched with sat. aq. NH_4Cl (75 mL) and extracted with Et_2O (3 × 150 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced

pressure and purified by column chromatography (10 → 30% of EtOAc in petrol) to give lactone **85** (4.6 g, 86%) as a yellow oil.

- ***R*$_f$**: 0.7 (30% EtOAc in petrol).
- **IR** (neat): 3442br, 1762s, 1266s, 1176m, 1025s.
- **^{1}H NMR** (400 MHz, $CDCl_3$): 7.52 – 7.63 (m, 2 H, C-H_{Ar}), 7.40 – 7.50 (m, 1 H, C-H_{Ar}), 7.34-7.37 (m, 2 H, C-H_{Ar}), 4.24 – 4.34 (m, 2 H, CH_2-O), 2.40 – 2.52 (m, 1 H, C≡C*H*), 2.22 – 2.34 (m, 3 H, CH_2), 1.95 – 2.06 (m, 3 H, CH_2), 1.69 – 1.81 (m, 1 H, CH_2), 1.48 – 1.61 (m, 1 H, CH_2).
- **^{13}C NMR** (100 MHz, $CDCl_3$): 175.7 (C=O), 137.2 (C_{Ar}), 130.1 (C_{Ar}), 129.0 (C_{Ar}), 83.5 (HC≡*C*-CH_2), 69.1 (C≡*C*H), 65.1 (*C*H_2-O), 53.7 (OC-*C*$_q$-S), 34.5 (*C*H_2-C$_q$-S), 33.7 (*C*H_2-CH_2-O), 23.5 (CH_2-*C*H_2-CH_2), 18.4 (*C*H_2-C≡).
- **LRMS** (ESI) 299.0 (100), 255.3 (50) **HRMS** (EI): M found 262.1025, $C_{15}H_{18}O_2S$ requires 262.1028.

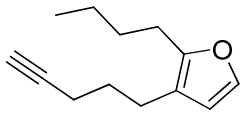
3-(Pent-4-ynyl)furan-2(5*H*)-one (**86**):



m-CPBA (2.89 g, 16.7 mmol) was added to a solution of lactone **85** (4.60 g, 17.7 mmol) in CH_2Cl_2 (140 mL) at 0 °C after 30 min, the mixture was quenched with sat. aq. $NaHCO_3$ (75 mL) and the aq. layer was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic extracts were dried ($MgSO_4$), concentrated under reduced pressure and then diluted in toluene (140 mL). This solution was allowed to stir at 110 °C for 5 h, then concentrated under reduced pressure and purified by column chromatography (20 → 30% EtOAc in hexanes) to give unsaturated lactone **86** (2.46 g, 92%) as a light yellow oil.

- ***R_f***: 0.6 (30% EtOAc in hexanes).
- **IR** (neat): 3334m, 2967m, 1749 s, 1472 m, 1345m, 1076m, 1058 m.
- **^{1}H NMR** (400 MHz, $CDCl_3$): 7.17 (s, 1 H, C*H*=), 4.79 (d, *J* = 2 Hz, 2 H, C*H*$_2$-O), 2.45 (t, *J* = 7 Hz, 2 H, C*H*$_2$-C=), 2.25 (td, *J* = 2, 7 Hz, 2 H, CH_2-C≡), 1.99 (t, *J* = 2 Hz, 1 H, C≡*H*), 1.77 – 1.89 (m, 2 H, CH_2-C*H*$_2$-CH_2).
- **^{13}C NMR** (100 MHz, $CDCl_3$): 174.2 (CO), 144.8 (*C*H=), 133.4 (C_q=), 83.3 (≡*C*-CH_2), 70.2 (*C*≡CH), 69.2 (*C*H_2-O), 26.0 (*C*H_2-C_q=), 24.3 (CH_2-*C*H_2-C_q=), 17.9 (C≡C-*C*H_2).
- **LRMS** (ESI): 141.0 (100), 151.1 (M-H^+, 70), 157 (45); **HRMS** (ESI): M+H^+ found 151.0746 $C_9H_{11}O_2$ requires 151.0760.

2-Butyl-3-(pent-4-ynyl)furan (**88**):



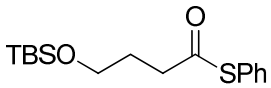
n-BuLi (1.25 mL, 1.6 M in hexanes, 2.00 mmol) was added to a solution of alkyne **86** (300 mg, 2.00 mmol) in THF (20 mL) at -78 °C and the reaction mixture was stirred at -78 °C for 2 h, then a solution of lactone (0.19 mL, 2.00 mmol) in THF (2 mL) was added and the reaction mixture was stirred 3 h at -78 °C. The reaction mixture was then quenched with sat. aq NH_4Cl (25mL) and extracted with Et_2O (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure and purified by column chromatography (30% of EtOAc in petrol) to give furan **88** (84 mg, 22%) as a clear oil.

- ***R_f***: 0.9 (30% EtOAc in hexanes).
- **IR** (neat): 3310m, 2930m, 1142w, 935w.
- **^{1}H NMR** (500 MHz, $CDCl_3$): 7.24 (d, *J* = 2 Hz, 1 H, =C*H*O), 6.18 – 6.26 (m, 1 H, C*H*=), 2.58 (t, *J* = 7 Hz, 2 H, C*H*$_2$-C_q), 2.47 (t, *J* = 7 Hz, 2 H, C*H*$_2$-C_q), 2.20 (td, *J* = 3; 7 Hz, 2 H, C*H*$_2$-C≡), 1.92 – 2.03 (m, 1 H, C≡C*H*), 1.74 (t, *J* = 7 Hz, 2 H, C_q-CH_2-

C*H*$_2$-CH$_2$-Cq), 1.54 – 1.66 (m, 2 H, C$_q$-CH$_2$-C*H*$_2$-CH$_2$-CH$_3$), 1.36 – 1.32 (m, 2 H, C$_q$-CH$_2$-CH$_2$-C*H*$_2$-CH$_3$), 0.93 (t, *J* = 7 Hz, 3 H, CH$_3$).

- **^{13}C NMR** (125 MHz, CDCl$_3$): 151.8 (*C*$_q$-O), 139.9 (*C*HO), 117.5 (*C*$_q$), 111.2 (*C*H=), 84.2 (*C*≡CH), 68.6 (C≡*C*H), 30.8 (*C*H$_2$), 29.2 (*C*H$_2$) 25.6 (*C*H$_2$), 23.4 (*C*H$_2$), 22.3 (*C*H$_2$), 17.7 (*C*H$_2$), 13.9 (*C*H$_3$).
- **LRMS** (ESI): 191.2 (100, M+H$^+$), 147.1 (60); **HRMS** (FI): M$^+$ found 190.1359, C$_{13}$H$_8$O requires 190.1358.

Phenyl 4-(*tert*-butyldimethylsilyloxy)butanethioate (**90**):

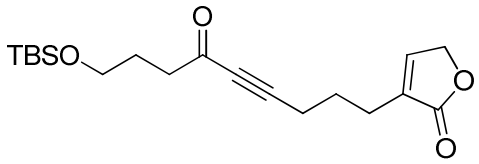


DCC (473 mg, 2.3 mmol) was added to a solution of acid **89**[44] (436 mg, 2.0 mmol), DMAP (28.0 mg, 0.23 mmol) and thiophenol (0.225 mL, 2.2 mmol) in THF (10 mL). The reaction mixture was stirred at room temperature for 60 h, then quenched with sat. aq. NH$_4$Cl (75 mL) and extracted with Et$_2$O (3 × 150 mL). The combined organic extracts were dried (Na$_2$SO$_4$), concentrated under reduced pressure and purified by column chromatography (pentane then 5% of EtOAc in pentane) to give the thioester **90** (434 mg, 70%) as a clear oil.

- ***R*$_f$**: 0.80 (5% EtOAc in pentane).
- **IR** (neat): 2955m, 1710s, 1255m, 1106m, 836m.
- **^{1}H NMR** (400 MHz, CDCl$_3$): 7.40 – 7.49 (m, 5 H, C-H$_{Ar}$), 3.68 (t, *J* = 6 Hz, 2 H, C*H*$_2$-O), 2.78 (t, *J* = 7 Hz, 2 H, C*H*$_2$-C$_q$), 1.88 – 1.99 (m, 2 H, C*H*$_2$), 0.95 (s, 9 H, ^{t}-Bu), 0.06 (s, 6 H, Si-CH$_3$).
- **^{13}C NMR** (100 MHz, CDCl$_3$): 197.4 (*C*=O), 134.5 (*C*$_{Ar}$), 129.3 (*C*$_{Ar}$), 129.2 (*C*$_{Ar}$), 127.9 (*C*$_{Ar}$), 61.7 (O-*C*H$_2$), 40.4 (*C*H$_2$-CO), 28.4 (*C*H$_2$), 25.9 (CH$_3$), 18.3 (*C*(CH$_3$)$_3$), –5.3 (Si-CH$_3$).

- **LRMS** (EI): 311.1 (100, $M+H^+$), 201.0 (90); **HRMS** (EI): M-^{t}Bu found 253.0645 $C_{12}H_{17}O_2SSi$ requires 253.0719.

3-(9-(*tert*-Butyldimethylsilyloxy)-6-oxonon-4-ynyl)furan-2(5*H*)-one (**79**):

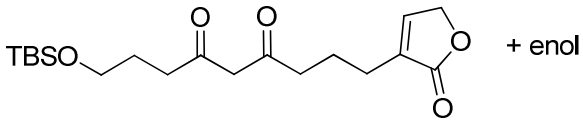


Alkyne **86** (150 mg, 1.0 mmol) was added to a solution of CuI (381 mg, 2.0 mmol), TFP (58.0 mg, 0.25 mmol), $PdCl_2$dppf (73.2 mg, 0.01 mmol), (i-Pr)$_2$NEt (0.17 mL, 1.0 mmol) and thioester **90** (340 mg, 1.1 mmol) in DMF (1.5 mL) and the reaction mixture was then degassed with argon and then stirred at 50 °C for 6 h. The reaction mixture was then diluted with Et_2O (1 mL) and brine (1 mL), passed through celite and washed with Et_2O (10 mL). The combined organic extracts were evaporated under reduced pressure and purified by column chromatography (30% EtOAc in petrol) to give the alkyne **79** (318 mg, 92%) as a light yellow oil

- ***R*$_f$**: 0.38 (35% EtOAc in petrol).
- **IR** (neat): 2930m, 1756s, 1672s, 1254s, 836m.
- **^{1}H NMR** (400 MHz, $CDCl_3$): 7.19 (s, 1 H, C*H*=), 4.80 (d, J = 2 Hz, 2 H, CH_2-O-CO), 3.63 (t, J = 6 Hz, 2 H, CH_2-OSi), 2.63 (t, J = 7 Hz, 2 H, CH_2-CO), 2.46 – 2.39 (m, 4 H, CH_2-C_q), 1.82 – 1.95 (m, 4 H, CH_2-CH_2-OSi and CH_2-CH_2-C≡), 0.89 (s, 9 H, ^{t}-Bu), 0.05 (s, 6 H, Si-CH_3).
- **^{13}C NMR** (100 MHz, $CDCl_3$): 187.9 (C≡C-*C*O), 174.1 (O-*C*O), 145.2 (*C*H=), 133.0 (C_q=), 92.3 (C≡*C*-CO), 81.5 (C≡*C*-CH_2), 70.3 (*C*H_2-O), 61.9 (*C*H_2-OSi), 42.1 (OC-CH_2), 27.0 (=C_q-CH_2), 25.9 (CH_3), 25.3 (C≡C-CH_2-*C*H_2), 24.5 (O=C-CH_2-*C*H_2), 18.52 (C≡C-*C*H_2), 18.3 (*C*(CH_3)$_3$), -5.3 (Si-*C*H_3).

- **LRMS** (ESI): 349.1 (100, M-H^+), 659.3 (80); **HRMS** (ESI): M+Na^+ found 373.1800 $C_{19}H_{30}NaO_3Si$ requires 373.1806.

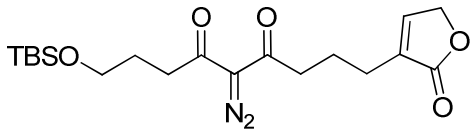
(*Z*)-3-(9-(*tert*-butyldimethylsilyloxy)-6-hydroxy-4-oxonon-5-enyl)furan-2(5*H*)-one (**78**)



A solution of chloro[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]gold(I)/$AgSbF_6$ (11 mg/a spatula tip (8 mg), 0.0125 mmol) in dioxane (1 mL), was stirred at rt for 5 min, then was added to a solution of alkyne **79** (350 mg, 1.0 mmol) in dioxane/water (4.00 mL/0.03 mL). After 40 min at rt, the reaction was quenched with Et_3N (2 drops) and diluted with water (20 mL) and extracted with EtOAc (3 x 40 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure and purified by column chromatography (40% of EtOAc in petrol) to give diketone **78** (35% enol form; 336 mg, 91%) as a clear oil.

- R_f: 0.46 (40% EtOAc in petrol).
- **IR** (neat): 2929m, 1756s, 1662br, 1101m, 836s.
- **^{1}H NMR** (400 MHz, $CDCl_3$): 15.41 – 15-46 (brs, 1 H, O*H*), 7.17 (d, *J* = 2 Hz, 1 H, CH=), 5.48 – 5.56 (m, 1 H, CH=C-OH), 4.79 (d, *J* = 2 Hz, 2 H, CH_2-O-CO), 3.60 – 3.69 (m, 2 H, CH_2-OSi), 2.62 – 2.58 (m, 1 H), 2.30 – 2.40 (m, 5 H, CH_2), 1.87 – 1.96 (m, 2 H, CH_2), 1.75 – 1.85 (m, 2 H, CH_2), 0.89 (s, 9 H, ^{t}-Bu), 0.06 (s, 6 H, Si-CH_3).
- **^{13}C NMR** (100 MHz, $CDCl_3$): 194.4, 192.9, 188.0, 174.2, 144.7, 133.6, 99.4, 70.2, 62.1, 37.5, 34.8, 28.6, 25.9, 24.5, 23.2, 18.3, -5.35.
- **LRMS** (ESI): 367.1 (100, M-H), 401.1 (55), 323.2 (20); **HRMS** (ESI): M+Na^+ found 391.1911 $C_{19}H_{32}NaO_5Si$ requires 391.1911.

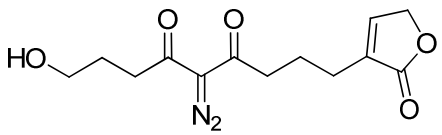
1-(*tert*-Butyldimethylsilyloxy)-5-diazo-9-(2-oxo-2,5-dihydrofuran-3-yl)nonane-4,6-dione (**91**):



ABSA (240 mg, 1.0 mmol) was added to a solution of diketone **78** (368 mg, 1.0 mmol) and Et_3N (0.1 mL, 1.0 mmol) in dry MeCN (5 mL) and the reaction mixture was stirred 4 h at rt. The reaction was then quenched with sat. aq. NH_4Cl (20 mL), and the aq. layer was extracted with Et_2O (3 × 100 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure and purified by column chromatography (30 → 50% EtOAc in Petrol) to give the diazodione **91** (377 mg, 95%) as a yellow light oil.

- ***R**_f*: 0.64 (40% EtOAc in petrol).
- **IR** (neat): 2930s, 2857s, 2117s, 1755, 1664, 836s.
- **^{1}H NMR** (400 MHz, $CDCl_3$): 7.19 (s, 1 H, CH=), 4.80 (d, *J* = 2 Hz, 2 H, CH_2-O), 3.67 (t, *J* = 6 Hz, 2 H, CH_2-OSi), 2.86 (t, *J* = 7 Hz, 2 H, CH_2-CO), 2.76 (t, *J* = 7 Hz, 2 H, CH_2-CO), 2.37 (t, *J* = 7 Hz, 2 H, CH_2-O), 1.91 – 2.00 (m, 2 H, CH_2-CH_2-CO), 1.91 – 1.86 (m, 2 H, CH_2-CH_2-CO), 0.89 (s, 9 H, ^{t}-Bu), 0.05 (s, 6 H, Si-CH_3).
- **^{13}C NMR** (100 MHz, $CDCl_3$): 191.10 (*C*O), 190.26 (*C*O), 174.1 (O-*C*O), 144.6 (*C*H=), 133.6 (C_q=), 83.7 (*C*=N_2), 70.2 (*C*H_2-Cq), 61.8 (*C*H_2-OSi), 40.0 (*C*H_2-CO), 36.7 (*C*H_2-CO), 29.6 (*C*H_2-C=), 25.0 (CH_3), 24.6 (*C*H_2-CH_2-CO), 21.7 (*C*H_2-CH_2-CO), 18.4 (C_q-*C*H_3), -5.3 (Si-CH_3).
- **LRMS** (ESI): 393.1 (100, M+H^+), 349.2 (70); **HRMS** (ESI): M+Na^+ found 417.1812 $C_{19}H_{30}N_2NaO_3Si$ requires 417.1816.

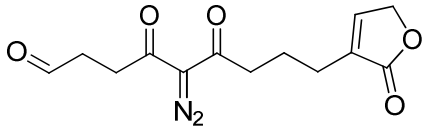
5-Diazo-1-hydroxy-9-(2-oxo-2,5-dihydrofuran-3-yl)nonane-4,6-dione (**92**):



A solution of diazodione **91** (396 mg, 0.75 mmol) in THF (0.75 mL), water (0.75 mL) and AcOH (2.25 mL) was stirred at rt for 15 h. The reaction mixture was then diluted with EtOAc\water (1:1; 60 mL) and the aq. layer was extracted with EtOAc (3 × 30 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure and purified by column chromatography (5% MeOH in CH_2Cl_2) to give the diazoalcohol **92** (216 mg crude, ≈ 100%) as a clear oil.

- ***R*$_f$**: 0.40 (5% MeOH in CH_2Cl_2).
- **IR** (neat): 3480br, 2933s, 2123s, 1749, 1659s.
- **^{1}H NMR** (400 MHz, $CDCl_3$): 7.20 (s, 1 H, C*H*=), 4.73 – 4.84 (m, 2 H, C*H*$_2$-O), 3.68 (t, *J* = 6 Hz, 2 H, C*H*$_2$-OH), 2.77 – 2.89 (m, 5 H, O*H* and C*H*$_2$-CO), 2.35 (t, *J* = 7 Hz, 2 H, C*H*$_2$-C_q=),1.88 – 2.00 (m, 4 H, C*H*$_2$-CH_2-CO).
- **^{13}C NMR** (100 MHz, $CDCl_3$): 191.1 (*C*O), 190.3 (*C*O), 174.4 (O-*C*O), 144.6 (*C*H=), 133.6 (*C*$_q$=), 84.1 (*C*=N_2), 70.3 (*C*H_2-O-C), 61.8 (*C*H_2-OH), 39.8 (*C*H_2-CO), 37.2 (*C*H_2-CO), 26.7 (*C*H_2-C=), 24.6 (*C*H_2-CH_2-CO), 21.8 (*C*H_2-CH_2-CO).
- **LRMS** (ESI): 279.7 (100, M+H$^+$), 235.1 (50); **HRMS** (ESI): M+Na$^+$ found 303.0949 $C_{13}H_{16}N_2NaO_5$ requires 303.0951.

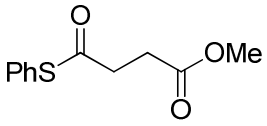
5-Diazo-4,6-dioxo-9-(2-oxo-2,5-dihydrofuran-3-yl)nonanal (**21**):



PCC (46.2 mg, 0.214 mmol) was added to a solution of above crude diazodione **92** (40 mg, 0.143 mmol) and dry NaOAc (3.5 mg, 0.043 mmol) in CH_2Cl_2 (1.4 mL). The reaction mixture was stirred 14 h at rt. A slurry of silica in Et_2O was then added and the mixture was concentrated under reduced pressure and purified by column chromatography (5% MeOH in CH_2Cl_2) to give diazoaldehyde **21** (31 mg, 80% from **91**) as a clear oil.

- ***R_f***: 0.5 (5% MeOH in CH_2Cl_2).
- **IR** (neat): 2929m, 2127s, 1747s, 1660s, 1201w.
- **^{1}H NMR** (400 MHz, $CDCl_3$): 9.82 (s, 1 H, C*H*O), 7.19 (s, 1 H, C*H*=), 4.79 (s, 2 H, C*H*$_2$-O), 2.96 – 3.09 (m, 2 H, C*H*$_2$-CO), 2.87 (d, *J* = 6 Hz, 2 H, C*H*$_2$-CO), 2.79 (t, *J* = 7 Hz, 2 H, C*H*$_2$-CHO), 2.39 – 2.32 (m, 2 H, C*H*$_2$-C_q=), 1.90 – 2.02 (m, 2 H, C*H*$_2$-CH_2-CHO).
- **^{13}C NMR** (100 MHz, $CDCl_3$): 200.0 (*C*HO) 191.10 (*C*O), 190.26 (*C*O), 174.2 (O-*C*O), 144.9 (*C*H=), 133.5 (C_q=), 83.9 (*C*=N_2), 70.3 (*C*H_2-O), 39.7 (*C*H_2-CO), 37.4 (*C*H_2-CO), 32.9 (*C*H_2-CHO), 26.7 (*C*H_2-C=), 24.6 (*C*H_2-CH_2-CO).
- **LRMS** (ESI): 293.5 (100), 277.0 (95), 249.1 (55); **HRMS** (ESI): M-H^+ found 277.0834 $C_{13}H_{13}N_2O_5$ requires 277.0830.

Methyl 4-oxo-4-(phenylthio)butanoate (**99**):

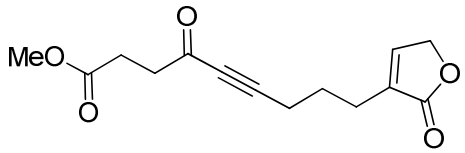


A solution of acid **97**[49] (3.00 g, 22.7 mmol) in $SOCl_2$ (3 mL) was heated under reflux for 2 h, then concentrated under reduced pressure and the resulted crude acid chloride **98** was used directly without further purification.

A solution of the above acid chloride **98** in CH_2Cl_2 (10 mL) was added slowly to a solution Et_3N (2.32 mL, 22.7 mmol) and thiophenol (3. 16 mL, 22.7 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was stirred at rt for 3 h, then quenched with sat. aq. $NaHCO_3$ (75mL) and extracted with Et_2O (3 × 150 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure and purified by column chromatography (0 → 20% of EtOAc in pentane) to give the thioester **99** (3.24 g, 64%) as a yellow light oil.

- ***R*$_f$**: 0.78 (5% EtOAc in petrol).
- **IR** (neat): 2952m, 1739s, 1708s, 1439s, 1207br, 1171, 1067s.
- **^{1}H NMR** (400 MHz, $CDCl_3$): 7.45 – 7.41 (m, 5 H, C-H_{Ar}), 3.70 (s, 3 H, CH_3), 3.03 (t, *J* = 7 Hz, 2 H, C*H*$_2$-COS), 2.71 (t, *J* = 7 Hz, 2 H, C*H*$_2$-CO).
- **^{13}C NMR** (100 MHz, $CDCl_3$): 196.2 (*C*O-SPh), 172.3 (*C*O_2Et), 134.6 (C_{Ar}), 129.5 (C_{Ar}), 129.2 (C_{Ar}), 127.3(C_{Ar}), 52.0 (*C*H_3), 38.1 (*C*H_2-COS), 28.9 (*C*H_2-CO_2Et).
- **LRMS** (ESI): 247.03 (100, M+Na^+).

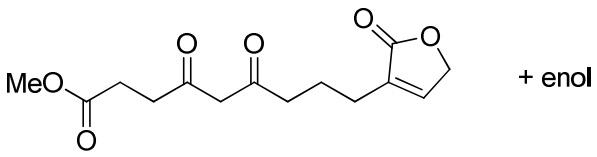
Methyl 4-oxo-9-(2-oxo-2,5-dihydrofuran-3-yl)non-5-ynoate (**100**):



Alkyne **86** (450 mg, 3 mmol) was added to a solution of (1.14 g, 6.0 mmol), TFP (174 mg, 0.75 mmol), $PdCl_2$dppf (219 mg, 0.30 mmol), (i-Pr)$_2$NEt (0.524 mL, 3 mmol) and thioester **99** (740 mg, 3.3 mmol) in DMF (7.5 mL) and the reaction mixture was then degassed with argon and then stirred at 50 °C for 4 h. The reaction mixture was then diluted with Et_2O (5 mL) and brine (5 mL), passed through celite and washed with Et_2O (10 mL). The combined organic extracts were evaporated under reduced pressure and purified by column chromatography (30 → 50% EtOAc in petrol) to give alkyne **100** (460 mg, 58%) as a light yellow oil

- R_f = 0.28 (35% EtOAc in petrol).
- **IR** (neat): 2952m, 2211s 1749s, 1674s, 1438m, 1345m, 1209s, 1156s.
- **^{1}H NMR** (400 MHz, $CDCl_3$): 7.20 (s, 1 H, C*H*=), 4.80 (d, *J* = 2 Hz, 2 H, CH_2-O-CO), 3.69 (s, 3 H, CH_3), 2.89 (t, *J* = 7 Hz, 2 H, CH_2-CO), 2.64 (t, *J* = 7 Hz, 2 H, CH_2-CO_2CH_3), 2.49 – 2.41 (m, 4 H, CH_2-C_q), 1.84 – 1.94 (m, 2 H, CH_2-CH_2-C≡).
- **^{13}C NMR** (100 MHz, $CDCl_3$): 185.4 (*C*O), 173.9 (*C*O_2-C≡), 172.5 (*C*O_2-C=), 145.2 (*C*H=), 132.9 (C_q=), 93.3 (C≡*C*-CO), 81.1 (*C*≡C-CO), 70.2, (*C*H_2-O), 51.9 (*C*H_3), 39.9 (*C*H_2-CO-C≡), 27.7 (*C*H_2-CO_2Me), 25.2 (*C*H_2-C=), 24.5 (CH_2-*C*H_2-CH_2), 18.5 (*C*H_2-C≡).
- **LRMS** (ESI): 263.11 (100, M-H$^+$), 231. 09 (50), 187.09 (80); **HRMS** (EI): M$^+$ found 264.1028 $C_{14}H_{16}O_5$ requires 264.0998.

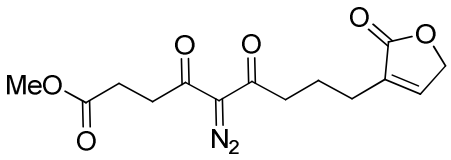
Methyl 4,6-dioxo-9-(2-oxo-2,5-dihydrofuran-3-yl)nonanoate (**101**):



$AgSbF_6$ (a spatula tip, ~ 10 mg) was added to a solution of alkyne **100** (400 mg, 1.5 mmol) in dioxane/water (5:1, 6.0 mL). The reaction mixture was stirred at rt for 90 min. then quenched with Et_3N (2 drops), diluted with water (20 mL) and extracted with EtOAc (3 x 40 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure and purified through a plug of silica (10% of Et_2O in CH_2Cl_2) to give diketone **101** (40% enol form; 363 mg, 86%) as a clear oil.

- ***R*$_f$**: 0.33 (10% of Et_2O in CH_2Cl_2).
- **IR** (neat): 2954m, 1748s, 1624s, 1438m, 1357m, 1205s.
- **^{1}H NMR** (400 MHz, $CDCl_3$): 15.09 (br. s., 1 H, O*H*), 7.15 (d, *J* = 2 Hz, 1 H, CH=), 5.50 (s, 0.5 H, CH=C-OH), 4.76 – 4.71 (m, 2 H), 3.64, 3.62, 3.59 (3 s, 3 H, CH_3 and CO-CH_2-CO), 2.74 – 2.80 (m, 1 H, CH_2), 2.53 – 2.65 (m, 4 H, CH_2), 2.18 – 2.29 (m, 3 H, CH_3), 1.83 (dq, *J* = 7, 14 Hz, 2 H, C*H*$_2$-CH_2-C=).
- **^{13}C NMR** (100 MHz, $CDCl_3$): 203.3, 202.5, 195.1, 189.4, 174.2, 172.9, 145.1, 133.4, 99.3, 70.2, 57.0, 51.8, 42.6, 38.0, 36.5, 33.6, 28.6, 27.6, 24.7, 24.4, 23.4, 21.0.
- **LRMS** (ESI): 283.1 (90, M+H$^+$), 300.1 (100), 305.1 (80. M+Na$^+$); **HRMS** (EI): M found 282.1102 $C_{15}H_{20}O_6$ requires 282.1104.

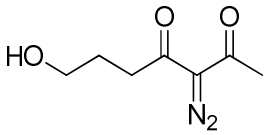
Methyl 5-diazo-4,6-dioxo-9-(2-oxo-2,5-dihydrofuran-3-yl)nonanoate (**93**):



ABSA (281 mg, 1.17 mmol) was added to a solution of diketone **101** (282 mg, 1.17 mmol) and Et_3N (0.12 mL, 1.17 mmol) in MeCN (5 mL) and the reaction mixture was stirred at rt for 5 h. The reaction was then quenched with sat. aq. NH_4Cl (20 mL) and extracted with Et_2O (3 × 100 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure and purified by column chromatography (10% of Et_2O in CH_2Cl_2) to give diazodione **93** (360 mg, 99%) as a yellow light oil.

- ***R*$_f$**: 0.28 (50% EtOAc in petrol).
- **IR** (neat): 2943s, 2129s, 1747, 1662, 1165s.
- **^{1}H NMR** (400 MHz, $CDCl_3$): 7.17 (t, *J* = 2 Hz, 1 H, CH=), 4.75 (d, *J* = 2.0 Hz, 2 H, CH_2-O), 3.65 (s, 3 H, CH_3), 2.99 (t, *J* = 7 Hz, 2 H, CH_2-CO-N_2), 2.77 (t, *J* = 7 Hz, 2 H, CH_2-CO_2CH_3), 2.59 – 2.69 (m, 2 H, CH_2-CO-N_2), 2.26 – 2.37 (m, 2 H, CH_2-C=), 1.82 – 1.93 (m, 2 H, CH_2-CH_2-C=).
- **^{13}C NMR** (100 MHz, $CDCl_3$): 190.3 (*C*O-CN_2), 189.0 (*C*O-CN_2), 174.2 (*C*O_2 CH_3), 172.9 (*C*O_2-CH_2), 145.0 (*C*H=), 133.4 (C_q=), 83.9 (*C*-N_2), 70.2 (*C*H_2-O), 51.9 (*C*H_3), 39.7 (*C*H_2-CO), 35.2 (*C*H_2-CO), 27.8 (*C*H_2-CO_2Me), 24.6 (*C*H_2-C=), 21.6 (CH_2-*C*H_2-CH_2).
- **LRMS** (ESI): 331.1 (30, M+Na^+), 410.2 (100), 639.2 (90); **HRMS** (EI): M found 308.1071 $C_{14}H_{16}N_2O_6$ requires 308.1008.

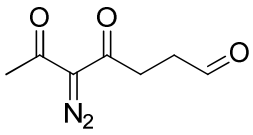
3-Diazo-7-hydroxyheptane-2,4-dione (**103**):



ABSA (500 mg, 2.08 mmol) was added to a solution of diketone[50] **102** (300 mg, 2.08 mmol) and Et_3N (0.43 mL, 4.37 mmol) in MeCN (15 mL). The reaction mixture was stirred 5 h at rt, then quenched with sat. aq. NH_4Cl (20 mL). The aq. layer was extracted with Et_2O (3 × 100 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure and purified by column chromatography (50% of Et_2O in CH_2Cl_2) to give diazodione **103** (254 mg, 72%) as a light yellow oil.

- ***R*$_f$**: 0.4 (50% Et_2O in CH_2Cl_2).
- **IR** (neat): 3501br, 2953s, 1720s, 1496s.
- **^{1}H NMR** (400 MHz, $CDCl_3$): 3.65 (t, *J* = 6 Hz, 2 H, CH_2-OH), 2.83 (t, *J* = 7 Hz, 2 H, CH_2-CO), 2.42 (s, 3 H, CH_3), 1.91 – 1.87 (m, 2 H, C*H*$_2$-CH_2-OH).
- **^{13}C NMR** (100 MHz, $CDCl_3$): 191.3 (CO), 188.6 (CH_3-*C*O), 84.4 (*C*-N_2), 61.7 (CH_2-*C*H_2-OH), 37.2 (*C*H_2-CO), 28.5(*C*H_2-CH_2-OH), 26.7 (CH_3).
- **LRMS** (ESI): 193.07 (40, M+Na^+), 225.09 (100), 166.04 (20); **HRMS** (FI): M found 170.0688 $C_7H_{10}N_2O_3$ requires 170.0691.

5-Diazo-4,6-dioxoheptanal (**104**):

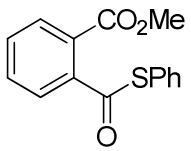


PCC (1.90 g, 5.8 mmol) was added to a solution of diazodione **103** (1.00 g, 5.8 mmol) and dry NaOAc (142 mg, 1.74 mmol) in CH_2Cl_2 (60 mL). The reaction mixture was stirred 14 h at rt, then a slurry of silica in Et_2O was added and the mixture was concentrated under

reduced pressure and purified by column chromatography (50 → 100% Et_2O in CH_2Cl_2) to give diazoaldehyde **103** (600 mg, 61%) as a clear oil.

- ***R*$_f$**: 0.4 (2% MeOH in CH_2Cl_2).
- **IR** (neat): 2134s, 1715s, 1663s, 1374s, 1298s, 1210m.
- **^{1}H NMR** (400 MHz, $CDCl_3$): 9.84 (s, 1 H, CHO), 3.11 – 3.03 (m, 2 H, CH_2-CHO), 2.84 – 2.93 (m, 2 H, CH_2-CO), 2.44 (s, 3 H, CH_3).
- **^{13}C NMR** (100 MHz, $CDCl_3$): 199.96 (*C*HO) 191.20 (*C*O), 189.5 (*C*O), 96.7 (*C*-N_2), 37.4 (*C*H_2-CHO), 33.0 (*C*H_2-CO), 28.4 (CH_3-CO).
- **HRMS** (FI): M^+ found 168.0534, $C_7H_8N_2O_3$ requires 168.0535.

Methyl 2-(phenylthiocarbonyl)benzoate (**114**):



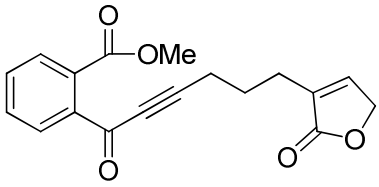
A solution of acid **112**[53] (1.00 g, 5.5 mmol) in $SOCl_2$ (2 mL) was heated under reflux for 2 h, then concentrated under reduced pressure and the resulted crude acid chloride **113** was used directly without further purification.

A solution of the above acid chloride **113** in CH_2Cl_2 (5 mL) was added to a solution Et_3N (1.52 mL, 11.0 mmol) and thiophenol (0.56 mL, 5.5 mmol) in CH_2Cl_2 (5 mL) at 0 °C. The reaction mixture was stirred at rt for 2 h, then quenched with sat. aq. $NaHCO_3$ (75mL) and extracted with Et_2O (3 × 150 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure and purified by column chromatography (0 → 5% EtOAc in pentane) to give thioester **114** (1.04 g, 70%) as a yellow light oil.

- ***R*$_f$**: 0.88 (5% EtOAc in petrol).
- **IR (neat)**: 2951m, 1728s, 1691s, 1440s, 1281br, 1201, 1134s, 1088s.

- **^{1}H NMR** (400 MHz, $CDCl_3$): 7.93 – 7.87 (m, 1 H, C-H_{Ar}), 7.71 – 7.68 (m, 1 H, C-H_{Ar}), 7.53 – 7.64 (m, 4 H, C-H_{Ar}), 7.51 – 7.42 (m, 3 H, C-H_{Ar}), 3.92 (s, 3 H, Me);
- **^{13}C NMR** (100 MHz, $CDCl_3$): 192.4 (CO-S), 166.8 (CO_2CH_3), 139.7(C_{Ar}), 134.6(C_{Ar}), 131.8 (C_{Ar}), 131.0 (C_{Ar}), 130.1 (C_{Ar}), 129.6 (C_{Ar}), 129.4 (C_{Ar}), 127.7 (C_{Ar}), 127.4 (C_{Ar}), 52.7 (CH_3).
- **LRMS** (ESI): 273.1 (50, M+H^+), 290.0 (50), 425.2 (100); **HRMS** (ESI): M+Na found 295.0402 $C_{15}H_{12}NaO_3S$ requires 295.0399.

Methyl 2-(6-(2-oxo-2,5-dihydrofuran-3-yl)hex-2-ynoyl)benzoate (**115**):



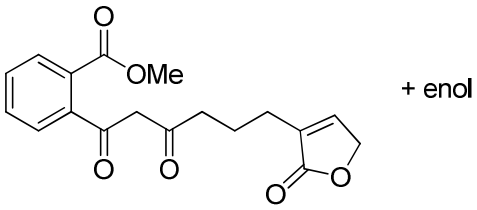
Alkyne **86** (300.0 mg, 2.0 mmol) was added to a solution of CuI (761.2 mg, 4 mmol), TFP (116.1 mg, 0.75 mmol), $PdCl_2$(dppf) (146.3 mg, 0.2 mmol), (*i*-Pr)$_2$NEt (0.349 mL, 2 mmol) and thioester **114** (600 mg, 2.2 mmol) in DMF (5 mL) and the reaction mixture was then degassed with argon and then stirred at 50 °C for 5 h. The reaction mixture was then diluted with Et_2O (2 mL) and brine (2 mL), passed through celite and washed with Et_2O (10 mL). The combined organic extracts were evaporated under reduced pressure and purified by column chromatography (40 → 50% EtOAc in petrol) to give alkyne **115** (440 mg, 70%) as a light yellow oil

- ***R$_f$***: 0.35 (40% EtOAc in petrol).
- **IR** (neat): 2952m, 1751s, 1598s, 1435m, 1290s.
- **^{1}H NMR** (400 MHz, $CDCl_3$): 7.93 – 7.90 (m, 1 H, C-H_{Ar}), 7.62 – 7.69 (m, 1 H, C-H_{Ar}), 7.55 – 7.62 (m, 2 H, C-H_{Ar}), 7.21 (s, 1 H, CH=), 4.80 (s, 2 H, CH_2-O), 3.91 (s, 3

H, CH_3), 2.51 – 2.57 (m, 2 H, CH_2-C≡), 2.44 – 2.51 (m, 2 H, CH_2-C=), 1.88 – 1.98 (m, 2 H, CH_2-CH_2-CH_2).

- **^{13}C NMR** (100 MHz, $CDCl_3$): 178.4 (C_{Ar}-*C*O), 174.0 (C=C-*C*O), 168.7 (*C*O_2CH_3), 145.4 (CH=), 137.7 C_{Ar}), 132.9 (C_{Ar}), 132.3 (C_{Ar}), 130.9 (C_{Ar}), 130.1 (C_q=), 128.8 (C_{Ar}), 95.9 (*C*H_2-C≡), 80.9 (CO-*C*≡), 70.2 (CH_2-O), 52.7 (*C*H_3), 25.8 (*C*H_2-C=), 24.6 (CH_2-*C*H_2-CH_2), 18.8 (*C*H_2-C≡).
- **LRMS** (ESI): 335.1 (100, M+Na^+); **HRMS** (ESI): M+Na^+ found 335.0891 $C_{18}H_{16}NaO_5$ requires 335.0890

Methyl 2-(3-oxo-6-(2-oxo-2,5-dihydrofuran-3-yl)hexanoyl)benzoate (**116**):

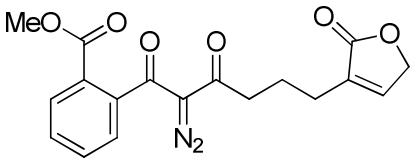


A solution of $AuCl(PPh_3)$ (24 mg, 0.05 mmol) and $AgSbF_6$ (a spatula tip, ~ 10 mg) in MeOH (1 mL) was stirred at rt for 5 min, then added to a solution of alkyne **115** (420 mg, 1.3 mmol) in MeOH/water (2:1; 6.0 mL). The reaction mixture was stirred at 60 °C for 3 h. The reaction was quenched with Et_3N (2 drops) and diluted with water (20 mL) and extracted with EtOAc (3 x 40 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure. The reaction mixture was dissolved in THF (5 mL) then 1 M HCl (3 mL) was added and stirred at room temperature for 4 h. The reaction was dissolved with water (20 mL) and extracted with EtOAc (3 x 40 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure and purified by column chromatography (Et_2O) to give diketone **116** (70% enol; 230 mg, 52%) as a yellow oil.

- ***R*$_f$**: 0.43 (Et_2O).
- **IR** (neat): 3436br, 2952m, 1750s, 1615s, 1435m, 1290m, 1201s.

- **^{1}H NMR** (400 MHz, $CDCl_3$): 15.50 (br. s., 1 H, =CH-O*H*), 7.76 – 7.75 (m, 0.6 H, C-H_{Ar}), 7.46 – 7.58 (m, 3 H, C-H_{Ar}), 7.12 – 7.24 (m, 1 H, C-H_{Ar}), 5.86 (s, 1 H , =C*H*-OH), 4.78 (s, 2 H), 3.94 – 3.79 (s, 4 H, CH_3 and CO-CH_2-CO), 2.46 – 2.28 (m, 4 H, CH_2), 1.97 – 1.76 (m, 2 H, CH_2).
- **^{13}C NMR** (100 MHz, $CDCl_3$): 192.3, 189.0, 174.2, 168.3, 145.1, 135.4, 133.5, 133.4, 133.2, 132.7, 131.3, 131.0, 130.6, 130.3, 129.9, 129.5, 128.0, 99.3, 66.1, 57.0, 52.6, 42.3, 37.4, 25.8, 24.8, 24.4, 23.4;
- **LRMS** (ESI): 329.1 (100, M-H^+), 297.1 (20); **HRMS** (ESI): M+Na^+ found 353.0995 $C_{18}H_{18}NaO_6$ requires 353.0996.

Methyl 2-(2-diazo-3-oxo-6-(2-oxo-2,5-dihydrofuran-3-yl)hexanoyl)benzoate (**117**):



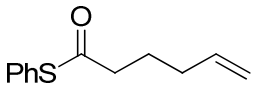
ABSA (137 mg, 0.57 mmol) was added to a solution of diketone **116** (200 mg, 0.60 mmol) and Et_3N (0.066 mL, 0.66 mmol) in MeCN (10 mL). The reaction mixture was stirred 5 h at rt, then quenched with sat. aq. NH_4Cl (20 mL). The aq. layer was extracted with Et_2O (3 × 30 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure and purified by column chromatography (Et_2O) to give diazodione **117** (360 mg, 83%) as a yellow light oil.

- ***R*$_f$**: 0.40 (Et_2O).
- **IR** (neat): 2123s, 1751s, 1655s, 1283s.
- **^{1}H NMR** (400 MHz, $CDCl_3$): 8.06 – 8.03 (m, 1 H, C-H_{Ar}), 7.68 – 7.65 (m, 1 H, C-H_{Ar}), 7.59 – 7.56 (m, 1 H, C-H_{Ar}), 7.40 – 7.37 (m, 1 H, C-H_{Ar}), 7.21 (s, 1 H, CH=),

4.79 (s, 2 H, CH_2-O), 3.90 (s, 3 H, CH_3), 2.94 (t, *J* = 6 Hz, 2 H, CH_2-CO), 2.37 (t, *J* = 7 Hz, 2 H, CH_2-CH=), 1.92 – 2.02 (m, 2 H; CH_2-C*H*$_2$-CH_2).

- **^{13}C NMR** (100 MHz, $CDCl_3$): 191.5 (CO-CN_2), 186.3 (CO-CN_2), 174.2 (CO_2 CH_3), 165.9 (CO_2-CH_2), 145.0 (CH=), 140.4 (C_{Ar}) , 133.6 (C_{Ar}), 133.1 (C_{Ar}), 130.7 (Cq=), 130.3 (C_{Ar}), 127.7 (C_{Ar}), 126.4 (C_{Ar}), 86.0 (*C*-N_2), 70.2 (*C*H_2-O), 52.7 (*C*H_3), 29.7 (*C*H_2-CO), 25.8 (*C*H_2-C=), 21.7 (CH_2-*C*H_2-CH_2).
- **LRMS** (ESI): 355.1 (100, M-H^+), 246.9 (90); **HRMS** (ESI): M+Na^+ found 379.0900 $C_{18}H_{18}N_2NaO_6$ requires 379.0901.

Phenyl hex-5-enethioate (**120**):



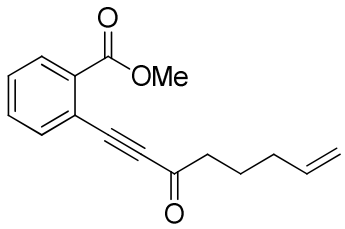
$COCl_2$ (3.30 g, 26.3 mmol) was added to a solution of hex-5-enoic acid (2.00 g, 17.5 mmol), followed by 2 drops of DMF. After 2 h at rt, the reaction mixture was concentrated under reduced pressure and the resulting crude acid chloride **119** was used directly without further purification.

A solution of the above acid chloride **119** in CH_2Cl_2 (15 mL) was added to a solution Et_3N (4.85 mL, 35 mmol) and thiophenol (1.62 mL, 15.7 mmol) in CH_2Cl_2 (30 mL) at 0 °C. The reaction mixture was allowed to warm at room temperature over 2 h, then quenched with sat. aq. $NaHCO_3$ (75 mL) and extracted with Et_2O (3 × 150 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure and purified by column chromatography (5% EtOAc in pentane) to give thioester **120** (2.8 g, 77%) as a lightyellow oil.

- ***Rf***: 0.84 (5% EtOAc in pentane).
- **IR** (neat): 2952m, 1708s, 1640s, 1478s, 1440br, 914, 746s.

- **^{1}H NMR** (400 MHz, $CDCl_3$): 7.45 – 7.39 (m, 5 H, C-H_{Ar}), 5.72 – 5.87 (m, 1 H, =CH), 4.96 – 5.13 (m, 2 H, =CH_2), 2.68 (t, *J* = 7 Hz, 2 H, CH_2-CO), 2.10 – 2.21 (m, 2 H, C*H*$_2$-CH=), 1.77 – 1.88 (m, 2 H, CH_2-C*H*$_2$-CH_2);
- **^{13}C NMR** (100 MHz, $CDCl_3$): 197.4 (CO), 129.3 (CH=), 129.2 (C_{Ar}), 118.5 (C_{Ar}), 116, 2 (Cq=), 115.7 (C_{Ar}), 42.9 (CH_2-CO), 32.9 (CH_2=), 24.6 (CH_2-CH_2-CH_2).
- **HRMS** (EI): M found 206.0761 $C_{12}H_{14}OS$ requires 206.0765.

Methyl 2-(3-oxohept-6-en-1-ynyl)benzoate (122):



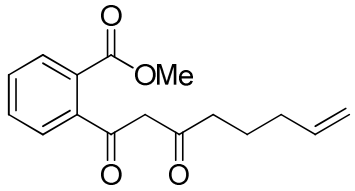
Alkyne **121** (320 mg, 2.0 mmol) was added to a solution of CuI (761.8 g, 4.0 mmol), TFP (116 mg, 0.5 mmol), $PdCl_2$(dppf) (146 mg, 0.2 mmol), (*i*-Pr)$_2$NEt (0.349 mL, 2.0 mmol) and thioester **120** (454 mg, 2.2 mmol) in DMF (5 mL) and the reaction mixture was then degassed with argon and then stirred at 50 °C for 3 h. The reaction mixture was then diluted with Et_2O (5 mL) and brine (5 mL), passed through celite and washed with Et_2O (10 mL). The combined organic extracts were evaporated under reduced pressure and purified by column chromatography (20 → 30% EtOAc in petrol) to give alkyne **122** (385 mg, 75%) as a light yellow oil

- ***R$_f$***: 0.62 (20% EtOAc in petrol).
- **IR** (neat): 1730s, 1670s, 1260s.
- **^{1}H NMR** (400 MHz, $CDCl_3$): 7.97 – 8.12 (m, 1 H, C-H_{Ar}), 7.63 – 7.73 (m, 1 H, C-H_{Ar}), 7.41 – 7.60 (m, 2 H, C-H_{Ar}), 5.62 – 5.91 (m, 1 H, CH=), 4.96 – 5.14 (m, 2 H,

=CH_2), 3.98 (s, 3 H, CH_3), 2.73 (t, *J* = 7.5 Hz, 2 H, CO- CH_2), 2.17 – 2.13 (m, 2 H, =CH-C*H*$_2$), 1.92 – 1.86 (m, 2 H, (CH_2-C*H*$_2$-CH_2).

- **^{13}C NMR** (100 MHz, $CDCl_3$): 188.0 (CO-C≡), 165.8 (CO_2CH_3), 137.7 (CH=), 135.1(C-H_{Ar}), 132.0 (C-H_{Ar}), 130.8 (C_{Ar}), 130.1 (C-H_{Ar}), 120.7 (C_{Ar}), 115.5 (=CH_2), 91.7 (C_{Ar}-*C*≡), 89.1 (CO-*C*≡), 52.4 (*C*H_3), 44.8 (*C*H_2-CO), 32.9 (*C*H_2-CH=), 23.1 (CH_2-*C*H_2-CH_2).
- **HRMS** (EI): M found 256.1067 $C_{16}H_{16}O_3$ requires 256.1099.

methyl 2-(3-oxooct-7-enoyl)benzoate (**123**):



A solution of $AuCl(PPh_3)$ (4.1 mg, 0.016 mmol) and $AgSbF_6$ (a spatula tip, ~ 3 mg) in MeOH (0.5 mL) stirred at rt for 5 min, was added to a solution of alkyne **122** (100 mg, 0.39 mmol) in MeOH/water (1:1; 4 mL). The reaction mixture was stirred at 60 ^oC for 3 h, then quenched with Et_3N (2 drops), diluted with water (20 mL) and extracted with EtOAc (3 x 40 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was dissolved in THF (5 mL), then 1 M HCl (3 mL) was added and the reaction mixture stirred at rt for 4 h. The reaction mixture was then dissolved with water (20 mL), extracted with EtOAc (3 x 40 mL), The combined organic extracts were evaporated under reduced pressure and purified by column chromatography (20% of Et_2O in pentane) to give diketone **123** (89 mg, 79%) as a clear oil.

- ***R*$_f$**: 0.3 (20% EtOAc in petrol).
- **^{1}H NMR** (400 MHz, $CDCl_3$): 15.56 (br. s., 1 H, =CH-O*H*), 7.72 – 7.80 (m, 1 H, C-H_{Ar}), 7.46 – 7.65 (m, 3 H, C-H_{Ar}), 5.72 – 5.89 (m, 2 H, CH_2=C*H* and C*H*$_2$-CO), 4.87

– 5.14 (m, 2 H, CH_2=CH), 3.87 (s, 3 H, CH_3), 2.33 – 2.48 (m, 2 H, CH_2), 2.10 – 2.21 (m, 2 H, CH_2), 1.64 – 1.88 (m, 2 H, CH_2). All other data as reported in the literature.[32]

5.3 General Procedures and Data for Chapter 3

Procedure A and A': Allylation using zinc

Zinc dust <10μm (77 mg, 1.18 mmol) was added to a solution of the aldehyde (0.77 mmol) and bromolactone **125** (178 mg, 1 mmol) in DMF (or THF for procedure A') (1 mL) and sat. aq NH_4Cl (2 drops). After stirring overnight, the reaction mixture was quenched with sat. aq NH_4Cl (1 mL), passed through celite® and washed through with Et_2O (10 mL). Evaporation under reduced pressure gave a residue which was purified though a small plug of silica.

Procedure B: Allylation with Catalytic chromium

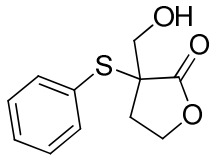
A flame-dried Schlenk tube containing $CrCl_3$ (10 mg, 0.07 mmol, 99% Aldrich) and Mn powder (108 mg, 1.97 mmol, 150μm) was charged with dry THF (3 mL) and (*i*-Pr)$_2$EtN (0.034 mL, 0.198 mmol). The resulting suspension was vigorously stirred under an atmosphere of argon for 1 h. This resulted in the disappearance of the characteristic purple colour of the chromium(III) salt and the formation of a white/grey suspension with a pale green supernatant. Bromolactone **125** (1 mmol) was added and the reaction mixture stirred for 1 h at rt. The allylation was then initiated by the addition of the aldehyde (0.66 mmol) and TMSCl (0.244 mL, 1.98 mmol) and the reaction mixture stirred under an atmosphere of argon at rt for 16 h. The resulting green/ brown suspension was quenched with sat. aq. $NaHCO_3$ (1 mL) and passed through a plug of celite. The filtrate was concentrated, then

dissolved in THF (1 mL), a few drops of 1 M HCl were added, and the resulting solution stirred for 1 h. The reaction was then diluted with water (20 mL). The aq layer extracted with EtOAc (3 × 20 mL), the combined organic extracts dried (Na_2SO_4), concentrated under reduced pressure, and purified by column chromatography.

Procedure C: Allylation using organozinc reagents

Commercial organozinc reagent (0.39 mmol) was added dropwise over 2 min to a stirred solution of the lactone **125** (50 mg, 0.28 mmol), TBAB (9.0 mg, 0.028 mmol) and CuCN (5.0 mg, 0.056 mmol) in THF (1 mL) at –78 °C. The reaction mixture was stirred for 30 min and slowly warmed to –20 °C and stirred for 15 min. The reaction mixture was then quenched with sat. aq NH_4Cl (1 mL), extracted with Et_2O (3 × 5 mL), concentrated under reduced pressure and purified by flash chromatography

3-(Hydroxymethyl)-3-(phenylthio)dihydrofuran-2(3H)-one (**126**):

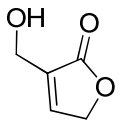


n-BuLi (6.9 mL, 1.6 M in hexanes, 11.4 mmol) was added to a solution of (*i*-Pr)$_2$NH (1.58 mL, 11.4 mmol) in THF (10 mL) at -78 °C and the reaction mixture was stirred 30 min at -78 °C, then lactone **84**[40] (1.8 g, 9.2 mm1) in THF (10 mL) was added and the reaction mixture was stirred at -78 °C for 60 min, then paraformaldehyde (828 mg, 27.6 mmol) was added to the reaction over a period of 30 min and the reaction mixture was then stirred at -78 °C for 3 h. The reaction was then quenched with sat. aq. NH_4Cl (20 mL) at -78 °C. The aq. layer was extracted with Et_2O (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$),

concentrated under reduced pressure and purified by column chromatography (20% Et_2O in CH_2Cl_2) to give the lactone **126** [55b] (0.91 g, 44%, 63% brsm) as a clear oil.

- ***R_f*:** 0.3 (40% EtOAc in petrol).
- **^{1}H NMR** (200 MHz, $CDCl_3$): 7.31 – 7.64 (m, 5 H, C-H_{Ar}), 4.23 – 4.50 (m, 2 H, CH_2-OH), 3.91 (d, *J* = 11 Hz, 1 H, CH_2-O), 3.74 (d, *J* = 11 Hz, 1 H, CH_2-O), 2.81 (ddd, *J* = 9, 10, 13 Hz, 1 H, CH_2), 2.07 – 2.26 (m, 1 H, CH_2), 1.95 (br. s., 1 H, OH); All other data as reported in the literature.[55b]

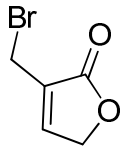
3-(Hydroxymethyl)furan-2(5*H*)-one (**127**):



m-CPBA (715 mg, 4.1 mmol) was added to a solution of lactone **126** (884 mg, 3.94 mmol) in CH_2Cl_2 (30 mL) at 0 °C. After 5 min, the mixture was quenched with sat. aq. $NaHCO_3$ (25 mL) and the aq. layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$), concentrated under reduced pressure and then diluted in toluene (30 mL). This solution was allowed to stir at 90 °C for 5 h, then concentrated under reduced pressure and purified by column chromatography (60% EtOAc in hexanes) to give unsaturated lactone **127** [55b] (330 mg, 73%) as a yellow light oil.

- ***R_f*:** 0.3 (70 % EtOAc in petrol)
- **^{1}H NMR** (200 MHz, $CDCl_3$): 7.40 (quin, *J* = 2 Hz, 1 H, C*H*=), 4.88 (q, *J* = 2 Hz, 2 H, CH_2-OH), 4.48 (q, *J* = 2 Hz, 2 H, CH_2-O), 2.11 (br. s., 1 H, O*H*); All other data as reported in the literature.[55b]

3-(Bromomethyl)furan-2(5*H*)-one **(125)**:

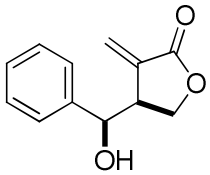


Trimethyphenylammonium tribromide (4.5 g, 12 mmol) was added to a solution of tulipalin **(47)** (1.0 g, 10 mmol) in dioxane (50 mL). The reaction mixture was stirred for 15 h, then Et_2O was added (100 mL). The reaction mixture was then filtered and concentrated under reduced pressure to give the crude dibromolactone **130** (2.9 g) which was used in the next step without further purification.

A mixture of the above dibromolactone, Li_2CO_3 (3.7 g, 50 mmol) and LiBr (4.3 g, 50 mmol) in DMF (30 mL) was stirred at 60 °C. After 10 h, the reaction mixture was cooled to room temperature, poured into water (300 mL), and extracted with Et_2O (3 X 100 mL). The combined organic extracts were dried ($MgSO_4$), concentrated under reduced pressure, and purified by column chromatography (30% EtOAc in petrol) to give the bromolactone **125**[55b] (980 mg, 55% from **47**) as a light yellow oil.

- ***R*$_f$**: 0.32 (30% EtOAc in petrol)
- **^{1}H NMR** (400 MHz, $CDCl_3$): 7.47 – 7.58 (m, *J* = 1.5 Hz, 1 H, CH=), 4.87 (q, *J* = 2 Hz, 2 H, CH_2-O), 4.12 (q, *J* = 1.5 Hz, 2 H, CH_2-Br).
- **^{13}C NMR** (100 MHz, $CDCl_3$): 171.7 (CO), 149.5 (CH=), 130.7 (Cq=), 70.3 (CH_2-O), 20.9 (CH_2-Br).
- **LRMS** (ESI): 198.9 (100, M+Na^+); **HRMS** (ESI): M+Na^+ found 198.9371; $C_5H_5O_2{}^{79}BrNa$ requires 198.9372.

4-(Hydroxy(phenyl)methyl)-3-methylenedihydrofuran-2(3*H*)-one **(132)**:

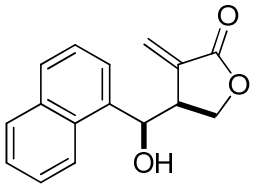


Following procedure A, using benzaldehyde (81 mg, 0.77 mmol), the above alcohol **132** (130 mg, 83%, 95:5 dr) was obtained after column chromatography (30% → 50% EtOAc in petrol) as a white solid.

- ***R*$_f$**: 0.32 (50% EtOAc in petrol)
- **mp**: 120 – 125 °C
- **IR** (neat): 3348br, 1759s, 1658s, 1274s, 1122br, 704s.
- **^{1}H NMR** (400 MHz, $CDCl_3$): 7.26 – 7.44 (m, 5 H, C-H_{Ar}), 6.29 (d, *J* = 2 Hz, 1 H, =CH_2), 5.71 (d, *J* = 2 Hz, 1 H, =CH_2), 4.68 (d, *J* = 7 Hz, 1 H, O-CH_2), 4.13 (t, *J* = 7 Hz, 1 H, O-CH_2), 4.04 (dd, *J* = 4, 9 Hz, 1 H, C*H*-OH), 3.30 – 3.45 (m, 1 H, C*H*-C_q=), 2.89 (br s, 1 H, OH).

  Discernable data for minor diastereoisomer: 6.15 (d, *J* = 2 Hz, 1 H, =CH_2), 4.99 (d, *J* = 2 Hz, 1 H, =CH_2).
- **^{13}C NMR** (100 MHz, $CDCl_3$): 171.1 (CO), 140.7 (C_q=), 134.9 (C_{Ar}), 128.8 (C-H_{Ar}), 128.5 (C-H_{Ar}), 126.6 (C-H_{Ar}), 125.5 (=CH), 75.4 (CH_2-OH), 67.8 (CH_2-O), 45.4 (*C*H-C_q=).
- **LRMS** (ESI): 431.15 (100), 227.07(50, M+Na^+); **HRMS** (ESI): M+Na^+ found 227.0678; $C_{12}H_{12}O_3Na$ requires 227.0679.

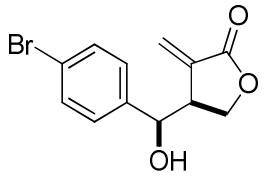
4-Hydroxy(naphthalen-2-yl)methyl)-3-methylenedihydrofuran-2(3*H*)-one **(137)**:



Following procedure A, using 1-naphthaldehyde (120 mg, 0.77 mmol), the above alcohol **137** (154 mg, 79%, 99:1 dr) was obtained after column chromatography (30 % → 50% EtOAc in petrol) as colourless crystals.

- ***R*$_f$**: 0.53 (50% EtOAc in petrol)
- **mp**: 154 – 158 °C.
- **IR** (neat): 3445s, 1755s, 1272s, 1123s.
- **^{1}H NMR** (500 MHz, $CDCl_3$): 8.11 (d, *J* = 8 Hz, 1 H, C-H_{Ar}), 7.87 – 8.01 (m, 1 H, C-H_{Ar}), 7.84 (d, *J* = 8 Hz, 1 H, C-H_{Ar}), 7.41 – 7.62 (m, 4 H, C-H_{Ar}), 6.33 (d, *J* = 2 Hz, 1 H, =CH_2), 5.47 (m, 2 H, =CH_2 and O-CH_2), 4.19 – 4.27 (m, 1 H, O-CH_2), 4.12 – 4.18 (m, 1 H, C*H*-OH), 3.54 – 3.71 (m, 1 H, C*H*-C_q=), 2.57 (br s, 1 H, OH).
- **^{13}C NMR** (125 MHz, $CDCl_3$): 170.8 (CO), 135.8 (C_q=), 134.6, (C_{Ar}), 133.9, (C-H_{Ar}), 130.3, (C-H_{Ar}), 129.3, (C-H_{Ar}), 129.2, (C-H_{Ar}), 126.7, (C-H_{Ar}), 126.0, (C-H_{Ar}), 125.8, (C-H_{Ar}), 125.1, (C-H_{Ar}), 124.7, (=CH), 122.6 (C-H_{Ar}), 72.8 (CH_2-OH), 68.4 (CH_2-O), 44.5 (*C*H-C_q=).
- **LRMS** (ESI): 531 (100), 277 (40, M+Na); **HRMS** (ESI): M+Na^+ found 277.0834; $C_{16}H_{14}O_3Na$ requires 277.0835.

4-(4-Bromophenyl)(hydroxy)methyl)-3-methylenedihydrofuran-2(3*H*)-one **(138)**:

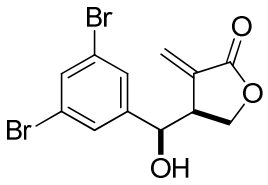


Following procedure A, using 4-bromobenzaldehyde (140 mg, 0.77 mmol), the above alcohol **138** (198 mg, 91%, 94:6 dr) was obtained after column chromatography (30% → 50% EtOAc in petrol) as a colourless gum.

- ***R*$_f$**: 0.47 (50% EtOAc in petrol)
- **IR** (neat): 3454s, 1727s, 1543s, 1125s.
- **^{1}H NMR** (500 MHz, $CDCl_3$): 7.53 (t, *J* = 2 Hz, 1 H, C-H_{Ar}), 7.25 (d, *J* = 2 Hz, 2 H, C-H_{Ar}), 6.37 (d, *J* = 2 Hz, 1 H, =CH_2,), 5.76 (d, *J* = 2 Hz, 1 H, =CH_2), 4.71 (dd, *J* = 7, 3 Hz, 1 H, O-CH_2), 4.22 (dd, *J* = 10, 8 Hz, 1 H, O-CH_2), 4.09 (dd, *J* = 10, 4 Hz, 1 H,), 3.33 – 3.42 (m, 1 H, C*H*-OH), 2.30 (d, *J* = 3.5 Hz, 1 H, OH).

  Discernable data for minor diastereoisomer: 6.24 (d, *J* = 2 Hz, 1 H, =CH_2), 5.10 (d, *J* = 2 Hz, 1 H, =CH_2), 4.54 (dd, *J* = 10, 4 Hz, 1 H, O-CH_2), 4.35 (dd, *J* = 10, 8 Hz, 1 H, O-CH_2).
- **^{13}C NMR** (125 MHz, $CDCl_3$): 170.4 (CO), 139.5 (C_q=), 134.6 (C-H_{Ar}), 132.0 (C-H_{Ar}), 128.2 (C-H_{Ar}), 125.6 (C-H_{Ar}), 122.6 (=CH), 75.0 (CH_2-OH), 67.3 (CH_2-O), 45.4 (*C*H-C_q=).
- **LRMS** (ESI): 306 (100, M+Na), 413 (60); **HRMS** (ESI): M+Na^+ found 304.9781; $C_{12}H_{11}BrO_3$ requires 304.9784.

4-(3,5-Dibromophenyl)(hydroxy)methyl)-3-methylenedihydrofuran-2(3*H*)-one **(139)**:

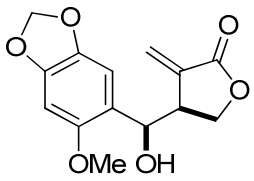


Following procedure A, using 3,5-dibromobenzaldehyde (203 mg, 0.77 mmol), the above alcohol **139** (217 mg, 78%, 95:5 dr) was obtained after column chromatography (30% → 50% EtOAc in petrol) as a white solid.

- ***R*$_f$**: 0.59 (50% EtOAc in petrol)
- **mp**: 120 – 125 °C.
- **IR** (neat): 3450s, 1747s, 1557s, 1271s, 1115s.
- **^{1}H NMR** (500 MHz, $CDCl_3$): 7.65 (s, 1 H, C-H_{Ar}), 7.45 (s, 2 H, C-H_{Ar}), 6.37 (d, *J* = 2 Hz, 1 H, =CH_2), 5.67 (d, *J* = 2 Hz, 1 H, =CH_2), 4.71 (dd, *J* = 4, 7 Hz, 1 H, O-CH_2), 4.28 – 4.23 (m, 1 H, O-CH_2), 4.13 (dd, *J* = 4, 9 Hz, 1 H, C*H*-OH), 3.20 – 3.41 (m, 1 H, C*H*-C_q=), 2.69 (s, 1 H, OH).

  Discernable data for minor diastereoisomer: 6.31 (d, *J* = 2 Hz, 1 H, =CH_2), 5.25 (d, *J* = 2 Hz, 1 H, =CH_2), 4.74 (dd, *J* = 4, 7 Hz, 1 H, O-CH_2), 4.50 (dd, *J* = 4, 9 Hz, 1 H, O-CH_2), 4.34 – 4.30 (m, 1 H, C*H*-OH).
- **^{13}C NMR** (125 MHz, $CDCl_3$): 170.4 (CO), 144.6 (C-H_{Ar}), 139.5 (C_q=), 134.2 (C-H_{Ar}), 134.0 (C-H_{Ar}), 128.5 (C-H_{Ar}),, 126.0 (=CH), 123.4 (C-H_{Ar}), 74.3 (CH_2-OH), 67.6 (CH_2-O), 45.4 (*C*H-C_q=).
- **LRMS** (ESI): 595 (100), 301 (100); **HRMS** (ESI): M+Na^+ found 384.8875; $C_{12}H_{10}Br_2O_3Na$ requires 384.8874.

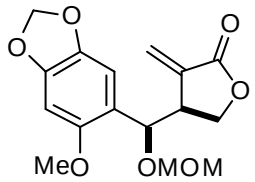
4-(Hydroxy(6-methoxybenzo[d][1,3]dioxol-5-yl)methyl)-3-methylenedihydrofuran-2(3*H*)-one (**140)**:



Following procedure A, using 6-methoxybenzo[d][1,3]dioxole-5-carbaldehyde[145] (138 mg, 0.77 mmol), the above alcohol **140** (156 mg, 73%, 90:10 dr) was obtained after column chromatography (50% EtOAc in petrol) as a white gum.

- ***R**f*:* 0.35 (50% EtOAc in petrol)
- **IR** (neat): 3453s, 1758s, 1484s, 1192s, 1037s.
- **^{1}H NMR** (500 MHz, $CDCl_3$): 6.81 (s, 1 H, C-H_{Ar}), 6.52 (s, 1 H, C-H_{Ar}), 6.30 (d, *J* = 2 Hz, 1 H, =CH_2), 5.92 (s, 2 H, O-CH_2-O) , 5.71 (d, *J* = 2 Hz, 1 H, =CH_2), 4.91 (dd, *J* = 5, 9 Hz, 1 H, O-CH_2), 4.14 – 4.22 (m, 1 H, O-CH_2), 4.06 (dd, *J* = 4, 9 Hz, 1 H, C*H*-OH), 3.78 (s, 3 H, OCH_3), 3.43 (m, 1 H, C*H*-C_q=), 2.75 (d, *J* = 5 Hz, 1 H, OH).
  Discernable data for minor diastereoisomer: 6.83 (s, 1 H, C-H_{Ar}), 6.53 (s, 1 H, C-H_{Ar}), 6.19 (d, *J* = 2 Hz, 1H, =CH_2), 5.94 (s, 2 H, O-CH_2-O), 5.17 (d, *J* = 2 Hz, 1 H, =CH_2), 4.88 (dd, *J* = 5, 9 Hz, 1 H, O-CH_2), 4.14 – 4.22 (m, 1 H, O-CH_2), 4.06 (dd, *J* = 4, 9 Hz, 1 H, C*H*-OH), 3.77 (s, 3 H, OCH_3), 3.43 (m, 1 H, C*H*-C_q=), 2.66 (d, *J* = 5 Hz, 1 H, OH).
- **^{13}C NMR** (125 MHz, $CDCl_3$): 170.1 (CO), 150.5 (C-H_{Ar}), 147.0(C-H_{Ar}), 140.3 (C_q=), 134.2 (C-H_{Ar}), 124.1 (=CH), 120.0 (C-H_{Ar}), 106.5 (C-H_{Ar}), 100.4 (C-H_{Ar}), 93.4 (O-CH_2-O), 70.0 (CH_2-OH), 67.0 (CH_2-O), 55.2 (CH_3), 43.5 (*C*H-C_q=).
- **LRMS** (ESI): 579 (100), 301.10 (30, M+Na); **HRMS** (ESI): M+Na^+ found 301.0684; $C_{14}H_{14}O_6Na$ requires 301.0683.

MOM ether of (**140)**:



MOMCl (0.065 mL, 0.86 mmol) was added to a solution of alcohol **140** (200 mg, 0.71 mmol) and (*i*-Pr)$_2$EtN (0.149 mL, 0.86 mmol) in CH_2Cl_2 (3 mL) at 0 °C. The reaction mixture was stirred overnight at room temperature, then quenched with sat. aq NH_4Cl (5 mL). The aq layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts dried (Na_2SO_4), concentrated under reduced pressure and purified by column chromatography (40% EtOAc in petrol) to give the MOM ether[68] (171 mg, 75%, 95: 5 dr) as colourless crystals.

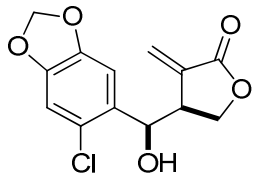
- ***R*$_f$**: 0.45 (50% EtOAc in petrol)
- **mp:** 89-93°C.
- **IR** (neat): 2921s, 1763s, 1484s, 1229s.
- **^{1}H NMR** (500 MHz, CDCl3): 6.79 (s, 1 H, C-H$_{Ar}$), 6.54 (s, 1 H, C-H$_{Ar}$), 6.30 (d, *J* = 2 Hz, 1 H, =CH$_2$), 5.94 (s, 2 H, O-CH$_2$-O), 5.44 (s, 1 H, =CH$_2$), 5.08 (d, *J* = 5 Hz, 1 H, O-CH$_2$), 4.48 (s, 2 H, O-CH$_2$-O), 4.02 - 4.29 (m, 2 H, O-CH$_2$ and C*H*-C$_q$=), 3.77 (s, 3 H, CH$_3$), 3.37 (s, 3 H, CH$_3$).

  Discernable data for minor diastereoisomer: 6.86 (s, 1 H, C-H$_{Ar}$), 6.51 (s, 1 H, C-H$_{Ar}$), 6.23 (d, *J* = 2 Hz, 1 H, =CH$_2$), 5.95 (s, 2 H, O-CH$_2$-O), 5.11 (d, *J* = 5 Hz, 1 H, =CH$_2$), 4.50 (s, 2 H, O-CH$_2$-O), 4.02 - 4.29 (m, 2 H, O-CH$_2$ and C*H*-C$_q$=), 3.73 (s, 3 H, CH$_3$), 3.33 (s, 3 H, CH$_3$).
- **^{13}C NMR** (125 MHz, CDCl3): = 171.2(CO), 152.2 (C-H$_{Ar}$), 148.0 (C-H$_{Ar}$), 141.3 (C$_q$=), 134.6 (C-H$_{Ar}$), 125.0 1 (=CH), 118.6 (C-H$_{Ar}$), 107.5 (C-H$_{Ar}$), 101.4 (C-H$_{Ar}$),

94.5 (O-CH_2-O), 94.3 (O-CH_2-O), 73.7 (CH_2-OH), 68.5 (CH_2-O), 56.3 (CH_3), 43.6 (*C*H-C_q=).

- **LRMS** (ESI): 375 (100), 345 (M+Na); **HRMS** (ESI): M+Na+ found 345.0942; $C_{16}H_{18}O_7Na$ requires 345.0945.

4-(6-Chlorobenzo[d][1,3]dioxol-5-yl)(hydroxy)methyl)-3-methylenedihydrofuran-2(3*H*)-one **(141)**:



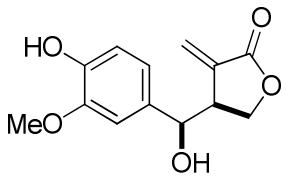
Following procedure A, using 6-chlorobenzo[d][1,3]dioxole-5-carbaldehyde (142 mg, 0.77 mmol), the above alcohol **141** (161 mg, 74%, 87:13 dr) was obtained after column chromatography (50% EtOAc in petrol) as a white gum.

- R_f: 0.38 (50% EtOAc in petrol).
- **IR** (neat): 3436s, 2911s, 1749s, 1477s, 1243s, 1117s, 1036s.
- **^{1}H NMR** (500 MHz, $CDCl_3$): 6.95 (s, 1 H, C-H_{Ar}), 6.81 (s, 1 H, C-H_{Ar}), 6.27 (d, *J* = 2 Hz, 1 H, =CH_2), 6.00 (d, *J* = 2 Hz, 2 H, O-CH_2-O), 5.47 (d, *J* = 2 Hz, 1 H, O-CH_2), 5.14 (d, *J* = 6 Hz, 1 H, O-CH_2), 4.26 – 4.40 (m, 1 H, C*H*-OH), 3.66 (s, 1 H, C*H*-OH), 3.40 (m, 1 H, C*H*-C_q=), 3.10 (br s, 1 H, OH).

  Discernable data for minor diastereoisomer: 7.06 (s, 1 H, C-H_{Ar}), 6.79 (s, 1 H, C-H_{Ar}), 6.26 (d, *J* = 2 Hz, 1 H, =CH_2), 6.00 (d, *J* = 2 Hz, 2 H, O-CH_2-O), 5.43 (d, *J* = 2 Hz, 1 H, =CH_2), 5.18 (d, *J* = 6 Hz, 1 H, O-CH_2), 4.26 – 4.40 (m, 1 H, O-CH_2), 3.67 (s, 1 H, C*H*-OH), 3.40 (m, 1 H, C*H*-C_q=), 3.10 (br s, 1 H, OH).

- **^{13}C NMR** (125 MHz, $CDCl_3$): 171.2 (CO), 147.9 (C-H_{Ar}), 147.1 (C_q=), 134.1 (C-H_{Ar}), 131.7 (C-H_{Ar}), 125.6 (=CH), 123.6 (C-H_{Ar}), 109.6 (O-CH_2-O), 107.9 (C-H_{Ar}), 102.0 (C-H_{Ar}), 71.6 (CH_2-OH), 68.4 (CH_2-O), 44.1 (*C*H-C_q=).
- **LRMS** (ESI): 589.08 (100), 305.4 (70, M+Na); **HRMS** (ESI): M+Na^+ found 305.0183; $C_{13}H_{11}O_5{}^{35}ClNa$ requires 305.0187.

4-Hydroxy(4-hydroxy-3-methoxyphenyl)methyl)-3-methylenedihydrofuran-2(3*H*)-one **(142)**:



Following procedure A, using vanillin (117 mg, 0.77 mmol), the above alcohol **142** (136 mg, 71%, 88:12 dr) was obtained after column chromatography (50% → 75% EtOAc in petrol) as a colourless crystal.

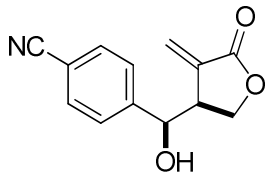
- ***R*$_f$**: 0.23 (50% EtOAc in petrol).
- **mp**: 127-135 °C
- **IR** (neat): 3450s, 1763s, 1513s, 1241.57s, 1031s.
- **^{1}H NMR** (500 MHz, $CDCl_3$): 6.91 (d, *J* = 8.1 Hz, 1 H, C-H_{Ar}), 6.87 (d, *J* = 2 Hz, 1 H, C-H_{Ar}), 6.80 – 6.85 (m, 1 H, C-H_{Ar}), 6.39 (d, *J* = 2 Hz, 1 H, =CH_2), 5.89 (d, *J* = 2 Hz, 1 H, =CH_2), 5.67 (s, 1 H, OH), 4.67 – 4.59 (m, 1 H, O-CH_2), 4.10 – 4.19 (m, 1 H, O-CH_2), 4.02 (dd, *J* = 4, 10 Hz, 1 H, C*H*-OH), 3.91 (s, 3 H, CH_3), 3.31 – 3.45 (m, 1 H, C*H*-C_q=), 2.13 (s, 1 H, OH).

  Discernable data for minor diastereoisomer: 6.91 (d, *J* = 8.1 Hz, 1 H, C-H_{Ar}), 6.86 (d, *J* = 2 Hz, 1 H, C-H_{Ar}), 6.80 – 6.85 (m, 1 H, C-H_{Ar}), 6.21 (d, *J* = 2 Hz, 1 H, =CH_2), 5.02 (d, *J* = 2 Hz, 1 H, =CH_2), 5.67 (s, 1 H, OH), 4.70 – 4.59 (m, 1 H, O-CH_2), 4.57 –

4.54 (m, 1 H, O-CH_2), 4.44 – 4.40 (m, 1 H, C*H*-OH), 3.90 (s, 3 H, CH_3), 3.31 – 3.45 (m, 1 H, C*H*-C_q=), 2.13 (s, 1 H, OH).

- **^{13}C NMR** (125 MHz, $CDCl_3$): 170.7 (CO), 146.9 (C-H_{Ar}), 146.0 (C_q=), 135.3 (C-H_{Ar}), 132.7 (C-H_{Ar}), 125.4 (=CH), 119.7(C-H_{Ar}), 114.5(C-H_{Ar}), 108.7(C-H_{Ar}), 75.7 (CH_2-OH), 67.5 (CH_2-O), 56.0 (CH_3), 45.6 (*C*H-C_q=).
- **LRMS** (ESI): 273.1 (100, M+Na), 523 (90); **HRMS** (ESI): M+Na^+ found 273.0736; $C_{13}H_{14}O_5Na$ requires 273.0733.

4-(Hydroxy(4-methylene-5-oxotetrahydrofuran-3-yl)methyl)benzonitrile **(143)**:



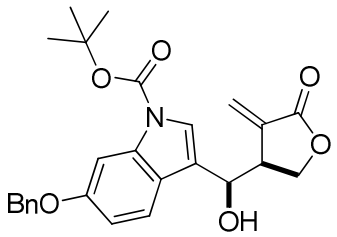
Following procedure A, using 4-cyanobenzaldehyde (101 mg, 0.77 mmol), the above alcohol **143** (144 mg, 82%, 90:10 dr) was obtained after column chromatography (50% → 70% EtOAc in petrol) as a colourless gum.

- ***R*$_f$**: 0.30 (50% EtOAc in petrol)
- **IR** (neat): 3562s, 1756s, 1481s, 1187s.
- **^{1}H NMR** (500 MHz, $CDCl_3$): 7.69 (d, *J* = 8.3 Hz, 2 H, C-H_{Ar}), 7.53 – 7.45 (m, 2 H, C-H_{Ar}), 6.37 (d, *J* = 2.3 Hz, 1 H, =CH_2), 5.61 (d, *J* = 1.8 Hz, 1 H, =CH_2), 4.95 – 4.78 (m, 1 H, O-CH_2), 4.35 – 4.22 (m, 1 H, O-CH_2), 4.19 (dd, *J* = 3.7, 9.7 Hz, 1 H, C*H*-OH), 3.46 – 3.33 (m, 1 H, C*H*-C_q=), 2.44 (br s, 1 H, OH).

  Discernable data for minor diastereoisomer: 7.69 (d, *J* = 8.3 Hz, 2 H, C-H_{Ar}), 7.39 – 7.60 (m, 2 H, C-H_{Ar}), 6.28 (d, *J* = 2.3 Hz, 1 H, =CH_2), 5.19 (d, *J* = 1.8 Hz, 1 H, =CH_2), 4.78 – 4.95 (m, 1 H, O-CH_2), 4.54 – 4.50 (dd, *J* = 4, 10 Hz 1 H, O-CH_2), 4.33 – 4.27 (m, 1 H, C*H*-OH), 3.33 – 3.46 (m, 1 H, C*H*-C_q=), 2.79 (br s, 1 H, OH).

- **^{13}C NMR** (125 MHz, $CDCl_3$): 170.1 (CO), 145.5 (C-H_{Ar}), 134.1 (C_q=), 131.0 (C-H_{Ar}), 132.5 (C-H_{Ar}), 131.3 (C-H_{Ar}), 127.6 (C-H_{Ar}), 127.3 (C-H_{Ar}), 125.7 (=CH), 118.2 (CN), 112.5 (C-H_{Ar}), 74.8 (CH_2-OH), 67.3 (CH_2-O), 45.4 (*C*H-C_q=).
- **LRMS** (ESI): 252.06 (60, M+Na); **HRMS** (ESI): M+Na^+ found 252.0638; $C_{13}H_{11}NO_3Na$ requires 252.0637.

tert-Butyl 6-(benzyloxy)-3-(-hydroxy-4-methylene-5-oxotetrahydrofuran-3-yl)methyl)-1*H*-indole-1-carboxylate **(144)**:



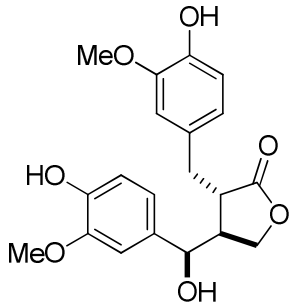
Following procedure A, using *tert*-butyl 7-(benzyloxy)-3-formyl-1*H*-indole-1-carboxylate (270 mg, 0.77 mmol, Aldrich®), the above alcohol **144** (232 mg, 67%, 90:10 dr) was obtained after column chromatography (40% → 60% EtOAc in petrol) as a yellow gum.

- ***R**$_f$*: 0.33 (50% EtOAc in petrol)
- **IR** (neat): 3468s, 1731s, 1735s, 1369s, 1152s.
- **^{1}H NMR** (500 MHz, $CDCl_3$): 7.86 (br s, 1 H, C-H_{Ar}), 7.32 (m, 7 H, C-H_{Ar}), 6.98 (d, *J* = 2 Hz, 1 H, C-H_{Ar}), 6.39 (d, *J* = 2 Hz, 1 H, =CH_2), 5.91 (d, *J* = 2 Hz, 1 H, =CH_2), 5.13 (s, 2 H, C*H*$_2$- C_{Ar}), 4.88 – 4.80 (m, 1 H, O-CH_2), 4.30 – 4.17 (m, 1 H, O-CH_2), 4.15 – 4.05 (m, 1 H, C*H*-OH), 3.71 – 3.52 (m, 1 H, C*H*-C_q=), 2.61 (br s, 1 H, OH), 1.63 (s, 9 H, ^{t}-Bu).

  Discernable data for minor diastereoisomer: 6.26 (d, *J* = 2 Hz, 1 H, =CH_2), 5.29 (d, *J* = 2 Hz, 1 H, =CH_2), 4.96 – 4.93 (m, 1 H, O-CH_2), 4.62 – 4.55 (m, 1 H, O-CH_2), 4.42 – 4.33 (m, 1 H, C*H*-OH).

- **^{13}C NMR** (125 MHz, $CDCl_3$): 170.8 (CO), 157.4 (C_{Ar}), 149.5(CON), 149.0 (C-H_{Ar}), 136.8 (C-H_{Ar}), 134.9 (C_q=), 128.6(C-H_{Ar}), 128.0 (C-H_{Ar}), 127.6 (C-H_{Ar}), 125.7 (=CH), 122.5 (C-H_{Ar}), 120.4 (C-H_{Ar}), 120.2 (C-H_{Ar}), 113.0 (C-H_{Ar}), 100.8 (C-H_{Ar}), 84.2 (C_q-^{t}-Bu, 70.4 (CH_2-OH), 69.6 (CH_2-Bz), 67.9 (CH_2-O), 44.1 (*C*H-C_q=), 28.1 (^{t}-Bu).
- **LRMS** (ESI): 472.20 (100, M+Na); **HRMS** (ESI): M+Na^+ found 472.1721; $C_{26}H_{27}NO_3Na$ requires 472.1731.

Hydroxymatairesinol **(146)**:



2-Methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (160 mg, 0.64 mmol) was added to a solution of alcohol **142** (100 mg, 0.4 mmol), [RhCl(cod)$_2$] (5.9 mg, 0.012 mmol) and Et_3N (0.056 mL, 0.40 mmol) in dioxane (1 mL) and water (0.33 mL). The reaction mixture was stirred at 100 °C in a microwave reactor (300 W) for 1 h. The residue was concentrated under reduced pressure and purified though a small plug of silica (50% EtOAc in petrol) to give (±)-hydroxymatairesinol[70] **(146)** (127 mg, 85%) as a white gum.

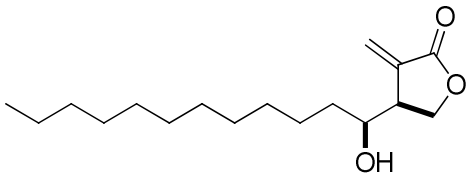
- ***R**$_f$*: 0.18 (50% EtOAc in petrol).
- **IR** (neat): 3562s, 1765s, 1526s, 1265s.
- **^{1}H NMR** (500 MHz, $CDCl_3$): 6.86 (d, *J* = 8 Hz, 1 H, C-H_{Ar}), 6.78 (d, *J* = 8 Hz, 1 H, C-H_{Ar}), 6.72 (dd, *J* = 2, 8 Hz, 1 H, C-H_{Ar}), 6.67 (s, 1 H, C-H_{Ar}), 6.51 – 6.64 (m, 2 H, C-H_{Ar}), 5.66 (s, 1 H, OH), 5.55 (s, 1 H, OH), 4.63 (dd, *J* = 2, 6 Hz, 1 H, C*H*-OH),

3.90 – 4.06 (m, 2 H, O-CH_2), 3.85 (s, 3 H, CH_3), 3.80 (s, 3.80, 3 H, CH_3), 2.96 – 3.05 (m, 1 H, C*H*-OH), 2.83 – 2.96 (m, 2 H, CH_2- C_{Ar}), 2.53 – 2.68 (m, 1 H, CH-CO), 2.09 (s, 1 H, C*H*-C_q=).

- **^{13}C NMR** (125 MHz, $CDCl_3$): 179.3 (CO), 146.8 (C_{Ar}), 146.5 C_{Ar}), 145.6 (C_{Ar}), 144.4 (C_{Ar}), 133.4 (C_{Ar}), 129.5 (C_{Ar}), 122.5 (C-H_{Ar}), 118.7 (C-H_{Ar}), 114.4 (C-H_{Ar}), 114.0 (C-H_{Ar}), 111.8 (C-H_{Ar}), 108.1 (C-H_{Ar}), 75.3 (CH_2-OH) , 68.6 (CH_2-O), 55.9 (CH_3), 55.8 (CH_3), 45.1 (*C*H-CO), 43.7 (*C*H-C_q=), 35.1(CH_2-Bz).
- **LRMS** (ESI): 771.3 (100), 375.1 (80), 397.1 (80, M+Na); **HRMS** (ESI): M+Na^+ found 397.1246; $C_{20}H_{22}O_7Na$ requires 397.1258.

  See ^{13}C NMR data comparaison of (±)-hydroxymatairesinol p. 40

4-(1-Hydroxydodecyl)-3-methylenedihydrofuran-2(3*H*)-one **(147)**:

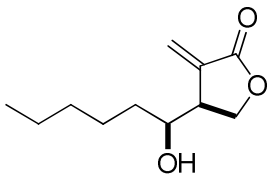


Following procedure B, using dodecanal (121 mg, 0.66 mmol), the above alcohol **147**[71] (175 mg, 94%) was obtained after column chromatography (15% → 30% EtOAc in petrol) as a colourless oil.

- ***R_f***: 0.45 (30% EtOAc in petrol)
- **IR** (neat): 2925s, 1769s, 1466s, 1113s.
- **^{1}H NMR** (500 MHz, $CDCl_3$): 6.32 (d, *J* = 2 Hz, 1 H, =CH_2), 5.64 (d, *J* = 2 Hz, 1 H, =CH_2), 4.25 – 4.38 (m, 2 H, O-CH_2), 3.64 – 3.84 (m, 1 H, CH-OH), 3.15 (dq, *J* = 4, 6 Hz, 1 H, *C*H-C_q=), 1.34 – 1.49 (m, 2 H, C*H*$_2$-CHOH), 1.22 – 1.34 (m, 18 H, C*H*$_2$), 0.87 (t, *J*= 6 Hz, 3 H, C*H*$_3$).

- **^{13}C NMR** (125 MHz, $CDCl_3$): 170.5 (CO), 135.1 (C_q=), 123.3 (=CH), 74.0 (CH_2-OH), 67.4 (CH_2-O), 44.1 (*C*H-C_q=), 32.2 (CH_2), 31.5 (CH_2), 29.2 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 25.2 (CH_2), 22.3 (CH_2), 13.8 (CH_3).
- **LRMS** (ESI): 305.2 (100, M+Na), 283.2 (70, M+H); **HRMS** (ESI): M+Na^+ found 305.2090; $C_{17}H_{30}O_3Na$ requires 305.2087.

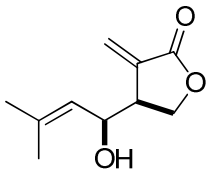
4-(1-Hydroxyhexyl)-3-methylenedihydrofuran-2(3*H*)-one **(148)**:



Following procedure B, using hexanal (66 mg, 0.66 mmol), the above alcohol **148** (121 mg, 93%) was obtained after column chromatography (20% → 30% EtOAc in petrol) as a colourless oil.

- ***R*$_f$**: 0.35 (30% EtOAc in petrol)
- **IR** (neat): 3425s, 1767s, 1456s, 1121s.
- **^{1}H NMR** (500 MHz, $CDCl_3$): 6.35 (d, *J* = 2 Hz, 1 H, =CH_2), 5.80 (d, *J* = 2 Hz, 1 H, =CH_2), 4.38 (dd, *J* = 10, 8Hz, 1 H, O-CH_2), 4.24 (dd, *J* = 10, 4 Hz, 1 H, O-CH_2), 3.55 – 3.76 (m, 1 H, C*H*-OH), 3.19 – 3.04 (m, 1 H, *C*H-C_q=), 2.20 (br s, 1 H, OH), 1.57 – 1.39 (m, 3 H, CH_2), 1.39 – 1.21 (m, 5 H, CH_2), 0.88 (t, *J* = 7 Hz, 3 H, CH_3).
- **^{13}C NMR** (125 MHz, $CDCl_3$): 170.9 (CO), 135.1 (C_q=), 124.6 (=CH), 73.2 (CH_2-OH), 68.1 (CH_2-O), 44.5 (*C*H-C_q=), 32.4 (CH_2), 31.6 (CH_2), 25.2 (CH_2), 22.5 (CH_2), 14.0 (CH_3).
- **LRMS** (ESI): 221.13 (100, M+Na), 253.17 (70); **HRMS** (ESI): M+Na^+ found 221.1155; $C_{11}H_{18}O_3Na$ requires 221.1148.

4-(1-Hydroxy-3-methylbut-2-en-1-yl)-3-methylenedihydrofuran-2(3*H*)-one **(149)**:

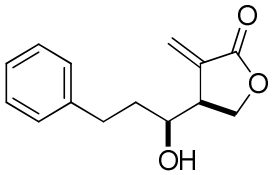


Following procedure B, using 3-methylbut-2-enal (55 mg, 0.66 mmol), the above alcohol **149** (66 mg, 55%, 88:12 dr) was obtained after column chromatography (30% → 50% EtOAc in petrol) as a colourless oil.

- ***R*$_f$**: 0.45 (50% EtOAc in petrol)
- **IR** (neat): 3448s, 1762s, 1273s, 1120s, 1027s.
- **^{1}H NMR** (500 MHz, $CDCl_3$): 6.34 (d, *J* = 2 Hz, 1 H, $=CH_2$), 5.89 (d, *J* = 2 Hz, 1 H, $=CH_2$), 5.18 (td, *J* = 2, 9 Hz, 1 H, =CH), 4.41 (dd, *J* = 8, 9 Hz, 1 H, O-CH_2), 4.31 (dd, *J* = 8, 9 Hz, 1 H, O-CH_2), 4.14 (dd, *J* = 4, 10 Hz, 1 H, C*H*-OH), 3.15 – 3.21 (m, 1 H, *C*H-C_q=), 1.76 (d, *J* = 2 Hz, 3 H, CH_3), 1.70 (d, *J* = 2 Hz, 3 H, CH_3).

  Discernable data for minor diastereoisomer: 6.32 (d, *J* = 2 Hz, 1 H, $=CH_2$), 5.71 (d, *J* = 2 Hz, 1 H, $=CH_2$), 5.18 (td, *J* = 2, 9 Hz, 1 H, =CH), 4.41 (dd, *J* = 8, 9 Hz, 1 H, O-CH_2), 4.31 (dd, *J* = 8, 9 Hz, 1 H, O-CH_2), 4.14 (dd, *J* = 4, 10 Hz, 1 H, C*H*-OH), 3.21 – 3.15 (m, 1 H, *C*H-C_q=), 1.78 (d, *J* = 2 Hz, 3 H, CH_3), 1.69 (d, *J* = 2 Hz, 3 H, CH_3)
- **^{13}C NMR** (125 MHz, $CDCl_3$): 170.7 (CO), 139.2 (CO-C_q=), 135.4 (C_q=), 124.6 ($=CH_2$), 123.4 (=CH), 69.7 (CH_2-OH), 67.3 (CH_2-O), 44.7 (*C*H-C_q=), 25.9 (CH_3), 18.6 (CH_3).
- **LRMS** (ESI): 205.1 (50, M+Na), 279.1 (100); **HRMS** (ESI): M+Na^+ found 205.0843; $C_{10}H_{14}O_3Na$ requires 205.0841.

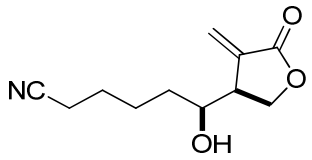
4-(1-Hydroxy-3-phenylpropyl)-3-methylenedihydrofuran-2(3*H*)-one **(150)**:



Following procedure B, using 3-phenylpropanal (88.5 mg, 0.66 mmol), the above alcohol **150** (114 mg, 75%) was obtained after column chromatography (30% → 50% EtOAc in petrol) as a colourless oil.

- ***R*$_f$**: 0.53 (50% EtOAc in petrol)
- **IR** (neat): 3458br, 1754s, 1659s, 1270s, 1087br, 701s.
- **^{1}H NMR** (500 MHz, $CDCl_3$): 7.26 – 7.36 (m, 2 H, C-H_{Ar}), 7.14 – 7.26 (m, 3 H, C-H_{Ar}), 6.35 (d, *J* = 2.3 Hz, 1 H, =CH_2), 5.78 (d, *J* = 2.0 Hz, 1 H, =CH_2), 4.29 – 4.44 (m, 1 H, O-CH_2), 4.23 (dd, *J* = 3.8, 9.3 Hz, 1 H, O-CH_2), 3.69 (ddd, *J* = 3.3, 6.0, 9.2 Hz, 1 H, CH_2-OH), 3.04 – 3.22 (m, 1 H, *C*H-C_q=), 2.89 (ddd, *J* = 5.6, 8.7, 14.0 Hz, 1 H, CH_2-Ar), 2.70 (dt, *J* = 8.1, 13.8 Hz, 1 H, CH_2-Ar), 2.35 – 1.95 (m, 1 H, OH), 1.68 – 1.89 (m, 2 H, CH_2).
- **^{13}C NMR** (125 MHz, $CDCl_3$): 170.7 (CO), 141.0 (C-H_{Ar}), 134.9 (C_q=), 128.6 (C-H_{Ar}), 128.4 (C-H_{Ar}), 126.2 (C-H_{Ar}), 124.8 (=CH_2), 72.3 (CH-OH), 68.0 (CH_2-O), 44.7 (*C*H-C_q=), 35.2 (CH_2-Ar), 32.0 (CH_2).
- **LRMS** (ESI): 487.18 (100), 255.09 (100, M+Na^+); **HRMS** (ESI): M+Na^+ found 255.0990; $C_{14}H_{16}O_3Na$ requires 255.0992.

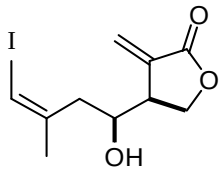
5-Hydroxy-5-(4-methylene-5-oxotetrahydrofuran-3-yl)hexanes nitrile **(151)**:



Following procedure B and using 6-oxohexanes nitrile[146] (64 mg, 0.66 mmol), the above alcohol **151** (83 mg, 65%) was obtained after column chromatography (40% → 60% EtOAc in petrol) as a colourless oil.

- ***R*$_f$**: 0.35 (50% EtOAc in petrol).
- **IR** (neat): 3552s, 1757s, 1471s, 1185s, 982s.
- **^{1}H NMR** (500 MHz, $CDCl_3$): 6.36 (d, *J* = 2 Hz, 1H, $=CH_2$), 5.66 (d, *J* = 2 Hz, 1 H, $=CH_2$), 4.43 – 4.22 (m, 2 H, O-CH_2), 3.79 (d, *J* = 5 Hz, 1 H, CH_2-OH), 3.19 (dd, *J* = 2, 4 Hz, 1 H, *C*H-C_q=), 2.36 (t, *J* = 7 Hz, 2 H, CH_2-CN), 1.75 – 1.60 (m, 4 H, CH_2), 1.43 (d, *J* = 7 Hz, 2 H, CH_2).
- **^{13}C NMR** (125 MHz, $CDCl_3$): 170.6 (CO), 135.2 (C_q=), 123.9, ($=CH_2$), 119.4 (CN), 74.1 (CH_2-OH), 67.2 (CH_2-O), 44.6 (*C*H-C_q=), 31.3 (CH_2-CN), 25.3 (CH_2), 24.9 (CH_2), 17.2 (CH_2).
- **LRMS** (ESI): 232.09 (80, M+Na); **HRMS** (ESI): M+Na^+ found 232.0952; $C_{11}H_{15}NO_3Na$ requires 232.0950.

4-((*Z*)-1-Hydroxy-4-iodo-3-methylbut-3-en-1-yl)-3-methylenedihydrofuran-2(3*H*)-one **(152)**:

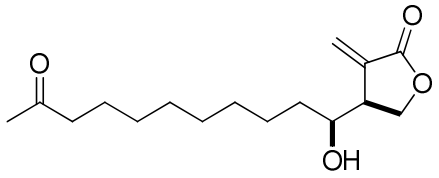


Following procedure B, using (Z)-4-iodo-3-methylbut-3-enal[147] (138.6 mg, 0.66 mmol), the above alcohol **152** (113 mg, 56%. 98:2 dr) was obtained after column chromatography (30% → 50% EtOAc in petrol) as a colourless oil.

- ***R**_f*: 0.42 (50% EtOAc in petrol).
- **IR** (neat): 3549s, 1756s, 1158s, 974s.
- **^{1}H NMR** (500 MHz, $CDCl_3$): 6.42 (d, *J* = 2 Hz, 1 H, $=CH_2$), 6.09 (s, 1 H, =CH), 5.93 (d, *J* = 2 Hz, 1 H, $=CH_2$), 4.44 (dd, *J* = 10, 8 Hz, 1 H, O-CH_2), 4.38 (dd, *J* = 10, 4 Hz, 1 H, O-CH_2), 3.98 – 3.90 (m, 1 H, C*H*.OH), 3.27 – 3.18 (m, 1 H, *C*H-C_q=), 2.51 (dd, *J* = 14, 10 Hz, 1 H, OH), 2.31 (dd, *J* = 14, 3 Hz, 2 H, CH_2), 1.98 (d, *J* = 0.9 Hz, 3 H, CH_3).

  Discernable data for minor diastereoisomer: 6.09 (d, *J* = 2 Hz, 1 H, $=CH_2$), 3.89 – 3.86 (m, 1 H, CH_2.OH).
- **^{13}C NMR** (125 MHz, $CDCl_3$): 170.7 (CO), 144.0 (CH_3-C_q=), 134.6 (C_q=), 125.3 ($=CH_2$), 77.9 (=CH), 71.5 (CH_2.OH), 67.9 (CH_2-O), 44.6 (*C*H-C_q=), 42.3 (CH_2), 24.8 (CH_3).
- **LRMS** (ESI): 331.02 (30, M+Na), 413.2 (100); **HRMS** (ESI): M+Na^+ found 330.9809; $C_{10}H_{13}IO_3Na$ requires 330.9802.

(1-Hydroxy-10-oxoundecyl)-3-methylenedihydrofuran-2(3*H*)-one **(153)**:

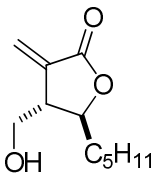


Following procedure B using 10-oxoundecanal[148] (121.6 mg, 0.66 mmol), the above alcohol **153** (130 mg, 70%) was obtained after column chromatography (20% → 50% EtOAc in petrol) as a colourless oil.

- ***R**_f*: 0.44 (30% EtOAc in petrol).
- **IR** (neat): 3563s, 1758s, 1732s, 1456s, 1183s.

- **^{1}H NMR** (500 MHz, $CDCl_3$): 6.39 (d, *J* = 2 Hz, 1 H, $=CH_2$), 5.82 (d, *J* = 2 Hz, 1 H, $=CH_2$), 4.40 (dd, *J* = 8, 10 Hz, 1H, O-CH_2), 4.25 (dd, *J* = 4, 10 Hz, 1 H, O-CH_2), 3.71 – 3.62 (m, *J* = 5, 5 Hz, 1 H, C*H*$_2$OH), 3.14 (dtd, *J* = 2, 4, 8 Hz, 1 H, *C*H-C_q=), 2.42 (t, *J* = 7 Hz, 2 H, OH), 2.14 (s, 3 H, CH_3), 1.72 – 1.56 (m, 2 H, C*H*$_2$-CO), 1.52 – 1.41 (m, 2 H, CH_2), 1.37 – 1.22 (m, 10 H, CH_2).
- **^{13}C NMR** (125 MHz, $CDCl_3$): 209.3 (CO), 170.6 (CO_2), 135.1 (C_q=), 124.6 ($=CH_2$), 73.2 (CH_2-OH), 67.8 (CH_2-O), 44.5 (*C*H-C_q=), 43.7 (CH_2), 33.5 (CH_2), 29.9 (CH_3), 29.3 (CH_2), 29.2 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 25.6 (CH_2), 23.7 (CH_2).
- **LRMS** (ESI): 305.17 (40, M+Na); **HRMS** (ESI): $M+Na^+$ found 305.1731; $C_{16}H_{26}O_4Na$ requires 305.1729.

4-(Hydroxymethyl)-3-methylene-5-pentyldihydrofuran-2(3*H*)-one **(159)**:



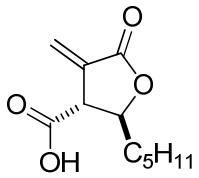
PTSA (2.4 mg, 0.0125 mmol) was added to a solution of lactone **159** (50 mg, 0.25 mmol), in MeOH (1 mL). The reaction mixture was stirred at 60 °C for 15 h, then concentrated under reduced pressure and the residue purified through a small plug of silica (50 % EtOAc in petrol) to give the primary alcohol **9**[73] (42 mg, 85%) as a light gum.

- ***R*$_f$**: 0.34 (40% EtOAc in petrol).
- **IR** (neat): 3458s, 1772s, 1475, 1123s.
- **^{1}H NMR** (500 MHz, $CDCl_3$): 6.33 (d, *J* = 2 Hz, 1 H, $=CH_2$), 5.72 (d, *J* = 2 Hz, 1 H, $=CH_2$), 4.40 (dt, *J* = 6, 4 Hz, 1 H, CH-O), 3.83 – 3.60 (m, 2 H, CH_2-OH), 2.94 – 2.72 (m, 1 H, *C*H-C_q=), 1.95 (br s, 1 H, OH), 1.79 – 1.59 (m, 2 H,), 1.58 – 1.47 (m, 1 H,

CH_2), 1.47 – 1.37 (m, 1 H, CH_2), 1.37 – 1.22 (m, 4 H, CH_2), 0.91 – 0.81 (t, *J* = 7 Hz, 3 H, CH_3).

- **^{13}C NMR** (125 MHz, $CDCl_3$): 170.1 (CO), 136.2 (C_q=), 123.5 (=CH_2), 80.8 (CH-O), 63.9 (CH_2-OH), 46.8 (*C*H-C_q=), 36.0 (CH_2), 31.4 (CH_2), 24.6 (CH_2), 22.5 (CH_2), 13.9 (CH_3).
- **LRMS** (ESI): 221.1 (70, M+Na), 419.2 (100). **HRMS** (ESI): M+Na^+ found 221.1155; $C_{11}H_{18}O_3Na$ requires 221.1154.

Methylenolactocin **(160)**:



A solution of primary alcohol **9** (40 mg, 0.2 mmol) in acetone (1 mL) was treated with freshly prepared Jones' reagent[149] at room temperature until a persistent orange color was observed. After 10 min, *i*-PrOH (2 drops) was added and the reaction mixture was diluted with H_2O (3 mL). The aq layer was extracted with CH_2Cl_2 (3 × 5 mL), the combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and purified by column chromatography (5% MeOH in CH_2Cl_2) to give (±)-methylenolactocin **(160)**[73] (30 mg, 72%) as a white solid.

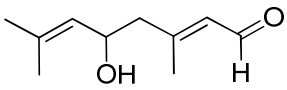
- ***R_f***: 0.34 (5% MeOH in CH_2Cl_2)
- **mp**: 78–80 °C (lit.[73] (±)-**10**: 82 °C)
- **IR**: 3463s, 1758s, 1661s, 1473s, 1123s.
- **^{1}H NMR** (500 MHz, $CDCl_3$): 6.47 (d, *J* = 2 Hz, 1 H, =CH_2), 6.03 (d, *J* = 2 Hz, 1 H, =CH_2), 4.90 – 4.70 (m, 1 H, CH-O), 3.64 (td, *J* = 6, 3Hz, 1 H, CH-CO_2H), 1.83 – 1.65

(m, 2 H, CH_2), 1.59 – 1.47 (m, 1 H, CH_2), 1.47 – 1.38 (m, 1 H, CH_2), 1.38 – 1.26 (m, 4 H, CH_2), 0.91 (t, *J* = 7 Hz, 3 H, CH_3)

- **^{13}C NMR** (125 MHz, $CDCl_3$): 173.5 (CO_2H), 168.1 (CO), 132.4 (C_q=), 125.8 (=CH_2), 78.8 (CH-O), 49.4 (CH-CO_2H), 35.7 (CH_2), 31.3 (CH_2), 24.4 (CH_2), 22.4 (CH_2), 13.9 (CH_3).
- **LRMS** (ESI): 235.1 (100, M+Na), 263.1 (70). **HRMS** (ESI): M+Na^+ found 235.0945; $C_{11}H_{16}O_4Na$ requires 235.0946.

  See ^{13}C NMR data comparaison of (±)-methylenolactocin p. 43

(*E*)-5-Hydroxy-3,7-dimethylocta-2,6-dienal (**165**):



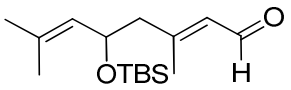
ATPH preparation: $AlMe_3$ (2.75 mL, 2.0 M in hexanes, 5.5 mmol) was added to a solution of 2,6-diphenylphenol (4.06 g. 16.5 mmol) in toluene (25 mL). The reaction mixture was stirred for 30 min at rt then used without further purification.

3-Methylbut-2-enal (**163**) (0.483 mL, 5.0 mmol) was added to the above solution of ATPH at -78 °C and stirred for 30 min, then LDA (3.0 mmol) in THF (5 mL) was added *via* canula to the reaction mixture. The reaction mixture was stirred for 30 min, then quenched with sat. aq. NH_4Cl (30 mL) and extracted with Et_2O (3 × 30 mL). The combined organic layers were dried (Na_2SO_4), concentrated under reduced pressure and purified by column chromatography (10 → 40% EtOAc in petrol) to give aldehyde **165** (130 mg, 31%) as a yellow oil.

- ***R_f***: 0.4 (40% EtOAc in petrol).
- **IR** (neat): 1745s, 1345s, 1183s.

- **^{1}H NMR** (400 MHz, $CDCl_3$): 9.92 (d, *J* = 8 Hz, 1 H, CHO), 5.88 (d, *J* = 8 Hz, 1 H, =C*H*-CHO), 5.15 (d, *J* = 8 Hz, 1 H, C*H*=CHOH), 4.56 (dt, *J* = 5, 8 Hz, 1 H, C*H*OH), 2.43 (dd, *J* = 8, 14 Hz, 1 H, CH_2), 2.29 (dd, *J* = 5, 14 Hz, 1 H, CH_2), 2.18 (s, 3 H, CH_3), 1.66 (s, 3 H, CH_3), 1.65 (s, 3 H, CH_3).
- **^{13}C NMR** (100 MHz, $CDCl_3$): 191.3 (*C*HO), 160.9 (*C*=CH-CHO), 135.9 ($(CH_3)_2C_q$=), 129.2 (=*C*H-CHOH), 127.0 ($(CH_3)_2C_q$=*C*H), 66.7 (*C*H-OH), 48.4 (CH_2), 25.7 (CH_3), 18.2 (CH_3), 18.1 (CH_3).
- **LRMS** (ESI): 465.3 (100), 397.3 (30); **HRMS** (ESI): M found 168.1156 $C_{10}H_{16}O_2$ requires 168.1156.

(*E*)-5-(*tert*-Butyldimethylsilyloxy)-3,7-dimethylocta-2,6-dienal (**166**):



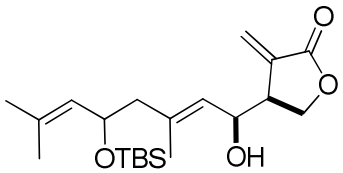
TBSCl (150.7 mg, 0.65 mmol), then imidazole (89.0 mg, 1.30 mmol) was added to a solution of aldehyde **165** (100 mg, 0.59 mmol) in DMF (2 mL). The reaction mixture was stirred at rt for 5 h, then quenched with sat. aq. NH_4Cl (15 mL) and extracted with Et_2O (3 × 25 mL). The combined organic layers were dried (Na_2SO_4), concentrated under reduced pressure and purified by column chromatography (10% EtOAc in petrol) to give aldehyde **166** (115 mg, 70%) as a yellow light oil.

- ***R*$_f$**: 0.7 (20% EtOAc in petrol).
- **IR** (neat): 3430s, 2956s, 2857s, 1717s, 1643s, 1292s, 1071s.
- **^{1}H NMR** (400 MHz, $CDCl_3$): 9.95 (d, *J* = 8 Hz, 1 H, CHO), 5.85 (d, *J* = 8 Hz, 1 H, =CH-CHO), 5.09 (d, *J* = 8 Hz, 1 H, C*H*=CHOSi), 4.52 (td, *J* = 5, 8 Hz, 1 H, C*H*OSi), 2.35 (dd, *J* = 8, 13 Hz, 1 H, CH_2), 2.22 (dd, *J* = 5, 13 Hz, 1 H, CH_2), 2.17 (s, 3 H,

CH_3), 1.66 (s, 3 H, CH_3), 1.62 (s, 3 H, CH_3), 0.79 (s, 9 H, ^{t}Bu), 0.04 (s, 3 H, Si-CH_3), 0.03 (s, 3 H, Si-CH_3).

- **^{13}C NMR** (100 MHz, $CDCl_3$): 190.9 (*C*HO), 161.1 (*C*=CH-CHO), 132.1 ($(CH_3)_2C_q$=), 129.6 (C*H*=CHOSi), 128.4 ($(CH_3)_2C_q$=*C*H), 68.7 (*C*H-OSi), 49.4 (CH_2), 25.7 (CH_3), 25.6 (^{t}Bu), 18.5 (CH_3), 18.2 (CH_3), 18.1 ($(CH_3)C_q$), -4.3 ($SiCH_3$), -5.0 ($SiCH_3$).
- **LRMS** (ESI): 305.2 (100, M+Na^+), 337.2 (100); **HRMS** (ESI): M+Na^+ found 305.1908 $C_{16}H_{30}O_2Si$ requires 305.1907.

(*E*)-4-(5-(*tert*-Butyldimethylsilyloxy)-1-hydroxy-3,7-dimethylocta-2,6-dienyl)-3-methylenedihydrofuran-2(3*H*)-one (**167**):

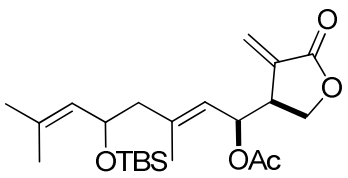


A flame-dried Schlenk tube containing $CrCl_3$ (6.2 mg, 0.038 mmol, 99% Aldrich) and Mn powder (54.9 mg, 1.167 mmol, 150 µm) was charged with dry THF (2 mL) and (*i*-Pr)$_2$EtN (0.013 mL, 0.0778 mmol). The resulting suspension was vigorously stirred under an atmosphere of argon for 1 h. This resulted in the disappearance of the characteristic purple color of the chromium(III) salt and the formation of a white/grey suspension with a pale green supernatant. Bromolactone **125** (103.2 mg, 0.58 mmol) was added and the reaction mixture stirred for 1 h at rt. The allylation was then initiated by the addition of the aldehyde **166** (110 mg, 0.389 mmol) and TMSCl (0.147 mL, 1.167 mmol) and the reaction mixture stirred under an atmosphere of argon at rt for 16 h. The resulting green/ brown suspension was quenched with sat. aq $NaHCO_3$ (1 mL) and passed through a plug of celite. The filtrate was concentrated, then dissolved in THF (1 mL), 3 drops of 1 M HCl were added, and the

resulting solution stirred for 1 h. The reaction was then diluted with water (20 mL). The aq layer extracted with EtOAc (3 × 20 mL), the combined organic extracts dried (Na_2SO_4), concentrated under reduced pressure, and purified by column chromatography (10 → 30% EtOAc in petrol) to give alcohol **167** (75 mg, 51%) as a light yellow oil.

- ***R*$_f$**: 0.35 (30% EtOAc in petrol).
- **IR** (neat): 1716s, 1384s, 1266s, 1115s, 1006s.
- **^{1}H NMR** (400 MHz, $CDCl_3$): 6.34 (t, *J* = 2 Hz, 1 H, CH_2=), 5.92 (s, 1 H, CH_2=), 5.18 (d, *J* = 9 Hz, 1 H, =C*H*-CHOH), 5.03 – 5.10 (m, 1 H, CH=), 4.43 – 4.53 (m, 1 H, CH_2-O), 4.34 – 4.43 (m, 1 H, CH_2-O), 4.29 (dt, *J* = 9, 13 Hz, 1 H, OH), 4.00 – 4.13 (m, 1 H, CH_2-OSi), 3.08 – 3.18 (m, 1 H, *C*H-C_q=), 2.24 (td, *J* = 7, 13 Hz, 1 H, CH_2), 2.05 – 2.16 (m, 1 H, CH_2), 1.72 (s, 6 H, CH_3), 1.59 – 1.64 (s, 3 H, CH_2), 0.83 – 0.89 (s, 9 H, ^{t}-Bu), 0.02 (s, 3 H, $SiCH_3$), 0.01 (s, 3 H, $SiCH_3$).
- **^{13}C NMR** (100 MHz, $CDCl_3$): 170.7 (CO_2-CH_2),139.5 (*C*=CH_2), 135.3 ((CH_3)$_2$*C*q=), 131.8 ((CH_3)(CH_2)*C*$_q$=), 128.9 ((CH_3)$_2$*C*$_q$=*C*H), 126.2 ((CH_3)(CH_2)*C*$_q$=*C*H), 124.7 (=CH_2), 69.6 (*C*H-OH), 68.9 (*C*H-OSi), 67.7 (CH_2-O), 48.9 (CH_2), 44.6 (*C*H-C_q=), 29.1(^{t}-Bu), 25.1 (CH_3), 25.7 (CH_3), 18.2 (CH_3), 18.1 (*C*$_q$$CH_3$), 17.5 ($CH_3$), -4.1 ($SiCH_3$), -4.7 ($SiCH_3$).
- **LRMS** (ESI): 403.2 (100, M+Na^+), **HRMS** (ESI): M+Na^+ found 403.2275 $C_{21}H_{34}O_4SiNa$ requires 403.2275

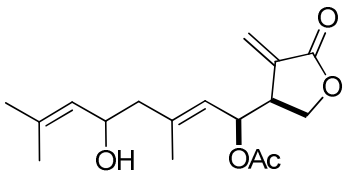
(*E*)-5-(*tert*-Butyldimethylsilyloxy)-3,7-dimethyl-1-(4-methylene-5-oxotetrahydrofuran-3-yl)octa-2,6-dienyl acetate (**168**):



AcCl (0.015 mL, 0.216 mmol) was added to a solution of alcohol **167** (70 mg, 0.197 mmol) and Et_3N (0.03 mL, 0.216 mmol) in CH_2Cl_2 (1 mL) at 0 °C. After 5 h at rt, the reaction mixture was quenched with sat. aq. $NaHCO_3$ (3 mL) and extracted with CH_2Cl_2 (3 X 5 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and purified by column chromatography (10 → 30% EtOAc in petrol) to give acetate **168** (44.1 mg, 52%) as a light yellow oil

- ***R*$_f$**: 0.5 (20% EtOAc in petrol).
- **IR** (neat): 1742s, 1723s 1374m, 1256s, 1105m, 935w.
- **^{1}H NMR** (200 MHz, $CDCl_3$): 6.33 (t, *J* = 2 Hz, 1 H, CH_2=), 5.76 (t, *J* = 2 Hz, 1 H, CH_2=), 5.49 – 5.64 (m, 1 H, =C*H*-CHOAc), 4.96 – 5.20 (m, 2 H, =C*H*-CHOSi and CH_2-O), 4.39 – 4.56 (m, 1 H, CH_2-O), 4.32 – 4.28 (m, 1 H, CH-OAc), 4.08 – 4.22 (m, 1 H, CH-OSi), 3.09 – 3.41 (m, 1 H, *C*H-C_q=), 2.05 – 2.37 (m, 2 H, CH_2), 2.03 (s, 3 H, CH_3), 1.77 (dd, *J* = 2, 5 Hz, 3 H, CH_3), 1.67 (t, *J* = 2 Hz, 3 H, CH_3), 1.60 (dd, *J* = 2, 4 Hz, 3 H. CH_3), 0.85 (s, 9 H, ^{t}-Bu), 0.00 (s, 6 H, $SiCH_3$).
- **^{13}C NMR** (126 MHz, $CDCl_3$): 170.1 (CO_2-CH_2), 169.7 (CO_2-CH_3), 141.4 (*C*=CH_2), 134.5 ((CH_3)$_2$*C*$_q$=), 131.6 ((CH_3)(CH_2)*C*q=), 128.9 ((CH_3)$_2$*C*$_q$=*C*H), 124.5 ((CH_3)(CH_2)*C*$_q$=*C*H), 121.6 (=CH_2), 71.3 (*C*H-OAc), 68.1 (*C*H-OSi), 66.9 (CH_2-O), 48.9 (CH_2), 42.6 (*C*H-C_q=), 29.7 (*C*$_q$(CH_3)$_3$), 25.8 (CH_3), 25.6 (CH_3), 21.0 (CH_3), 18.2 (CH_3), 17.6 (CH_3), -4.3 ($SiCH_3$)
- **LRMS** (ESI): 867.5 (100), 445.2 (60, M+Na); **HRMS** (ESI): M+Na^+ found 445.2379 $C_{23}H_{38}O_5SiNa$ requires 445.2381.

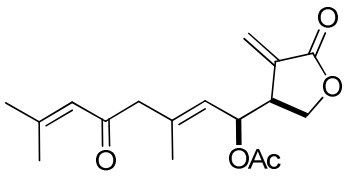
(*E*)-5-Hydroxy-3,7-dimethyl-1-(4-methylene-5-oxotetrahydrofuran-3-yl)octa-2,6-dienyl acetate (**169**):



TBAF (0.10 mL, 1 M in THF, 0.10 mmol) was added to a solution of acetal **168** (40 mg, 0.09 mmol) in THF (1.00 mL). The reaction mixture was stirred at rt for 15 h, then quenched with sat. aq. NH_4Cl (1 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and purified by column chromatography (40 → 50% EtOAc in petrol) to give alcohol **169** (15.1 mg, 60%) as a light yellow oil.

- ***R*$_f$**: 0.3 (40% EtOAc in petrol).
- **IR** (neat): 3463s, 1766s, 1740s, 1372m, 1234s, 1020w.
- **^{1}H NMR** (200 MHz, $CDCl_3$): 6.37 – 6.35 (m, 1 H, CH_2=), 5.74 – 5.86 (m, 1 H, CH_2=), 5.42 – 5.62 (m, 1 H, =C*H*-CHOH), 5.05 – 5.25 (m, 2 H =C*H*-CHOSi and CH_2-O), 4.38 – 4.56 (m, 1 H, CH_2-O), 4.05 – 4.38 (m, 3 H, C*H*-O*H* and C*H*-OAc), 3.24 – 3.41 (m, 1 H, *C*H-C_q=), 2.10 – 2.30 (m, 2 H, C*H*$_2$), 2.06 (s, 3 H, C*H*$_3$), 1.81 (s, 3 H, C*H*$_3$), 1.71 (2 s, 6 H, C*H*$_3$).
- **^{13}C NMR** (126 MHz, $CDCl_3$): 170.1 (CO_2-CH_2), 169.9 (CO_2-CH_3), 140.9 (*C*=CH_2), 135.7 ((CH_3)$_2$*C*$_q$=), 134.4 ((CH_3)(CH_2)*C*$_q$=), 127.0 ((CH_3)$_2$*C*$_q$=*C*H), 124.7 ((CH_3)(CH_2)*C*$_q$=*C*H), 121.9 (=CH_2), 71.7 (*C*H-OH), 66.8 (*C*H-OAc), 66.3 (CH_2-O), 47.8 (CH_2), 42.4 (*C*H-C_q=), 25.7 (CH_3), 21.0 (CH_3), 18.2 (CH_3), 17.6 (CH_3).
- **LRMS** (ESI): 186.22 (100), 242.30 (75), 331.17 (30, M+Na); **HRMS** (ESI): M+Na^+ found 331.1518 $C_{17}H_{24}O_5Na$ requires 331.1516.

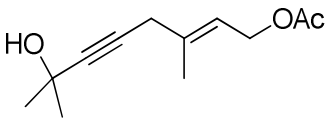
(*E*)-3,7-Dimethyl-1-(4-methylene-5-oxotetrahydrofuran-3-yl)-5-oxoocta-2,6-dienyl acetate (**170**):



Dess-Martin reagent (0.16 mL, 0.3 M in CH_2Cl_2, 0.048 mmol) was added to a solution of alcohol **169** (15 mg, 0.048 mmol) at 0 °C in CH_2Cl_2 (1 mL). The reaction mixture was stirred for 2 h at rt, then quenched with a mixture of sat. aq. $NaHCO_3$ (1 mL) and sat. aq. $Na_2S_2O_3$ (1 mL), and then extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and purified by column chromatography (20 → 40% EtOAc in petrol) to give synthetic acetoxyantecotulide (**170**) (11.2 mg, 75%) as a light yellow oil.

- ***R*$_f$**: 0.4 (30% EtOAc in petrol).
- **IR** (neat): 1767s, 1737s, 1409s, 1232s, 1113m, 1043m.
- **^{1}H NMR** (400 MHz, $CDCl_3$): 6.35 (d, *J* = 2 Hz, CH_2=), 6.01 – 6.07 (m, 1 H, =CH-CO), 5.80 (d, *J* = 2 Hz, 1 H, CH_2=), 5.58 (dd, *J* = 7, 9 Hz, 1 H, =C*H*-CH-OAc), 5.19 (dd, *J* = 1, 9 Hz, 1 H, CH-OAc), 4.36 (dd, *J* = 8, 9 Hz, 1 H, CH_2-O), 4.28 (dd, *J* = 3, 10 Hz, 1 H, CH_2-O), 3.31 – 3.41 (m, 1 H, *C*H-C_q=), 3.10 (s, 2 H, CH_2-CO), 2.15 (s, 3 H, CH_3), 2.06 (s, 3 H, CH_3), 1.91 (s, 3 H, CH_3), 1.81 (m, 3 H, CH_3).
- **^{13}C NMR** (100 MHz, $CDCl_3$): 197.4 (CO), 170.0 (CO_2-CH_2), 169.9 (CO_2-CH_3), 157.2 ((CH_3)$_2$*C*$_q$=), 138.6 (*C*=CH_2), 134.4 ((CH_3)(CH_2)*C*$_q$=), 128.0 ((CH_3)$_2$*C*$_q$=*C*H), 124.8 ((CH_3)(CH_2)*C*$_q$=*C*H), 123.1 (C=*C*H$_2$), 71.4 (*C*H-OAc), 66.9 (*C*H$_2$-O), 54.8 (CH_2), 27.7 (CH_3), 21.0 (CH_3), 20.9 (CH_3), 15.3 (CH_3).
- **LRMS** (ESI): 329.1 (100, M+Na^+), **HRMS** (EI): M+Na^+ found 329.1361 $C_{17}H_{22}O_5Na$ requires 329.1359.

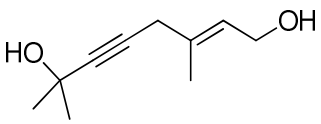
(*E*)-7-Hydroxy-3,7-dimethyloct-2-en-5-ynyl acetate (**177**):



Allylic acetate[81] **175** (0.74 g, 3.57 mmol) was added to a solution of 2-methylbut-3-yn-2-ol (**176**) (600 mg, 7.14 mmol), CuI (34 mg, 0.178 mmol), K_2CO_3 (591 mg, 4.28 mmol) and TBAB (172.6 mg, 0.535 mmol) in DMF (5 mL). The reaction mixture was stirred 4 h at rt, then 4 h at 40 °C. The reaction was then quenched with sat. aq. NH_4Cl (20 mL). The aq. layer was extracted with Et_2O (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography (20% EtOAc in petrol) to give alkyne **177** (505 mg, 67%) as a clear oil.

- ***R*$_f$**: 0.4 (20% EtOAc in petrol).
- **IR** (neat): 3430s, 1740s, 1367s, 1236s, 1025s, 950s
- **^{1}H NMR** (200 MHz, $CDCl_3$): 5.51 – 5.68 (m, 1 H, =CH), 4.58 (d, *J* = 7 Hz, 2 H, CH_2-O), 2.91 (s, 2 H, CH_2), 2.29 (s, 1 H, OH), 2.04 (s, 3 H, CH_3), 1.52 (s, 6 H, CH_3).
- **^{13}C NMR** (126 MHz, $CDCl_3$): 171.1 (CO), 136.8 (C_q=), 119.59 (C_q=*C*H), 88.08 (C_q-C≡), 78.5 (C≡), 65.1 (C_q-OH), 61.1 (CH_2-OH), 31.6 (CH_3), 28.5 (CH_2), 20.9 (CH_3), 16.4 (CH_3).
- **LRMS** (ESI): 132 (100), 282 (60); **HRMS** (FI): M^+ found 210.1255 $C_{12}H_{18}O_3Na$ requires 210.1256.

(*E*)-3,7-Dimethyloct-2-en-5-yne-1,7-diol (**179**):

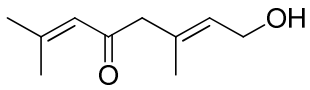


Allylic alcohol[81] **178** (1.14 g, 6.9 mmol) was added to a solution of 2-methylbut-3-yn-2-ol (1.74 g, 20.7 mmol), CuI (65 mg, 0.345 mmol) in Et_3N (7 mL). The reaction mixture was

stirred at 60 °C for 16 h, then concentrated under reduced pressure and purified by column chromatography (40 → 100% EtOAc in petrol) to give alkyne **179** (380 mg, 32%) as a clear oil.

- ***R*$_f$**: 0.3 (50% EtOAc in petrol).
- **IR** (neat): 3346s, 2981w, 2932s, 1673s, 1377m, 1238s, 1165m, 1004m, 949w.
- **^{1}H NMR** (400 MHz, $CDCl_3$): 5.69 (t, *J* = 7 Hz, 1 H, CH=), 4.19 (d, *J* = 7 Hz, 2 H. CH_2-OH), 2.92 (s, 2 H, CH_2), 2.28 (br. s., 1 H, OH), 1.73 (s, 3 H, CH_3), 1.51 (s, 6 H, CH_3).
- **^{13}C NMR** (100 MHz, $CDCl_3$): 134.2 (*C*=CH), 124.7 (C=*C*H), 88.0 (C_q-C≡), 79.0 (C≡), 65.3 (C_q-OH), 59.2 (CH_2-OH), 31.7 (CH_3), 28.6 (CH_3), 16.4 (CH_3).
- **LRMS** (ESI): 191.1 (40, M+Na^+) 375.2 (100), **HRMS** (ESI): M+Na^+ found 191.1041 $C_{10}H_{16}O_2Na$ requires 191.1043.

(*E*)-8-Hydroxy-2,6-dimethylocta-2,6-dien-4-one (**180**):

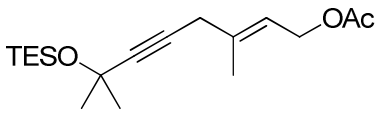


$MoO_2(acac)_2$ (1 mg, 0.023 mmol), $AuCl(PPh_3)$ (1.5 mg, 0.023 mmol) and AgOTf (0.8 mg, 0.023 mmol) were added successively to a solution of alkyne **179** (40 mg, 0.23 mmol) in toluene (1 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 6 h then passed through celite and washed with Et_2O (10 mL). The residue was concentrated under reduced pressure and purified by column chromatography (50% Et_2O in petrol) to give unsaturated ketone **180** (37 mg, 94%) as a light yellow oil.

- ***R*$_f$**: 0.4 (40% EtOAc in petrol).
- **IR** (neat): 3317s, 2913w, 1683s, 1617s, 1444s, 1382m, 1008m.

- **^{1}H NMR** (400 MHz, $CDCl_3$): 6.11 (s, 1 H, CO-CH=), 5.51 (t, *J* = 7 Hz, 1 H, CH=), 4.21 – 4.18 (m., 2 H, C*H*$_2$-OH), 3.10 (s, 2 H, CH_2), 2.15 (s, 3 H, CH_3), 2.00 (br. s., 1 H, OH), 1.88 (s, 3 H, CH_3), 1.68 (s, 3 H, CH_3).
- **^{13}C NMR** (100 MHz, $CDCl_3$): 198.6 (CO), 156.6 (*C*$_q$=CH-CO), 133.4 (C_q=CH), 128.3 (=*C*H-CH_2-OH), 122.9 (=*C*H-CO), 59.2 (CH_2-OH), 54.9 (CH_2-CO), 27.8 (CH_3), 20.8 (CH_3), 16.7 (CH_3).
- **LRMS** (ESI): 191.1 (100, M+Na^+), **HRMS** (ESI): M+Na^+ found 191.1041 $C_{10}H_{16}O_2Na$ requires 191.1043

(*E*)-3,7-Dimethyl-7-(triethylsilyloxy)oct-2-en-5-ynyl acetate (**182**):

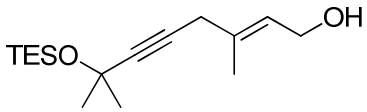


Path A: Triethylsilyl triflate (0.577 mg, 2.55 mmol) was added to a solution of alkyne **177** (488 mg, 2.32 mmol) and pyridine (0.206 mL, 2.55 mmol) in CH_2Cl_2 (5 mL) at 0 °C. The reaction mixture was stirred 30 min at rt, then water (20 mL) was added. The aq. layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography (0 → 10% Et_2O in petrol) to give alkyne **182** (640 mg, 85 %) as a clear oil.

Path B: Allylic acetate[81] **175** (0.74 g, 3.57 mmol) was added to a solution of alkyne **181**[85] (1.41 g mg, 7.14 mmol), CuI (34 mg, 0.178 mmol), K_2CO_3 (591 mg, 4.28 mmol) and TBAB (172.6 mg, 0.535 mmol) in DMF (5 mL). The reaction mixture was stirred 15 h at rt, then quenched with sat. aq. NH_4Cl (20 mL). The aq. layer was extracted with Et_2O (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography (20% EtOAc in petrol) to give alkyne **182** (774 mg, 67%) as a clear oil.

- ***R*$_f$**: 0.8 (10% EtOAc in petrol).
- **IR** (neat): 1747s, 1365s, 1231s, 1160s, 960s.
- **^{1}H NMR** (500 MHz, $CDCl_3$): 5.62 – 5.59 (m, 1 H, CH=), 4.62 (d, *J* = 7 Hz, 2 H, CH_2-O), 2.93 (s, 2 H, CH_2), 2.06 (s, 3 H, CH_3), 1.77 (s, 3 H, CH_3), 1.48 and 1.46 (2 s, 6 H, CH_3), 0.98 (t, *J* = 7 Hz, 9 H, CH_3), 0.67 (q, *J* = 8 Hz, 6 H, $SiCH_2$).
- **^{13}C NMR** (126 MHz, $CDCl_3$): 171.0 (CO), 136.9 (C_q=), 119.7 (=CH), 88.4 (C_q-C≡), 78.9 (C≡), 66.3 (C_q-O), 61.1 (CH_2-O), 33.2 (CH_3), 28.8 (CH_3), 21.0 (CH_3), 16.4 (CH_3), 7.0 (CH_2), 6.0 (CH_2).
- **LRMS** (ESI): 721.3 (100), 347.2 (10, M+Na). **HRMS** (ESI): M+Na^+ found 347.2016 $C_{18}H_{32}O_3SiNa$ requires 347.2013.

(*E*)-3,7-Dimethyl-7-(triethylsilyloxy)oct-2-en-5-yn-1-ol (**183**):

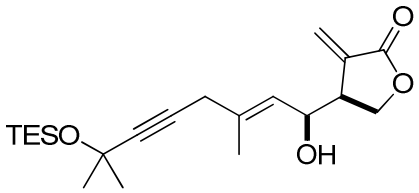


K_2CO_3 (792 mg, 5.7 mmol) was added to a solution of alkyne **182** (324.5 mg, 1.9 mmol) in MeOH (15 mL). The reaction mixture was stirred 1 h at rt, then quenched with sat. aq. NH_4Cl (20 mL). The aq. layer was extracted with Et_2O (3 × 100 mL) and the combined organic extracts dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography (20 → 30% EtOAc in petrol) to give alkyne **182** (504 mg, 93%) as a clear oil.

- ***R*$_f$**: 0.4 (40% EtOAc in petrol).
- **IR** (neat): 3330s, 2955s, 2876s, 1459s, 1243s, 1160s, 1036s.
- **^{1}H NMR** (500 MHz, $CDCl_3$): 5.62 – 5.75 (m, 1 H, CH=), 4.20 (t, *J* = 6 Hz, 2 H, CH_2-O), 2.92 (s, 2 H, CH_2), 1.75 (s, 3 H, CH_3), 1.48 (s, 3 H, CH_3), 0.96 (t, *J* = 7 Hz, 9 H, CH_3), 0.66 (q, *J* = 8 Hz, 6 H, $SiCH_2$).

- **^{13}C NMR** (126 MHz, $CDCl_3$): 134.6 (C_q=), 124.7 (=CH), 118.3(=CH), 88.2 (C_q-C≡), 79.1 (C≡), 66.3 (C_q-O), 59.3 (CH_2-O), 33.3 (CH_3), 28.8 (CH_3), 16.3 (CH_3), 7.0 (CH_2), 6.0 (CH_2).
- **LRMS** (ESI): 281.2 (30, M-H^+), 313.2 (100). **HRMS** (ESI): M+Na^+ found 305.1906 $C_{16}H_{30}O_2SiNa$ requires 305.1907.

(*E*)-4-(1-Hydroxy-3,7-dimethyl-7-(triethylsilyloxy)oct-2-en-5-ynyl)-3-methylenedihydrofuran-2(3*H*)-one (**185**):



major

Dess-Martin reagent (225 mg, 0.53 mmol) was added to a solution of alcohol **183** (150 mg, 0.53 mmol) in CH_2Cl_2 (3 mL) at 0 °C. The reaction mixture was stirred 4 h at 0 °C, then quenched with a mixture of sat. aq. $NaHCO_3$ (2 mL) and sat. aq. $Na_2S_2O_3$ (2 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure to give crude aldehyde **184** (153 mg).

Zinc Method: A solution of the above crude aldehyde **184** in DMF (1 mL) was added to a solution of bromolactone **125** (107 mg, 0.609 mmol) and Zn dust (34 mg, < 10μm, 0.53 mmol) in DMF (2 mL). The reaction mixture was stirred 30 min at rt, then quenched with sat. aq. NH_4Cl (20 mL). The aq. layer was extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography (20 → 40% EtOAc in petrol) to give alkyne **185** (130 mg, 65%, 4:1 dr) as a light yellow oil.

- R_f: 0.5 (40% EtOAc in petrol).

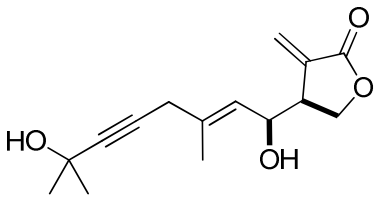
- **IR** (neat): 3445br, 2955w, 2876s, 1756s, 1160m, 1037m.
- **Major: ^{1}H NMR** (500 MHz, $CDCl_3$): 6.34 (d, *J* = 2 Hz, 1 H, $=CH_2$), 5.91 (d, *J* = 2 Hz, 1 H, $=CH_2$), 5.46 – 5.53 (m, 1 H, CH=), 4.40 – 4.48 (m, 1 H, CH_2-O), 4.32 (dd, *J* = 8, 9 Hz, 1 H, CH_2-O), 4.08 – 4.15 (m, 1 H, C*H*-OH), 3.13 – 3.21 (m, 1 H, $=C_q$-C*H*), 2.92 (s, 2 H, CH_2), 1.76 (d, *J* = 1 Hz, 3 H, CH_3),1.47 (2 s, 6 H, CH_3), 0.95 (t, *J* = 7 Hz, 9 H, CH_3), 0.63 (q, *J* = 8 Hz, 6 H, $SiCH_2$).
- **^{13}C NMR** (126 MHz, $CDCl_3$): 170.7 (CO), 137.3 (C=CH_2), 135.1 (C_q=CH), 124.8 (C_q=*C*H), 124.5 (*C*=CH_2), 88.9 (C_q-C≡), 78.5 (C≡), 69.5 (C_q-O), 67.3 (CH-OH), 66.3 (CH_2-O), 44.6 (CH_2), 33.2 (C_q-CH_2), 28.9 (CH_3), 27.3 (CH_3), 17.1 (CH_3), 7.0 (CH_3), 6.3 (CH_2).
- Discernable data for minor diastereoisomer **^{1}H NMR** (500 MHz, $CDCl_3$): 6.32 (d, *J* = 2 Hz, 1 H, $=CH_2$), 5.71 (d, *J* = 2 Hz, 1 H, $=CH_2$), 1.72 (d, *J* = 1 Hz, 3 H, CH_3)
- Discernable data for minor diastereoisomer **^{13}C NMR** (126 MHz, CDC_{l3}): 170.8 (CO), 137.2 (C=CH_2), 134.6 (*Cq*=CH), 124.9 (Cq=*C*H), 124.6 (*C*=CH_2), 88.9 (C_q-C≡), 78.5 (C≡), 69.4 (*Cq*-O), 67.8 (CH-OH), 66.3 (C_{H2}-O), 44.5 (C_{H2}), 33.1 ($_{Cq}$-C_{H2}), 28.8 (C_{H3}), 27.3 (C_{H3}), 17.1 (C_{H3}), 7.0 (C_{H3}), 6.3 (C_{H2}).
- **LRMS** (ESI): 287.14 (100), 379.25 (30, M+H^+), 396.27 (80); **HRMS** (ESI): M+Na^+ found 401.2120 $C_{21}H_{34}O_4SiNa$ requires 401.2124.

Chromium Method: A flame-dried Schlenk tube containing $CrCl_3$ (10 mg, 0.07 mmol, 99% Aldrich) and Mn powder (87 mg, 1.59 mmol, 150µm) was charged with dry THF (3 mL), dry MeCN (0.3 mL) and (*i*-Pr)$_2$EtN (0.027 mL, 0.153 mmol). The resulting suspension was vigorously stirred under an atmosphere of argon for 1 h. This resulted in the disappearance of the characteristic purple color of the chromium(III) salt and the formation of a white/grey suspension with a pale green supernatant. Bromolactone **125** (141 mg, 0.8 mmol) was added

and the reaction mixture stirred for 1 h at rt. The allylation was then initiated by the addition of aldehyde **184** (0.53 mmol) and TMSCl (freshly distilled and stored over polyvinylpyridine) (0.195 mL, 1.59 mmol) and the reaction mixture stirred under an atmosphere of argon at room temperature for 4 h. The resulting green/ brown suspension was quenched with sat. aq $NaHCO_3$ (1 mL) and passed through a plug of celite. The filtrate was concentrated, then dissolved in THF (1 mL), 1 drop of 1 M HCl was added, and the resulting solution stirred for 30 min at 0 °C. The reaction was then diluted with water (20 mL), the aq layer extracted with EtOAc (3 × 20 mL), the combined organic extracts dried (Na_2SO_4), concentrated under reduced pressure and purified by column chromatography (10 → 40% EtOAc in petrol) to give alkyne **185** (124 mg, 62%, 97:3 dr) as a light yellow oil.

- R_f: 0.5 (40% EtOAc in petrol).
- **IR** (neat): 3445br, 2955s, 2876s, 1756s, 1160s, 1037s.
- **^{1}H NMR** (500 MHz, $CDCl_3$): 6.36 (d, *J* = 2 Hz, 1 H, $=CH_2$), 5.92 (d, *J* = 1.5 Hz, 1 H, $=CH_2$), 5.50 (dd, *J* = 2, 9 Hz, 1 H, CH=), 4.45 (dd, *J* = 8, 9 Hz, 1 H, CH_2-O), 4.32 (dd, *J* = 8, 9 Hz, 1 H, CH_2-O), 4.13 (dd, *J* = 4, 9 Hz, 1 H, C*H*-OH), 3.19 (dddd, *J* = 2, 4, 6, 8 Hz, 1 H, $=C_q$-C*H*), 2.93 (s, 2 H, CH_2), 1.77 (d, *J* = 1.3 Hz, 3 H, CH_3), 1.48 (2s, 6 H, CH_3), 0.96 (t, *J* = 8 Hz, 9 H, CH_3), 0.64 (q, *J* = 8 Hz, 6 H, Si-CH_2).
- **^{13}C NMR** (126 MHz, $CDCl_3$): 170.6 (CO), 137.4 (C=CH_2), 135.1 (C_q=CH), 124.8 (C_q=*C*H), 124.4 (*C*=CH_2), 88.9 (C_q-C≡), 78.4 (C≡), 69.5 (C_q-O), 67.2 (CH-OH), 66.3 (CH_2-O), 44.6 (CH_2), 33.2 (CH_3), 28.9 (C_q-CH_2), 17.1(CH_3), 7.0 (CH_3), 6.0 (CH_2).
- **LRMS** (ESI): 287.14 (100), 379.25 (30, M+H^+), 396.27 (80); **HRMS** (ESI): M+Na^+ found 401.2120 $C_{21}H_{34}O_4SiNa$ requires 401.2124.

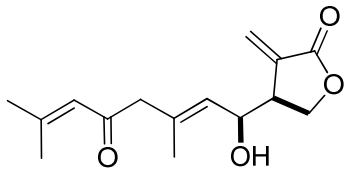
4-(E)-1,7-Dihydroxy-3,7-dimethyloct-2-en-5-yn-1-yl)-3-methylenedihydrofuran-2(3*H*)-one (**172**):



TBAF (0.10 mL, 1 M in THF, 0.10 mmol) was added to a solution of lactone **185** (37 mg, 0.09 mmol) in THF (1.00 mL). The reaction mixture was stirred at rt for 15 h, then quenched with sat. aq. NH_4Cl (1 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure, and purified by column chromatography (60 → 70% EtOAc in petrol) to give alcohol **172** (19.3 mg, 73%) as a light yellow oil.

- ***R*$_f$**: 0.4 (70% EtOAc in petrol).
- **IR** (neat): 3475br, 1769s, 1741s, 1234s, 1021w.
- **^{1}H NMR** (500 MHz, $CDCl_3$): 6.33 (d, *J* = 2 Hz, 1 H, $=CH_2$), 5.77 (d, *J* = 2 Hz, 1 H, $=CH_2$), 5.52 (dd, *J* = 2, 9 Hz, 1 H, CH=), 4.35 (dd, *J* = 3.9, 9.8 Hz, 1 H, C*H*-OH), 3.28 - 3.14 (m, 1 H, , $=C_q$-C*H*), 2.92 (s, 2 H, CH_2), 2.51 (br. s., 1 H, OH), 2.19 (br. s., 1 H, OH), 1.73 (s, 3 H), 1.51 (2s, 6 H, CH_3).
- **^{13}C NMR** (126 MHz, $CDCl_3$): 171.1 (CO), 137.1 ($C=CH_2$), 134.6 (C_q=CH), 124.8 (C_q=*C*H), 124.3 (*C*=CH_2), 88.8 (C_q-C≡), 78.2 (C≡), 69.5 (C_q-O), 67.9 (CH-OH), 65.2 (CH_2-O), 44.6 (CH_2), 31.6 (CH_3), 28.5 (C_q-CH_2), 17.3(CH_3).
- **LRMS (ESI):** 287.1 (100, M+Na$^+$); **HRMS** (ESI): M+Na$^+$ found 287.1253 $C_{15}H_{20}O_4Na$ requires 287.1254.

(*E*)-4-(1-Hydroxy-3,7-dimethyl-5-oxoocta-2,6-dienyl)-3-methylenedihydrofuran-2(3*H*)-one (**171**):



major

From Zinc Chemistry: $MoO_2(acac)_2$ (0.6 mg, 0.018 mmol), $AuCl(PPh_3)$ (0.87 mg, 0.018 mmol) and AgOTf (0.45 mg, 0.018 mmol) were succesively added to a solution of alkyne **185** (47 mg, 0.178 mmol) in toluene (1 mL, reagent grade) at 0 °C. The reaction mixture was stirred 3 h at 0 °C, then 3 h at rt. The reaction mixture was passed then through celite and washed with Et_2O (10 mL). The filtrate was concentrated under reduced pressure and purified though a small plug of silica (40 → 50% EtOAc in petrol) to give synthetic *syn*-hydroxyanthecotulide **171** (43 mg, 91%, 7:3 dr) as a light yellow oil.

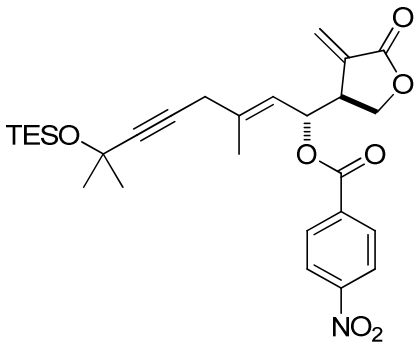
- ***R*$_f$:** 0.4 (50% EtOAc in hexanes).
- **IR** (neat): 3430br, 2915s, 1726s, 1615s, 1174s, 1016s.
- **^{1}H NMR** (500 MHz, $CDCl_3$): 6.33 (d, *J* = 2 Hz, 1 H, $=CH_2$), 6.06 – 6.08 (m, 1 H, =C*H*-CHOH), 5.89 (d, *J* = 1 Hz, 1 H, $=CH_2$), 5.22 – 5.33 (m, 1 H, =CH-CO), 4.44 – 4.54 (m, 1 H, CH-OH), 4.37 – 4.44 (m, 1 H, CH_2-O), 4.28 – 4.37 (m, 1 H, CH_2-O), 4.18 – 4.28 (m, 1 H, OH), 3.17 – 3.28 (m, 1 H, $=C_q$-C*H*), 3.08 – 3.17 (m, 2 H, CH_2), 2.16 (s, 3 H, CH_3), 1.91 (s, 3 H, CH_3), 1.70 (s, 3 H, CH_3).
- Discernable data for minor diastereoisomer**:** 5.82 (d, *J* = 1 Hz, 1 H, $=CH_2$), 4.44 – 4.54 (m, 1 H, CH-OH), 1.72 (s, 3 H, CH_3).
- **^{13}C NMR** (126 MHz, $CDCl_3$): 197.9 (CO), 170.6, (CO_2), 157.4 (($(CH_3)_2C_q$=), 136.1 (Cq=CH_2), 135.2 (($(CH_3)(CH_2)C_q$=C*H*), 127.7 (($(CH_3)_2C_q$=C*H*), 69.4 (CH-OH), 67.1 (CH_2-O), 54.6 (CH_2), 27.7 (CH_3), 20.9 (CH_3), 17.5(CH_3).

- Discernable data for minor diastereoisomer 197.8 (CO), 170.8 (CO_2), 157.3 ((CH_3)$_2$$C_q$=), 136.0 (Cq=$CH_2$), 134.3 (($CH_3$)($CH_2$)$C_q$=C*H*), 128.3 (($CH_3$)$_2$$C_q$=C*H*), 69.4 (CH-OH), 54.6 (CH_2), 27.7 (CH_3), 20.9 (CH_3), 17.6 (CH_3).
- **LRMS (ESI):** 242.3 (100), 287.1 (30, M+Na^+), 338.25 (80); **HRMS** (ESI): M+Na^+ found 287.1254 $C_{15}H_{20}O_4Na$ requires 287.1254.

From Chromium Chemistry: Following the procedure as above but with alkyne **185** (30 mg, 0.113 mmol) give synthetic *syn*-hydroxyanthecotulide **172** (27 mg, 90%) as a light yellow oil.

- ***R*$_f$**: 0.4 (50% EtOAc in hexanes).
- **IR** (neat): 3430br, 2915s, 1726s, 1615s, 1174s, 1016s.
- **^{1}H NMR** (500 MHz, $CDCl_3$): 6.36 (d, *J* = 2 Hz, 1 H, =CH_2), 6.06 (s, 1 H, =C*H*-CHOH), 5.89 (d, *J* = 1 Hz, 1 H, =CH_2), 5.27 (br d, *J* = 9 Hz, 1 H, =CH-CO), 4.48 (t, *J* = 8 Hz, 1 H, CH-OH), 4.33 (dd, *J* = 8, 9 Hz, 1 H, CH_2-O), 4.23 (dd, *J* = 10, 4 Hz, 1 H, CH_2-O), 3.28 – 3.19 (m, 1 H, =C_q-C*H*), 3.14 (d, *J* = 15 Hz, 1 H, CH_2), 3.09 (d, *J* = 15 Hz, 1 H, CH_2), 2.15 (s, 3 H, CH_3), 1.91 (s, 3 H, CH_3), 1.70 (s, 3 H, CH_3).
- **^{13}C NMR** (126 MHz, $CDCl_3$): 197.9 (CO), 170.6, (CO_2), 157.3 ((CH_3)$_2$$C_q$=), 136.2 (Cq=$CH_2$), 135.2 (($CH_3$)($CH_2$)$C_q$=C*H*), 127.7 (($CH_3$)$_2$$C_q$=C*H*), 69.5 (CH-OH), 67.1 (CH_2-O), 54.7 (CH_2), 27.7 (CH_3), 20.9 (CH_3), 17.5 (CH_3).
- **LRMS (ESI):** 242.3 (100), 287.1 (30, M+Na^+), 338.25 (80); **HRMS** (ESI): M+Na^+ found 287.1254 $C_{15}H_{20}O_4Na$ requires 287.1254.

3,7-Dimethyl-1-4-methylene-5-oxotetrahydrofuran-3-yl)-7(triethylsilyloxy) oct-2-en-5-ynyl 4-nitrobenzoate (**186**):



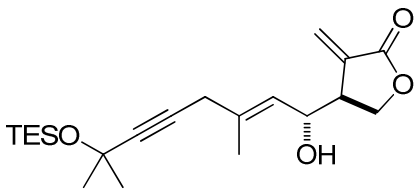
DEAD (361.9 mg, 2.08 mmol) was added dropwise over 5 min to a solution of lactone **185** (400 mg, 1.04 mmol), PPh_3 (544.9 mg, 2.08 mmol) and *p*-nitrobenzoic acid (347 mg, 2.08 mmol) in THF (15 mL) at −78 °C. The reaction mixture was stirred 1 h at −78 °C, then 2 h at 0 °C, and finally 14 h at rt. The reaction was then quenched with sat. aq. NH_4Cl (10 mL) and the aq. layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography (10% → 30% EtOAc in petrol) to give ester **186** (340 mg, 62%) as fine white crystals.

- ***R*$_f$**: 0.4 (40% EtOAc in petrol).
- **mp**: 118–121 °C.
- **IR** (neat): 1747s, 1556s, 1271m, 1148s.
- **^{1}H NMR** (500 MHz, $CDCl_3$): 8.25 – 8.39 (m, 2 H, C-H_{Ar}), 8.07 – 8.17 (m, 2 H, C-H_{Ar}), 6.42 (d, *J* = 2 Hz, 1 H, =CH_2), 5.90 (dd, *J* = 6, 9 Hz, 1 H, =CH), 5.84 (d, *J* = 2 Hz, 1 H, =CH_2), 5.58 (dd, *J* = 2, 9 Hz, 1 H,C*H*-O), 4.52 (dd, *J* = 8, 9 Hz, 1 H, CH_2-O), 4.37 (dd, *J* = 4, 9 Hz, 1 H, CH_2-O), 3.33 – 3.54 (m, 1 H, =C_q-CH), 2.97 (s, 2 H, CH_2), 1.91 (s, 3 H, CH_3), 1.47 (2 s, 6 H, CH_3), 0.90 (t, J = 7 Hz, 9 H, CH_3), 0.61 (q, *J* = 8 Hz, 6 H, CH_2).
- **^{13}C NMR** (126 MHz, $CDCl_3$): 169.8 (CO_2-CH_2), 163.6 (CO_2-C_{Ar}), 150.8 (C_{Ar}), 140.6 (C_q=CH_2), 135.0 (C_{Ar}), 133.7 (C_{Ar}), 130.7 (*C*$_q$=CH-), 125.3 (C_{Ar}), 123.7 (C_q=*C*H),

119.6 (C_q=CH_2), 89.4 (C≡), 78.0 (C≡), 73.2 (C*H*-O), 66.9 (C_q-O), 66.3 (CH_2-O), 42.7 (=C_q-CH), 33.2 (CH_3), 28.9 (CH_3), 23.8 (CH_3), 17.6 (CH_3), 7.0 (CH_2).

- **LRMS** (ESI): 431.0 (100, M-TES), 384.9 (100); **HRMS** (ESI): M found 527.9134 $C_{28}H_{37}NO_7Si$ requires 527.2339.

4-(*E*)-1-Hydroxy-3,7-dimethyl-7-((triethylsilyl)oxy)oct-2-en-5-yn-1-yl)-3-methylenedihydrofuran-2(3H)-one (**187**):

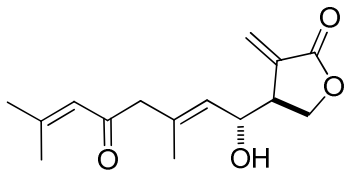


Na_2CO_3 (40 mg, 0.38 mmol) was added to a solution of lactone **186** (180 mg, 0.34 mmol) with one drop of water in THF (5 mL) at 0 °C. The reaction mixture was stirred at 0 °C and carefully monitored by TLC until reaction was complete (~ 1 – 2 h). The reaction mixture was quenched with sat. aq. NH_4Cl (10 mL). The aq. layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography (30% → 50% EtOAc in petrol) to give the lactone **187** (90 mg, 70%) as a clear oil.

- ***R*$_f$**: 0.5 (40% EtOAc in petrol).
- **IR** (neat): 3443br, 2950s, 1746s, 1162s, 1042s.
- **^{1}H NMR** (500 MHz, $CDCl_3$): 6.34 (d, *J* = 2 Hz, 1 H, =CH_2), 5.73 (d, *J* = 2 Hz, 1 H, =CH_2), 5.53 (dd, *J* = 1, 9 Hz, 1 H, CH=), 4.52 – 4.40 (m, 3 H, CH_2-O and C*H*-OH), 3.24 – 3.08 (m, 1 H, =C_q-C*H*), 2.95 (s, 2 H, CH_2), 1.74 (s, 3 H, CH_3), 1.49 (s, 6 H, CH_3), 0.97 (d, *J* = 7 Hz, 9 H, CH_3), 0.66 (q, *J* = 8 Hz, 6 H, Si-CH_2).

- **^{13}C NMR** (126 MHz, $CDCl_3$): 170.6 (CO), 137.5 (C=CH_2), 134.6 (C_q=CH), 124.9 (C_q=*C*H), 124.4 (*C*=CH_2), 89.0 (C≡), 78.4 (C≡), 69.6 (C_q-O), 67.7 (CH-OH), 66.3 (CH_2-O), 44.5 (CH_2), 33.3 (CH_3), 28.9 (C_q-CH_2), 17.2(CH_3), 7.0 (CH_3), 6.1 (CH_2).
- **LRMS** (ESI): 379.23 (50, M+H), 401.21 (100, M+Na^+); **HRMS** (ESI): M+Na^+ found 401.2120 $C_{21}H_{34}O_4SiNa$ requires 401.2124.

(*E*)-4-(1-Hydroxy-3,7-dimethyl-5-oxoocta-2,6-dienyl)-3-methylenedihydrofuran-2(3*H*)-one (**2**):

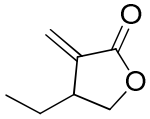


$MoO_2(acac)_2$ (0.6 mg, 0.0178 mmol), $AuCl(PPh_3)$ (0.87 mg, 0.0178 mmol) and AgOTf (0.45 mg, 0.0178 mmol) were succesively added to a solution of alkyne **187** (47 mg, 0.178 mmol) in toluene (1 mL, reagent grade) at 0 °C. The reaction mixture was stirred 3 h at 0 °C, then 3 h at rt. The reaction mixture was passed through celite and washed with Et_2O (5 mL). Organic layer was concentrated under reduced pressure and purified though a small plug of silica (40 → 50% EtOAc in petrol) to give synthetic *anti*-hydroxyanthecotulide (**2**) (43 mg, 91%) as a light yellow oil.

- ***R*$_f$**: 0.4 (50% EtOAc in hexanes).
- **IR** (neat): 3430br, 2915s, 1726s, 1615s, 1174s, 1016s.
- **^{1}H NMR** (500 MHz, $CDCl_3$): 6.33 (d, *J* = 2 Hz, 1 H, =CH_2), 6.08 (s, 1 H, =C*H*-CHOH), 5.82 (d, *J* = 2 Hz, 1 H, =CH_2), 5.27 (br d, *J* = 9 Hz, 1 H, =CH-CO), 4.45 (t, *J* = 8 Hz, 1 H, CH-OH), 4.37 (dd, *J* = 4, 7 Hz, 2 H, CH_2-O), 3.21 – 3.17 (m, 1 H, =C_q-C*H*), 3.18 (d, *J* = 16 Hz, 1 H, CH_2), 3.11 (d, *J* = 16 Hz, 1 H, CH_2), 2.14 (s, 3 H, CH_3), 1.91 (s, 3 H, CH_3), 1.68 (s, 3 H, CH_3).

- **^{13}C NMR** (126 MHz, $CDCl_3$): 197.8 (CO), 170.8 (CO_2), 157.4 (($CH_3)_2C_q$=), 136.3 (Cq=CH_2), 134.4 ((CH_3)(CH_2)C_q=C*H*), 128.2 (($CH_3)_2C_q$=C*H*), 69.4 (CH-OH), 67.8 (CH_2-O), 54.6 (CH_2), 27.8 (CH_3), 20.9 (CH_3), 17.7 (CH_3).
- **LRMS (ESI):** 242.3 (100), 287.1 (30, M+Na^+), 338.25 (80); **HRMS** (ESI): M+Na^+ found 287.1254 $C_{15}H_{20}O_4Na$ requires 287.1254.

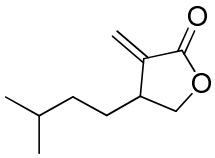
4-Ethyl-3-methylenedihydrofuran-2(3*H*)-one (**188**):



Following procedure C: using diethylzinc (0.80 mL, 0.5 M in pentane, 0.39 mmol), the above lactone **188** (22 mg, 63%) was obtained after column chromatography (20% → 33% EtOAc in petrol) as a clear oil.

- ***R**$_f$*: 0.3 (20% EtOAc in petrol).
- **^{1}H NMR** (200 MHz, CDCl3): 6.29 (d, *J* = 2 Hz, 1 H), 5.61 (d, *J* = 2 Hz, 1 H), 4.50 – 4.44 (m, 1 H), 4.00 (dd, *J* = 9, 6 Hz, 1 H), 3.05 – 2.98 (m, 1 H), 1.80 – 1.68 (m, 2 H), 1.02 – 0.94 (m, 3 H); All other data as previously reported.[150]

4-Isopentyl-3-methylenedihydrofuran-2(3*H*)-one (**189):**

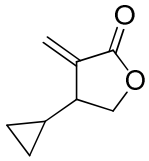


Following procedure C: using isopentylzinc bromide (0.80 mL, 0.5 M in pentane, 0.39 mmol), the above lactone **189** (34 mg, 74%) was obtained after column chromatography (20% → 33% EtOAc in petrol) as a clear oil.

- ***R**$_f$*: 0.4 (20% EtOAc in petrol).

- **IR** (neat): 1762s, 1514s, 1251m, 1159m.
- **^{1}H NMR** (500 MHz, $CDCl_3$): 6.20 (d, *J* = 2 Hz, 1 H, $=CH_2$), 5.54 (d, *J* = 2 Hz, 1 H, $=CH_2$), 4.39 (t, *J* = 9 Hz, 1 H, O-CH_2), 3.91 (dd, *J* = 9, 6 Hz, 1 H, , O-CH_2), 2.97 – 2.94 (m, 1 H, $=C_q$-C*H*), 1.79 – 1.56 (m, 2 H, CH_2), 1.56 – 1.34 (m, 2 H, CH_2), 1.26 – 1.04 (m, 1 H, CH), 0.84 (s, 3 H, CH_3), 0.82 (s, 3 H, CH_3).
- **^{13}C NMR** (126 MHz, $CDCl_3$):169.9 (CO), 137.5(*C*=CH_2), 120.8 (C=*C*H_2), 70.2 (O-CH_2), 37.9 (=C_q-*C*H), 34.4 (CH), 30.6 (CH_2), 27.0 (CH), 21.5 (CH_2), 21.4 (CH_3).
- **LRMS** (ESI): 191.11 (40, M+Na), 242.29 (100); **HRMS** (ESI): M+Na^+ found 191.1043 $C_{10}H_{16}O_2Na$ requires 191.1043.

4-Cyclopropyl-3-methylenedihydrofuran-2(3*H*)-one (**190**):

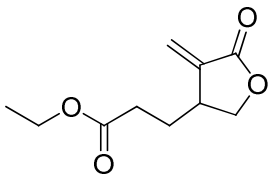


Following procedure C: using cyclopropylzinc bromide (0.80 mL, 0.5 M in pentane, 0.39 mmol), the above lactone **190** (27 mg, 72%) was obtained after column chromatography (20% → 33% EtOAc in petrol) as a clear oil.

- ***R*$_f$**: 0.35 (20% EtOAc in petrol).
- **IR** (neat): 1764s, 1253s, 1112s, 1020s.
- **^{1}H NMR** (500 MHz, $CDCl_3$): 6.29 (d, *J* = 2 Hz, 1 H, $=CH_2$), 5.81 (d, *J* = 2 Hz, 1 H, $=CH_2$), 4.48 (t, *J* = 9 Hz, 1 H, O-CH_2), 4.09 (dd, *J* = 9, 6 Hz, 1 H, O-CH_2), 2.57 – 2.26 (m, 1 H, $=C_q$-C*H*), 0.74 – 0.60 (m, 1 H, CH), 0.60 – 0.44 (m, 1 H, CH_2), 0.37 – 0.33 (m, 2 H, CH_2), 0.25 – 0.20 (m, 1 H, CH_2).
- **^{13}C NMR** (126 MHz, $CDCl_3$): 170.9 (CO), 138.1 (*C*=CH_2), 122.3 (C=*C*H_2), 71.0 (O-CH_2), 43.6 (=C_q-*C*H), 14.0 (CH), 3.0 (CH_2), 1.7 (CH_2).

- **LRMS** (ESI): 161.07 (100, M+Na); **HRMS** (ESI): M+Na^+ found 161.0573 $C_8H_{10}O_2Na$ requires 161.0572.

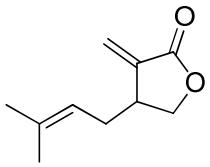
Ethyl 3-(4-methylene-5-oxotetrahydrofuran-3-yl)propanoate (**191**):



Following procedure C: using 3-ethoxy-3-oxopropyl)zinc bromide (0.80 mL, 0.5 M in pentane, 0.39 mmol), the above lactone **191** (46 mg, 83%) was obtained after column chromatography (33% → 40% EtOAc in petrol) as a clear oil.

- ***R_f***: 0.4 (40% EtOAc in petrol).
- **IR** (neat): 1731s, 1663s, 1252m, 1159w.
- **^{1}H NMR** (400 MHz, $CDCl_3$): 6.33 (d, *J* = 2 Hz, 1 H, =CH_2), 5.67 (d, *J* = 2 Hz, 1 H, =CH_2), 4.47 (t, *J* = 9 Hz, 1 H, O-CH_2), 4.16 (q, *J* = 7 Hz, 2 H, CH_2-OCO), 4.01 (dd, *J* = 6, 9 Hz, 1 H, O-CH_2), 3.16 – 3.11 (m, 1 H, =C_q-C*H*), 2.39 (t, *J* = 7 Hz, 2 H, CH_2-CO), 2.07 – 1.97 (m, 1 H, CH_2), 1.96 – 1.79 (m, 1 H, CH_2), 1.28 (t, *J* = 7 Hz, 3 H, CH_3).
- **^{13}C NMR** (126 MHz, $CDCl_3$): 185.5 (COEt), 182.4 ($CO_{lactone}$), 137.6 (*C*=CH_2), 122.7 (C=*C*H_2), 70.7 (O-CH_2), 60.8 (O-CH_2-CH_3), 38.0 (=C_q-*C*H), 30.8 (CH_2), 28.6 (CH_2), 14.2 (CH_3).
- **LRMS** (ESI): 221.09 (30, M+Na), 242.28 (100); **HRMS** (ESI): M+Na^+ found 221.0783 $C_{10}H_{14}O_4Na$ requires 221.0784.

4-(3-Methylbut-2-en-1-yl)-3-methylenedihydrofuran-2(3*H*)-one (**192**):

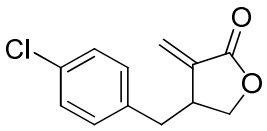


TMSCl (one drop) and 1,2-dibromoethane (one drop) were added to a solution of Zn dust (198 mg, 3.2 mmol) in THF (1 mL). The solution was heated in a sealed tube for 30 s, cooled to 0 °C, then 1-bromo-3-methylbut-2-ene (0.405 mL, 2.7 mmol) was added and stirred for 2 h at 0 °C. Without further purification, this allylzinc bromide was added dropwise over 5 min to a stirred solution of lactone **125** (306 mg, 1.8 mmol), TBAB (58 mg, 0.18 mmol) and CuCN (32 mg, 0.36 mmol) in THF (3 mL) at -78 °C. The reaction mixture was stirred for 30 min at -78 °C, then slowly warmed to –20 °C and stirred for 15 min. The reaction mixture was then quenched with sat. aq. NH_4Cl (2 mL). The aq. layer was extracted with Et_2O (3 × 5 mL) and the combined organic extracts was dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography (20% → 33% petrol/EtOAc) to give lactone X (209 mg, 71%) as a clear oil.

- ***R*$_f$**: 0.3 (30% EtOAc in petrol).
- **IR** (neat): 2972m, 1765s, 1268m, 1114.7w.
- **^{1}H NMR** (400 MHz, $CDCl_3$): 6.24 (d, *J* = 2 Hz, 1 H, $=CH_2$), 5.62 (d, *J* = 2 Hz, 1 H, $=CH_2$), 5.23 – 4.73 (m, 1 H, =CH), 4.40 (dd, *J* = 9, 8 Hz, 1 H, O-CH_2), 3.96 (dd, *J* = 9, 6 Hz, 1 H, O-CH_2), 3.15 – 3.01 (m, 1 H, $=C_q$-C*H*), 2.59 – 2.02 (m, 2 H, CH_2), 1.71 (s, 3 H, CH_3), 1.61 (s, 3 H, CH_3).
- **^{13}C NMR** (126 MHz, $CDCl_3$): 170.9 (CO), 138.1 (*C*=CH_2), 135.4 (*C*$_q$=CH), 122.0 (C=*C*H_2), 119.3 (C_q=*C*H)**,** 70.6 (O-CH_2), 38.9 (=C_q-*C*H), 32.1 (CH_2), 25.8 (CH_3), 18.0 (CH_3).

- **LRMS** (ESI): 167.12 (60, M+H^+); 205.10 (100); **HRMS** (ESI): M+Na^+ found 189.0891 $C_{10}H_{14}O_2Na$ requires 189.0886.

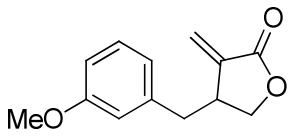
4-(4-Chlorobenzyl)-3-methylenedihydrofuran-2(3*H*)-one (**193**):



Following procedure C: using 4-chlorobenzyl)zinc bromide (0.80 mL, 0.5 M in pentane, 0.39 mmol), the above lactone **193** (49.5 mg, 66%) was obtained after column chromatography (20% → 33% EtOAc in petrol) as a clear oil.

- R_f: 0.3 (40% EtOAc in petrol).
- **IR** (neat): 1763s, 1492s, 1267m, 1115w, 1015w.
- **^{1}H NMR** (400 MHz, $CDCl_3$): 7.21 – 7.08 (m, 2 H, C-H_{Ar}), 7.08 – 6.97 (m, 2 H, C-H_{Ar}), 6.27 (d, *J* = 2 Hz, 1 H, =CH_2), 5.41 (d, *J* = 2 Hz, 1 H, =CH_2), 4.35 (dd, *J* = 9, 8 Hz, 1 H, O-CH_2), 4.06 (dd, *J* = 9, 6 Hz, 1 H, O-CH_2), 3.45 – 3.28 (m, 1 H, =C_q-C*H*), 2.94 (dd, *J* = 14, 7 Hz, 1 H, CH_2), 2.81 (dd, *J* = 14, 9 Hz, 1 H, CH_2).
- **^{13}C NMR** (126 MHz, $CDCl_3$): 170.5 (CO), 163.0 (C_{Ar}), 160.6 (C_{Ar}), 137.4 (*C*=CH_2), 133.1 (C_{Ar}), 130.3 (C_{Ar}), 122.8 (C=*C*H_2), 115.7 (C_{Ar}), 115.5 (C_{Ar}), 70.4 (O-CH_2), 40.2 (CH_2), 39.1 (=C_q-*C*H).
- **LRMS** (ESI): 223.04 (100, M+H); **HRMS** (ESI): M+Na^+ found 222.0449 $C_{12}H_{11}O_2Cl$ requires 222.0448.

4-(3-Methoxybenzyl)-3-methylenedihydrofuran-2(3*H*)-one (**194**):

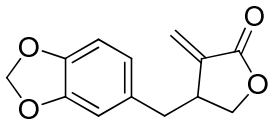


TMSCl (one drop) and 1,2-dibromoethane (one drop) were added to a solution of Zn dust (131 mg, 2 mmol) in THF (1 mL). The solution was heated in a sealed tube for 30 s, cooled to 0 °C, then 3-methoxybenzyl chloride (0.218 mL, 1.5 mmol) was added and stirred for 2 h at 0 °C. Without further purification, this benzylzinc bromide was added dropwise over 5 min to a stirred solution of lactone **125** (177 mg, 1 mmol), TBAB (31 mg, 0.1 mmol) and CuCN (17.8 mg, 0.2 mmol) in THF (3 mL) at -78 °C. The reaction mixture was stirred for 30 min at -78 °C, then slowly warmed to –20 °C and stirred for 15 min. The reaction mixture was then quenched with sat. aq. NH_4Cl (2 mL). The aq. layer was extracted with Et_2O (3 × 5 mL) and the combined organic extracts was dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography (20% → 33% petrol/EtOAc) to give lactone **194** (141 mg, 65%) as a clear oil.

- ***R*$_f$**: 0.3 (30% EtOAc in petrol).
- **IR** (neat): 1763s, 1610s, 1248m, 1162w.
- **^{1}H NMR** (400 MHz, $CDCl_3$): 7.25 (t, *J* = 8 Hz, 1 H, C-H_{Ar}), 6.84 – 6.75 (m, 2 H, C-H_{Ar}), 6.75 – 6.67 (m, 1 H, C-H_{Ar}), 6.28 (d, *J* = 2 Hz, 1 H, =CH_2), 5.47 (d, *J* = 2 Hz, 1 H, =CH_2), 4.35 (dd, *J* = 8, 9 Hz, 1 H, O-CH_2), 4.07 (dd, *J* = 5, 9 Hz, 1 H, O-CH_2), 3.81 (s, 3 H, CH_3), 3.42 – 3.27 (m, 1 H, =C_q-C*H*), 2.96 (dd, *J* = 7, 14 Hz, 1 H, CH_2), 2.78 (dd, *J* = 9, 14 Hz, 1 H, CH_2).
- **^{13}C NMR** (126 MHz, $CDCl_3$): 170.6 (CO), 159.8 (C_{Ar}), 139.0 (C_{Ar}), 137.6 (*C*=CH_2), 129.8 (C_{Ar}), 122.7 (C=*C*H_2), 121.2 (C_{Ar}), 114.8 (C_{Ar}), 112.0 (C_{Ar}), 70.6 (O-CH_2), 55.2 (CH_3), 40.0 (CH_2), 39.9 (=C_q-*C*H).

- **LRMS** (ESI): 219.11 (100, $M+H^+$); **HRMS** (ESI): $M+Na^+$ found 241.0842 $C_{13}H_{14}O_3Na$ requires 241.0841

4-(Benzo[d][1,3]dioxol-5-ylmethyl)-3-methylenedihydrofuran-2(3*H*)-one (**195**):

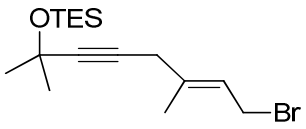


TMSCl (one drop) and 1,2-dibromoethane (one drop) were added to a solution of Zn dust (131 mg, 2 mmol) in THF (1 mL). The solution was heated in a sealed tube for 30 s, cooled to 0 °C, then (chloromethyl)benzo[*d*][1,3]dioxole[151] (255.9 mg, 1.5 mmol) was added and stirred for 2 h at 0 °C. Without further purification, this benzylzinc bromide was added dropwise over 5 min to a stirred solution of lactone **125** (177 mg, 1 mmol), TBAB (31 mg, 0.1 mmol) and CuCN (17.8 mg, 0.2 mmol) in THF (3 mL) at -78 °C. The reaction mixture was stirred for 30 min at -78 °C, then slowly warmed to –20 °C and stirred for 15 min. The reaction mixture was then quenched with sat. aq. NH_4Cl (2 mL). The aq. layer was extracted with Et_2O (3 × 5 mL) and the combined organic extracts was dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography (20% → 33% petrol/EtOAc) to give lactone **195** (167 mg, 72%) as a clear oil.

- ***R*$_f$**: 0.35 (40% EtOAc in petrol).
- **IR** (neat): 1760s, 1612s, 1514s, 1250m.
- **^{1}H NMR** (400 MHz, $CDCl_3$): 6.76 (d, *J* = 8 Hz, 1 H, C-H_{Ar}), 6.67 (d, *J* = 2 Hz, 1 H, C-H_{Ar}), 6.62 (dd, *J* = 2, 8 Hz, 1 H, C-H_{Ar}), 6.28 (d, *J* = 2 Hz, 1 H, =CH_2), 5.96 (s, 2 H, O-CH_2-O), 5.46 (d, *J* = 2 Hz, 1 H, =CH_2), 4.35 (dd, *J* = 7, 9 Hz, 1 H, O-CH_2), 4.06 (dd, *J* = 5, 9 Hz, 1 H, O-CH_2), 3.49 – 3.33 (m, 1 H, =C_q-C*H*), 2.89 (dd, *J* = 14, 7 Hz, 1 H, CH_2), 2.73 (dd, *J* = 9, 14 Hz, 1 H, CH_2).

- **^{13}C NMR** (126 MHz, $CDCl_3$): 170.6 (CO), 147.9 (C_{Ar}), 146.5 (C_{Ar}), 137.5 (*C*=CH_2), 131.1 (C_{Ar}), 122.7 (C=*C*H_2), 122.0 (C_{Ar}), 109.0 (C_{Ar}), 108.4 (C_{Ar}), 101.0 (O-CH_2-O), 70.5 (O-CH_2), 40.3 (CH_2), 39.6 (=C_q-*C*H).
- **LRMS** (ESI): 233.09 (100, M+H^+); **HRMS** (ESI): M+Na^+ found 255.0633 $C_{13}H_{12}O_4Na$ requires 255.0633.

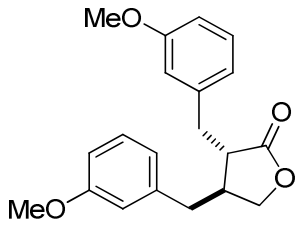
(*E*)-((8-Bromo-2,6-dimethyloct-6-en-3-yn-2-yl)oxy)triethylsilane (**196**):



CBr_4 (895 mg, 2.7 mmol) was added to a solution of allylic alcohol **183** (507 mg, 1.8 mmol), PPh_3 (708 mg, 2.7 mmol) and 2,6-lutidine (0.138 mL, 2.7 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was stirred at rt for 1 h, then quenched with sat. aq. $NaHCO_3$ (2 mL). The aq. layer was extracted with CH_2Cl_2 (3 × 5 mL), dried ($MgSO_4$), concentrated under reduced pressure and purified by column chromatography (25% EtOAc in petrol) to give allylic bromide **196** (470 mg, 84%) as a clear oil.

- ***R*$_f$**: 0.3 (40% EtOAc in petrol).
- **IR** (neat): 2956m, 1242m, 1162m, 1038m, 742w.
- **^{1}H NMR** (400 MHz, $CDCl_3$): 5.87 – 5.74 (m, 1 H, =CH), 4.03 (d, *J* = 8. Hz, 2 H, Br-CH_2), 3.00 – 2.89 (m, 2 H, CH_2), 1.83 – 1.75 (m, 3 H, =C-CH_3), 1.48 (s, 6 H, CH_3), 1.06 – 0.86 (m, 9 H, CH_3), 0.77 – 0.55 (m, 6 H, Si-CH_2).
- **^{13}C NMR** (126 MHz, $CDCl_3$): 137.9 (*C*$_q$=CH), 121.7 (C_q=*C*H), 88.6 (C≡), 78.5 (C≡), 66.3 (C_q-O), 33.2 (CH_2-Br), 33.1 (O-C_q(*C*H_3)$_2$), 28.8 (CH_2),16.0 (CH_3), 7.0 (Si-CH_2), 6.0 (Si-CH_2- CH_2).
- **LRMS** (ESI): 367.14 and 369.14 (75, M+Na), 431.11 (100); **HRMS** (ESI): M+Na^+ found 367.1066 $C_{16}H_{29}ONa^{79}BrSi$ requires 367.1063.

3,4-bis(3-Methoxybenzyl)dihydrofuran-2(3*H*)-one (**211**):

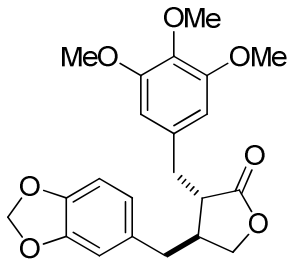


major

(3-Methoxyphenyl)boronic acid (97 mg, 0.64 mmol) was added to a solution of alcohol **194** (87 mg, 0.4 mmol), $[RhCl(cod)_2]_2$ (5.9 mg, 0.012 mmol) and Et_3N (0.056 mL, 0.40 mmol) in dioxane (1 mL) and water (0.33 mL). The reaction mixture was stirred at 100 °C in a microwave reactor (300 W) for 1 h, then concentrated under reduced pressure and purified though a small plug of silica (75% EtOAc in petrol) to give lactone **211**[98] (71 mg, 55%, 87:13 dr) as a yellow oil.

- R_f: 0.35 (80% EtOAc in petrol).
- **IR** (neat): 1763s, 1621s, 1524s, 1251w.
- **^{1}H NMR** (400 MHz, $CDCl_3$): 7.25 – 7.15 (m, 2 H, C-H_{Ar}), 6.83 – 6.70 (m, 4 H, C-H_{Ar}), 6.60 (d, *J* = 8 Hz, 1 H, C-H_{Ar}), 6.56 – 6.50 (m, 1 H, C-H_{Ar}), 4.12 (dd, *J* = 7, 9 Hz, 1 H, O-CH_2), 3.87 (dd, *J* = 8, 9 Hz, 1 H, O-CH_2), 3.79 and 3.76 (2 s, 6 H, CH_3), 3.07 (dd, *J* = 5, 14 Hz, 1 H, CH-CO), 2.92 (dd, *J* = 7, 14 Hz, 1 H, C_q-C*H*), 2.70 – 2.57 (m, 2 H, CH_2), 2.57 – 2.46 (m, 2 H, CH_2).
- **^{13}C NMR** (126 MHz, $CDCl_3$): 178.5, 159.8, 159.8, 139.5, 139.3, 129.7, 129.6, 121.6, 120.9, 114.8, 114.5, 112.3, 111.8, 71.2, 55.1, 55.1, 46.3, 41.2, 38.5, 35.1
- **LRMS** (ESI-): 327.5 (70, M-H), 452 (100).

4-(Benzo[d][1,3]dioxol-5-ylmethyl)-3-(3,4,5-trimethoxybenzyl)dihydrofuran-2(3*H*)-one (**206**):

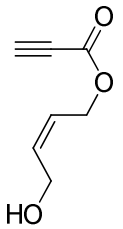


4,4,5,5-Tetramethyl-2-(3,4,5-trimethoxyphenyl)-1,3,2-dioxaborolane (160 mg, 0.64 mmol) was added to a solution of alcohol **195** (92 mg, 0.4 mmol), $[RhCl(cod)_2]_2$ (5.9 mg, 0.012 mmol) and Et_3N (0.056 mL, 0.40 mmol) in dioxane (1 mL) and water (0.33 mL). The reaction mixture was stirred at 100 °C in a microwave reactor (300 W) for 1 h, then concentrated under reduced pressure and purified though a small plug of silica (80% EtOAc in petrol) to give lactone **206**[97] (127 mg, 62%, 77:23 dr) as a yellow oil.

- ***R*$_f$**: 0.35 (40% EtOAc in petrol).
- **IR** (neat): 1761s, 1611s, 1523s, 1249s.
- **^{1}H NMR** (400 MHz, $CDCl_3$): 6.72 – 6.68 (m, 1 H, C-H_{Ar}), 6.56 – 6.42 (m, 2 H, C-H_{Ar}), 6.36 (s, 2 H, C-H_{Ar}), 5.94 (s, 2 H, O-CH_2-O), 4.19 (dd, *J* = 7, 9 Hz, 1H, O-CH_2) 3.93 – 3.74 (m, 10 H, O-CH_2 and CH_3), 2.94 – 2.88 (m, 2 H, CH), 2.73 – 2.43 (m, 4 H, CH_2).
- **^{13}C NMR** (126 MHz, $CDCl_3$):178.5, 153.2, 147.9, 146.3, 136.8, 133.4, 131.5, 121.5, 108.8, 108.3, 106.2, 101.1, 71.2, 60.8, 56.1, 46.4, 41.0, 38.3, 35.2
- **LRMS** (ESI+): 401.15 (100, M+H).

5.4 Data for Chapter 4

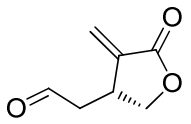
(*Z*)-4-Hydroxybut-2-en-1-yl propiolate (**248**):



DCC (9.28 g, 45.0 mmol) and DMAP (0.36 g, 0.30 mmol) in Et_2O (100 mL) was added dropwise over 20 min to a solution of (*Z*)-but-2-ene-1,4-diol (**245**) (3.52 g, 40.0 mmol) and propiolic acid (**247**) (3.08 g, 44.0 mmol) in Et_2O (20 mL) at – 30 °C. The reaction mixture was stirred overnight at rt, then quenched with sat. aq NH_4Cl (50 mL). The aq layer was extracted with Et_2O (3 × 50 mL) and the combined organic extracts dried (Na_2SO_4), concentrated under reduced pressure and purified by column chromatography (40% EtOAc in petrol) to give the enyne **248** (4.65 g, 83%) as a yellow oil.

- R_f: 0.40 (40% EtOAc in petrol).
- **IR** (neat): 3279br, 2119w, 1705s, 1214s, 1027m, 944w, 754m.
- **^{1}H NMR** (400 MHz, $CDCl_3$): 5.96 – 5.71 (m, 1 H), 5.71 – 5.44 (m, 1 H), 4.73 (d, *J* = 6 Hz, 2 H), 4.17 (d, *J* = 6 Hz, 2 H), 3.12 – 2.82 (br s + s, 2 H).
- **^{13}C NMR** (100 MHz, $CDCl_3$): 152.7, 134.5, 123.8, 75.6, 74.3, 61.8, 58.1.
- **LRMS** (ESI): 115.1 (90), 159.2 (75), 303.1 (100); **HRMS** (FI): M^+ found 140.0479; $C_7H_8O_3$ requires 140.0473.

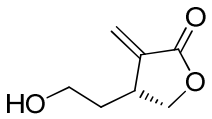
(*R*)-2-(4-Methylene-5-oxotetrahydrofuran-3-yl)acetaldehyde (**234**):



Acetone (2.5 mL) was added to a mixture of $[Rh(cod)Cl]_2$ (25.1 mg, 0.051 mol) and $AgSbF_6$ (35.0 mg, 0.102 mol) in a 25 mL round–bottom flask which had been purged 3 times with argon. A white precipitate formed immediately. After stirring at rt for 20 min, the yellow suspension was filtered under argon into a flask containing (*R*)-BINAP (63.4 mg, 0.102 mol). The resulting acetone solution was stirred for 20 min and then added directly to a solution of enyne **248** (570 mg, 4.07 mmol) in 1,2–dichlorethane (10 mL) at rt. The reaction mixture was stirred for 15 h at rt, then concentrated under reduced pressure and purified by column chromatography (50% EtOAc in petrol) to give the aldehyde **234** (416 mg, 73%) as a yellow oil.

- $\boldsymbol{R_f}$: 0.35 (50% EtOAc in petrol).
- $[\alpha]^{23}_{D}$ +91.4 (*c* 0.76, $CHCl_3$).
- **IR** (neat): 1757s, 1717s, 1409s, 1270m, 1120m, 750m.
- **^{1}H NMR** (500 MHz, $CDCl_3$): 9.84 (s, 1 H), 6.33 (d, *J* = 2 Hz, 1 H), 5.65 (d, *J* = 2 Hz, 1 H), 4.67 (t, *J* = 9 Hz, 1 H), 3.93 (dd, *J* = 6, 9 Hz, 1 H), 3.63 – 3.43 (m, 1 H), 2.99 (dd, *J* = 5, 19 Hz, 1 H), 2.78 (dd, *J* = 9, 19 Hz, 1 H).
- **^{13}C NMR** (125 MHz, $CDCl_3$): 198.7, 169.9, 137.0, 122.7, 70.8, 48.1, 32.8.
- **LRMS** (ESI): 277.1 (100), 413.3 (80); **HRMS** (FI): M^+ found 140.0478; $C_7H_8O_3$ requires 140.0473.

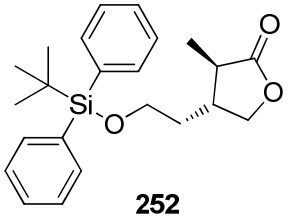
(*R*)-4-(2-Hydroxyethyl)-3-methylenedihydrofuran-2(3*H*)-one (**251**):



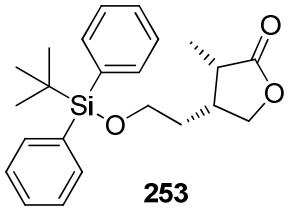
BH_3•THF (0.31 mL, 1 M in THF, 0.31 mmol) was added to a solution of aldehyde **234** (39 mg, 0.28 mmol) in THF (1 mL) at 0 °C. The reaction mixture was stirred 1 h at rt, then quenched with sat. aq NH_4Cl (3 mL). The aq layer was extracted with EtOAc (3 × 5 mL) and the combined organic extracts dried (Na_2SO_4), concentrated under reduced pressure and purified by column chromatography (80% EtOAc in petrol) to give the alcohol **251** (33 mg, 85%) as a yellow oil.

- ***R*$_f$**: 0.2 (80% EtOAc in petrol).
- $[\alpha]^{23}_D$ +48.3 (*c* 0.18, $CHCl_3$).
- **IR** (neat): 3439brs, 1761s, 1421s, 730w.
- **^{1}H NMR** (500 MHz, $CDCl_3$): 6.31 (d, *J* = 2 Hz, 1 H), 5.65 (d, *J* = 2 Hz, 1 H), 4.55 (dd, *J* = 8, 9 Hz, 1 H), 4.14 – 4.03 (m, 1 H), 3.86 – 3.75 (m, 2 H), 3.32 – 3.24 (m, 1 H), 2.01 – 1.88 (m, 1 H), 1.85 – 1.72 (m, 1 H), 1.67 – 1.49 (brs, 1 H).
- **^{13}C NMR** (125 MHz, $CDCl_3$): 170.7, 138.2, 122.0, 71.4, 60.0, 36.4, 35.9
- **LRMS** (ESI): 102.1 (20), 165.1 (M+Na), 413.3 (100); **HRMS** (ESI): M+Na^+ found 165.0523; $C_7H_{10}O_3Na$ requires 165.0522.

(3*R*,4*R*)-4-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-3-methyldihydrofuran-2(3*H*)-one (**252**) and (3*S*,4*R*)-4-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-3-methyldihydrofuran-2(3*H*)-one (**253**).



252



253

10% Pd/C (5 mg) was added to a solution of alcohol **251** (50 mg, 0.35 mmol) in MeOH (1 mL). The reaction mixture was stirred 4 h at rt under a H_2 balloon, then the filtrate was passed through a plug of celite and washed with Et_2O (3 × 5 mL). The filtrate was concentrated under reduced pressure to give primary alcohol (41.3 mg, 56: 44 dr by analysis of crude ^{1}H NMR, 82%) as a yellow oil.

TBDPSCl (43 mg, 0.15 mmol) was added to a solution of the above crude alcohol (15 mg, 0.10 mmol) and imidazole (15 mg, 0.22 mmol) in DMF (1 mL). The reaction mixture was stirred 15 h at rt, then quenched with sat. aq NH_4Cl (3 mL). The aq layer was extracted with Et_2O (3 × 5 mL) and the combined organic extracts dried (Na_2SO_4), concentrated under reduced pressure and purified by column chromatography (10 % EtOAc in petrol).

First eluted the lactone **252**[118] (9.5 mg, 24%) as yellow oil.

- ***R**f*: 0.40 (10% EtOAc in petrol).
- $[\alpha]^{23}_D$ +14.0 (*c* 0.35, $CHCl_3$); {lit. [118] ent–**8a** $[\alpha]^{23}_D$ –15.5 (*c* 2.73, $CHCl_3$)}.
- **IR** (neat): 2932w, 1776s, 1732s, 1472s, 1381m, 1175m, 1111m.
- **^{1}H NMR** (500 MHz, $CDCl_3$): 7.64 (d, *J* = 7 Hz, 4 H), 7.51 – 7.36 (m, 6 H), 4.44 (dd, *J* = 8, 9 Hz, 1 H), 3.85 (dd, *J* = 8, 9 Hz, 1 H), 3.76 – 3.64 (m, 2 H), 2.35 – 2.24 (m, 1

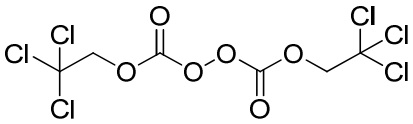
H), 2.24 – 2.12 (m, 1 H), 1.91 – 1.83 (m, 1 H), 1.70 – 1.58 (m, 1 H), 1.24 (d, *J* = 7 Hz, 3 H), 1.06 (s, 9 H).

- **^{13}C NMR** (125 MHz, $CDCl_3$): = 179.5, 135.5, 133.3, 133.2, 129.8, 127.8, 72.1, 62.1, 41.9, 40.3, 34.6, 26.8, 19.1, 13.7.
- **LRMS** (ESI): 405.1 (M+Na); **HRMS** (ESI): M+Na^+ found 405.1863; $C_{23}H_{30}O_3SiNa$ requires 405.1862.

Second eluted lactone **253** (12.0 mg, 30%) as yellow oil.

- ***R*$_f$**: 0.38 (10% EtOAc in petrol).
- $[\alpha]^{23}_D$ +2.2 (*c* 0.31, $CHCl_3$).
- **IR** (neat): 2931w, 1776s, 1731s, 1472s, 1380m, 1175m, 1113m.
- **^{1}H NMR** (500 MHz, $CDCl_3$): 7.65 (d, *J* = 7 Hz, 4 H), 7.52 – 7.32 (m, 6 H), 4.26 (dd, *J* = 6, 9 Hz, 1 H), 4.01 (dd, *J* = 6, 9 Hz, 1 H), 3.80 – 3.58 (m, 2 H), 1.81 – 1.65 (m, 1 H), 1.53 – 1.41 (m, 1 H), 1.14 (d, *J* = 7 Hz, 3 H), 1.06 (s, 9 H).
- **^{13}C NMR** (125 MHz, $CDCl_3$): 180.1, 135.5, 133.3, 133.3, 129.8, 127.8, 70.9, 61.8, 37.7, 36.6, 29.8, 26.8, 19.1, 10.3.
- **LRMS** (ESI): 405.1 (M+Na); **HRMS** (ESI): M+Na^+ found 405.1862; $C_{23}H_{30}O_3SiNa$ requires 405.1862.

Bis(2,2,2-trichloroethyl) peroxydicarbonate (**266**):

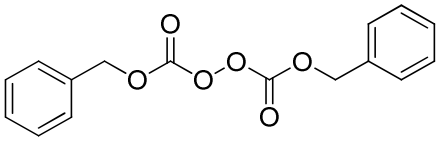


A solution of H_2O_2 (0.67 mL, 30% in H_2O, 6.0 mmol) and NaOH (0.5 g, 12.5 mmol) in water (5 mL) was added carefully to a solution of acid chloride **265** (1.66 mL, 12 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, then hexanes (15 mL) was added and the solid

filtered, then washed with water (5 mL) then hexanes (10 mL) to give peroxide **266** (0.81 g, 36%) as wet white powder.

- ***R*$_f$**: 0.5 (10% EtOAc in petrol).
- **IR** (neat): 1782s, 1434s, 1263s, 867m.
- **^{1}H NMR** (500 MHz, $CDCl_3$): 4.92 (s, 4 H, CH_2).
- **^{13}C NMR** (125 MHz, $CDCl_3$): 152.0 (CO), 93.1 (CCl_3), 78.1 (CH_2).

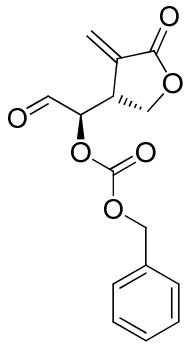
Dibenzyl peroxydicarbonate (**268**)[124b]



A solution of H_2O_2 (1.35 mL, 30% in H_2O, 12.0 mmol) and NaOH (1.0 g, 25 mmol) in water (10 mL) was added carefully to a solution of acid chloride **267** (3.4 mL, 24 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, then hexanes (15 mL) was added and the solid filtered, then washed with water (5 mL) then hexanes (10 mL) to give peroxide **268**[124a] (2.3 g, 65%) as wet white powder.

- ***R*$_f$**: 0.30 (20% EtOAc in petrol).
- **IR** (neat): 1799s, 1456s, 1372m, 1226s, 1205m, 1056m.
- **^{1}H NMR** (500 MHz, $CDCl_3$): 7.42 – 7.37 (m, 10 H, C-H_{Ar}), 5.32 (s, 4H, CH_2).
- **^{13}C NMR** (125 MHz, $CDCl_3$): 153.1 (CO), 133.6 (C_{Ar}), 129.2 (C_{Ar}), 128.8 (C_{Ar}), 128.6 (C_{Ar}), 72.3 (CH_2).

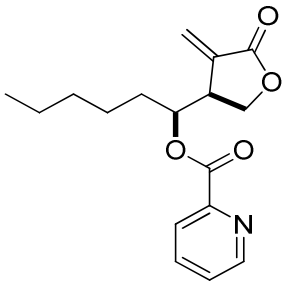
Benzyl ((R)-1-((R)-4-methylene-5-oxotetrahydrofuran-3-yl)-2-oxoethyl) carbonate (**271**):



MacMillan's catalyst **273**[152] (9.3 mg, 0.0428 mmol) was added to a solution of (*R*)-aldehyde **234** (30 mg, 0.214 mmol), *p*-nitrobenzoic acid (7.1 mg, 0.0428 mmol) and peroxide **268** (129.4 mg, 0.428 mmol) in THF (1 mL). The solution was stirred at rt for 15 h, then quenched with sat. aq. $NaHCO_3$ (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure and purified by column chromatography (40% EtOAc in petrol) to give crude aldehyde **271** (17.3 mg, 34%, 97:3 dr) as a yellow oil.

- ***R*$_f$:** 0.35 (50% EtOAc in petrol).
- **IR** (neat): 1752s, 1727s, 1698, 1409s, 1270s.
- **^{1}H NMR** (500 MHz, $CDCl_3$): 9.66 (s, 1 H, CHO), 7.48 – 7.31 (m, 5 H, C-H_{Ar}), 6.44 (d, *J* = 3 Hz, 1 H, =CH_2), 5.83 (d, *J* = 2 Hz, 1 H, =CH_2), 5.27 – 5.18 (m, 3 H, CH-O, C_{ar}-CH_2), 4.43 (dd, *J* = 2, 9 Hz, 1 H, CH_2-O), 4.28 (dd, *J* = 5, 9 Hz, 1 H, CH_2-O), 3.82 – 3.67 (m, 1 H, =C_q-C*H*).
- **^{13}C NMR** (125 MHz, $CDCl_3$): = 196.4 (CHO), 169.0 (CO_2), 154.4 (CO_3), 134.1 (C_q=CH_2), 132.5 (C_{Ar}), 129.0 (C_{Ar}), 128.8 (C_{Ar}), 128.4 (C_{Ar}), 125.2 (C_q=CH_2), 80.1 (CH-O), 71.0 (CH_2-O), 65.4 (CH_2), 38.5 (C_q-CH_2).
- **LRMS** (ESI-): 289.1 (20, M-H^+), 305.07 (100); **HRMS** (ESI): M+H^+ found 289.0718; $C_{15}H_{13}O_6$ requires 289.0718.

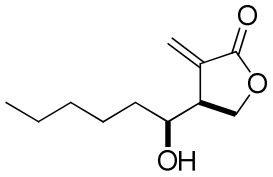
1-(4-Methylene-5-oxotetrahydrofuran-3-yl)hexyl picolinate (**276**):



DCC (72 mg, 0.35 mmol) was added to a solution of picolinic acid (43 mg, 0.35 mmol), DMAP (4.4 mg, 0.035 mmol) and lactone **148** (70 mg, 0. 35 mmol) in THF (3 mL). The reaction mixture was stirred at rt for 15 h, then quenched with sat. aq. NH_4Cl (5 mL) and extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure and purified by column chromatography (40% of EtOAc in petrol) to give lactone **276** (67 mg, 68%) as a clear oil.

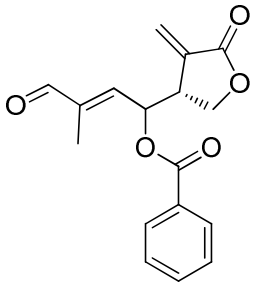
- R_f: 0.25 (30% EtOAc in petrol).
- **IR** (neat): 1763s, 1522s, 1262s.
- **^{1}H NMR** (500 MHz, $CDCl_3$): 8.74 (d, *J* = 4 Hz, 1 H, C-H_{Ar}), 8.05 (d, *J* = 8 Hz, 1 H, C-H_{Ar}), 7.91 – 7.77 (m, 1 H, C-H_{Ar}), 7.49 (ddd, *J* = 1, 5, 8 Hz, 1 H, C-H_{Ar}), 6.35 (d, *J* = 3 Hz, 1 H, =CH_2), 5.82 (d, *J* = 2 Hz, 1 H, =CH_2), 4.58 – 4.44 (m, 2 H, O-CH_2 and O-CH), 4.44 – 4.35 (m, 1 H, O-CH_2), 3.30 – 3.10 (m, 1 H, *C*H-C_q=), 1.75 – 1.55 (m, 2 H, CH_2), 1.44 – 1.38 (m, 2 H, CH_2), 1.30 – 1.18 (m, 4 H, CH_2), 0.81 (t, *J* = 7 Hz, 3 H, CH_3).
- **^{13}C NMR** (125 MHz, $CDCl_3$): 169.4 (CO_2), 164.8 (CO), 150.1 (C_{ar}), 147.3 (C_{ar}), 137.2 (C_{ar}), 135.4 (C_q=), 127.3 (C_{ar}), 125.2 (C_{ar}), 124.6 (=CH_2), 80.6 (CH-OH), 66.0 (CH_2-O), 43.8 (*C*H-C_q=), 35.9 (*C*H_2), 31.4 (*C*H_2), 24.5 (*C*H_2), 22.4 (*C*H_2), 13.9 (*C*H_2).
- **LRMS** (ESI): 304.1 (50, M+H^+), 326.1 (100, M+Na^+); **HRMS** (ESI): M+Na^+ found 326.1367; $C_{17}H_{21}NO_4Na$ requires 326.1363.

4-(1-Hydroxyhexyl)-3-methylenedihydrofuran-2(3*H*)-one **(148)**:



Anhydrous $CuSO_4$ (1.6 mg, 0.01 mmol) was added to a solution of lactone **275** (30.3 mg, 0.1 mmol), in MeOH/$CHCl_3$ (v/v: 0.1/0.9 mL). The reaction mixture was stirred at rt for 1 h, then concentrated under reduced pressure and purified by column chromatography (40% of EtOAc in petrol) to give lactone **148** (19 mg, 99%) as a clear oil. For data (see p. 134)

(*E*)-3-Methyl-1-((R)-4-methylene-5-oxotetrahydrofuran-3-yl)-4-oxobut-2-en-1-yl benzoate (**275**):

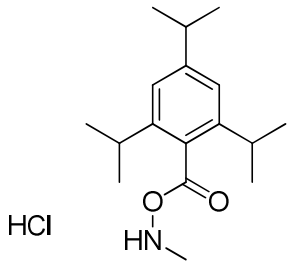


N-acylamine **276** (52.2 mg, 0.278 mmol) was added to a solution of aldehyde **234** (30 mg, 0.214 mmol), in THF (2 mL). The solution was stirred at rt for 15 h, then ylide **236** (135.6 mg, 0. 428 mmol) was added to this solution and the reaction mixture stirred at rt for 3 days. The mixture was concentrated under reduced pressure and purified by column chromatography (40 % EtOAc in petrol) to give the crude unsaturated aldehyde **275** (17 mg, 27%, 1:1 dr) as a yellow oil.

- ***R_f***: 0.40 (40% EtOAc in petrol).
- **IR** (neat): 2933w, 17612s, 1686s, 1412s, 1272m.

- **^{1}H NMR** (500 MHz, $CDCl_3$): 9.49 and 9.48 (s, 1 H, CHO), 8.05 – 7.88 (m, 2 H, C-H_{Ar}), 7.68 – 7.55 (m, 1 H, C-H_{Ar}), 7.53 – 7.41 (m, 2 H, C-H_{Ar}), 6.49 – 6.44 (m, 1 H, CH_2=), 6.43 – 6.30 (m, 1 H, CH=), 6.03 (ddd, *J* = 2, 6, 9 Hz, 1 H, CH-O), 5.87 and 5.85 (d, *J* = 2 Hz, 1 H, CH_2=), 4.57 – 4.35 (m, 2 H, CH_2-O), 3.68 – 3.54 (m, 1 H, =C_q-C*H*), 1.96 (s, 3H).
- **^{13}C NMR** (125 MHz, $CDCl_3$): = 193.8 (CHO) , 2 × 169.4 (CO), 2 × 165.3 (CO), 143.6 and 143.4 (C_q=CH_2), 143.1 and 143.0 (C_{ar}), 133.8 (C_{ar}), 133.4 and 133.2 (C_{ar}), 2 × 129.7 (C_{ar}), 129.5 (C_{ar}), 128.7 (C_q=), 125.8 and 125.6 5 (C_q=CH_2), 71.4 and 71.3 (CH-O), 66.9 and 66.4 (CH_2-O), 42.2 and 42.1 (*C*H-C_q=), 10.3 (CH_3).
- **LRMS** (ESI): 323.1 (70, M+Na), 803.3 (100); **HRMS** (ESI): M+Na+ found 323.0890; $C_{17}H_{16}O_5Na$ requires 323.0890.

tert-Butyl methyl((2,4,6-triisopropylbenzoyl)oxy)carbamate (**281**)

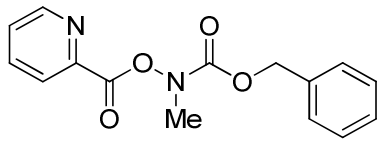


A solution of triisopropylbenzoyl chloride[153] (424 mg, 1.6 mmol) in CH_2Cl_2 (3 mL) was added slowly at 0 °C to a solution of Et_3N (0.22 mL, 1.6 mmol), DMAP (3.8 mg, 0.003 mmol) and *N*-methylhydroxylamine (238 mg, 1.6 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was stirred at rt for 15 h, then quenched with sat. aq. $NaHCO_3$ (25 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure to give the crude acyloxyamine (400 mg, 67%) as a yellow light oil. HCl in Et_2O (5 ml, 2 M in Et_2O) was added to a solution of the crude acyloxyamine (400 mg, 1.06 mmol) in Et_2O (1 mL). The reaction

mixture was stirred at rt for 15 h. The solid was filtered and washed with Et_2O to give *N*-acyloxyamine **281** (282 mg, 53%) as white needles.

- **mp**: 145-147 °C.
- **IR** (neat): 1715s, 1588s, 1422m, 1260s.
- **^{1}H NMR** (500 MHz, DMSO): 7.09 (s, 2 H, C-H_{Ar}), 2.83 – 2.70 (m, 6 H, CH and N-CH_3), 1.20 (t, *J* = 7 Hz 18 H, CH_3).
- **^{13}C NMR** (125 MHz, DMSO): 168.9 (CO), 150.4 (C_{ar}), 144.8 (C_{ar}), 128.3 (C_{ar}), 120.7 (C_{ar}), 38.7 (*C*H_3), 33.7 (*C*H_2), 30.9 (*C*H_2), 23.9 (*C*H_3), 23.9 (*C*H_3), 23.8 (*C*H_3).
- **LRMS** (ESI): 300.20 (30, M+Na^+), 234.3 (100); **HRMS** (ESI): M+Na^+ found 300.1939; $C_{17}H_{27}NO_2Na$ requires 300.1934.

Benzyl methyl(picolinoyloxy)carbamate (**288**):

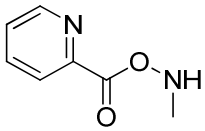


DCC (252 mg, 1.22 mmol) was added to a solution of picolinic acid (150.5 mg, 1.22 mmol), DMAP (15.4 mg, 0.12 mmol) and hydroxylamine **287** (200 mg, 1.22 mmol) in THF (5 mL). The reaction mixture was stirred at rt for 15 h, then quenched with sat. aq. NH_4Cl (5 mL) and extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure and purified by column chromatography (10% of EtOAc in petrol) to give acyloxoyamine **288** (187 mg, 54%) as a clear oil.

- ***R*$_f$**: 0.35 (10% EtOAc in petrol).
- **IR** (neat): 2962m, 1774s, 1724s, 1527s, 1263m.
- **^{1}H NMR** (500 MHz, $CDCl_3$): 8.82 – 8.61 (m, 1 H, C-H_{Ar}), 8.10 (d, *J* = 8 Hz, 1 H, C-H_{Ar}), 7.93 – 7.71 (m, 1 H, C-H_{Ar}), 7.49 (ddd, *J* = 1, 5, 8 Hz, 1 H, C-H_{Ar}), 7.31 – 7.26 (m, 5 H, C-H_{Ar}), 5.17 (s, 2 H, CH_2), 3.41 (s, 3 H, CH_3).

- **^{13}C NMR** (125 MHz, $CDCl_3$): 163.1 (CO), 156.0 (CO_2N), 150.2 (C_{Ar}), 145.8 (C_{Ar}), 137.3 (C_{Ar}), 135.6 (C_{Ar}), 128.5 (C_{Ar}), 128.3 (C_{Ar}), 127.9 (C_{Ar}), 125.9 (C_{Ar}), 68.3 (CH_2), 38.2 (CH_3).
- **LRMS** (ESI): 287.1 (100, $M+H^+$), 309.1 (100, $M+Na^+$); **HRMS** (ESI): $M+Na^+$ found 309.0848; $C_{15}H_{14}N_2O_4Na$ requires 309.0846.

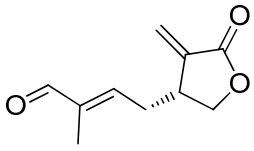
N-methyl-*O*-picolinoylhydroxylamine (**289**):



5% Pd/C (14 mg) was added to a solution of acyloxyamine **288** (286.3 mg, 1 mmol) in MeOH (5 mL) under a ballon of H_2. The reaction mixture was stirred at rt for 5 h, then the solution was passed trough a plug of celite and washed with CH_2Cl_2 (10 mL). The filtrate was concentrated to give crude hydroxylamine **289** (127.7 mg, 82%) as a white gum.

- ***R*$_f$**: 0.3 (5% MeOH in CH_2CL_2; decomposition).
- **IR** (neat): 2930m, 1768s, 1516s.
- **^{1}H NMR** (500 MHz, CDC_{l3}): 8.44 (br. s., 1 H, C-H_{Ar}), 8.03 (d, *J* = 7 Hz, 1 H, C-H_{Ar}), 7.65 (t, *J* = 7 Hz, 1 H, C-H_{Ar}), 7.24 - 7.04 (m, 1 H, C-H_{Ar}), 2.57 (s, 3 H, CH_3).
- **^{13}C NMR** (125 MHz, $CDCl_3$): 170.9 (CO), 154.0 (C_{Ar}), 148.2 (C_{Ar}), 136.8 (C_{Ar}), 124.3 (C_{Ar}), 53.4 (CH_3).

(*R*,*E*)-2-Methyl-4-(4-methylene-5-oxotetrahydrofuran-3-yl)but-2-enal (**293**):

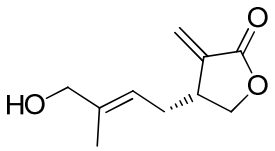


Acetone (2.5 mL) was added to a mixture of $[Rh(cod)Cl]_2$ (25.1 mg, 0.051 mol) and $AgSbF_6$ (35.0 mg, 0.102 mol) in a 25 mL round–bottom flask which had been purged 3 times with

argon. A white precipitate formed immediately. After stirring at rt for 20 min, the yellow suspension was filtered under argon into a flask containing (*R*)-BINAP (63.4 mg, 0.102 mol). The resulting acetone solution was stirred for 20 min and then added directly to a solution of enyne **248** (570 mg, 4.07 mmol) in 1,2–dichlorethane (10 mL) and stirred 15 h at rt. Ylide **236** (1.68 g, 5.28 mmol) was then added and the reaction mixture stirred at rt for 3 d. The mixture was concentrated then under reduced pressure and purified by column chromatography (50 % EtOAc in petrol) to give *E*-α,β-unsaturated aldehyde **293** (490 mg, 67%, 96:4 er by chiral HPLC, see S23) as a yellow oil.

- R_f: 0.38 (50% EtOAc in petrol).
- $[\alpha]^{23}_{D}$ +117.3 (*c* 0.38, $CHCl_3$).
- **IR** (neat): 2936w, 1761s, 1684s, 1405s, 1268m, 1117m, 1012w, 816w.
- **^{1}H NMR** (500 MHz, $CDCl_3$): 9.44 (s, 1 H), 6.48 – 6.40 (m, 1 H), 6.36 (d, *J* = 2 Hz, 1 H), 5.69 (d, *J* = 2 Hz, 1 H), 4.51 (dd, *J* = 8, 9 Hz, 1 H), 4.02 (dd, *J* = 5, 9 Hz, 1 H), 3.38 – 3.20 (m, 1 H), 2.86 – 2.71 (m, 1 H), 2.71 – 2.58 (m, 1 H), 1.78 (s, 3 H).
- **^{13}C NMR** (125 MHz, $CDCl_3$): = 194.3, 169.9, 147.2, 142.1, 137.1, 123.0, 70.1, 37.9, 32.7, 9.7.
- **LRMS** (ESI): 203.1 (M+Na), 464.4 (100); **HRMS** (ESI): M+Na^+ found 203.0681; $C_{10}H_{12}O_3Na$ requires 203.0679.

(*R*,*E*)-4-(4-Hydroxy-3-methylbut-2-en-1-yl)-3-methylenedihydrofuran-2(3*H*)-one (**294**):

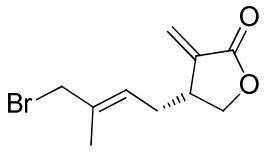


$CeCl_3.7\ H_2O$ (245.5 mg, 0.66 mmol) and aldehyde **293** (100 mg, 0.55 mmol) in MeOH (5 mL) was added slowly to a solution of $NaBH_4$ (21 mg, 0.55 mmol) in MeOH (5 mL) at 0 °C.

The reaction mixture was stirred 2 h at 0 °C, then quenched with sat. aq NH_4Cl (20 mL). The aq layer was extracted with CH_2Cl_2 (3 × 25 mL) and the combined organic extracts dried (Na_2SO_4), concentrated under reduced pressure and purified by column chromatography (70% EtOAc in petrol) to give the allylic alcohol **294** (87 mg, 87%) as a yellow oil.

- R_f: 0.35 (70% EtOAc in petrol).
- $[\alpha]^{23}_D$ +63.2 (*c* 0.56, $CHCl_3$).
- **IR** (neat): 3410br, 2916s, 1759s, 1409s, 1274s, 1119s, 817s.
- **^{1}H NMR** (500 MHz, $CDCl_3$): 6.29 (d, *J* = 2 Hz, 1 H), 5.66 (d, *J* = 2 Hz, 1 H), 5.45 – 5.34 (m, 1 H), 4.44 (dd, *J* = 8, 9 Hz, 1 H), 4.05 (d, *J* = 5 Hz, 2 H), 4.00 (dd, *J* = 5, 9 Hz, 1 H), 3.15 (m, 1 H), 2.49 – 2.38 (m, 1 H), 2.38 – 2.29 (m, 1 H), 1.68 (s, 3 H), 1.41 (t, *J* = 7 Hz, 1 H).
- **^{13}C NMR** (125 MHz, $CDCl_3$): = 170.7, 138.5, 137.9, 122.3, 120.0, 70.5, 68.2, 38.6, 31.7, 14.0.
- **LRMS** (ESI): 239.1 (40), 351.3 (50), 413,2 (100); **HRMS** (FI): M^+ found 182.0947; $C_{10}H_{14}O_3$ requires 182.0943.

(*R*,*E*)-4-(4-Bromo-3-methylbut-2-en-1-yl)-3-methylenedihydrofuran-2(3H)-one (**295**):

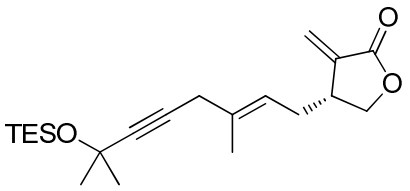


CBr_4 (253 mg, 0.760 mmol) and PPh_3 (200 mg, 0.760 mmol) was added to a solution of allylic alcohol **294** (92 mg, 0.505 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was stirred for 2 h at rt, then quenched with sat. aq NH_4Cl (10 mL). The aq layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts dried (Na_2SO_4),

concentrated under reduced pressure and purified by column chromatography (30% EtOAc in petrol) to give the allylic bromide **295** (158 mg, 91%) as a yellow oil.

- ***R*$_f$**: 0.45 (30% EtOAc in petrol).
- $[\alpha]^{23}_{D}$ +61.4 (*c* 0.15, $CHCl_3$).
- **IR** (neat): 1762s, 1117m, 750w.
- **^{1}H NMR** (500 MHz, $CDCl_3$): 6.30 (d, *J* = 2 Hz, 1 H), 5.66 (d, *J* = 2 Hz, 1 H), 5.57 (t, *J* = 7 Hz, 1 H), 4.44 (dd, *J* = 8, 9 Hz, 1 H), 4.03 – 3.91 (m, 2 + 1 H), 3.27 – 3.04 (m, 1 H), 2.42 (td, *J* = 7, 14 Hz, 1 H), 2.32 (td, *J* = 7, 14 Hz, 1 H), 1.85 – 1.74 (m, 3 H).
- **^{13}C NMR** (125 MHz, $CDCl_3$): 170.5, 137.5, 135.9, 125.6, 122.6, 70.3, 40.2, 38.4, 32.2, 15.1.
- **LRMS** (ESI): 267.1 and 269.1 (70, M+Na), 413.6 (100); **HRMS** (FI): M^+ found 244.0105; $C_{10}H_{13}O_2{}^{79}Br$ requires 244.0099.

(*R*,*E*)-4-(3,7-Dimethyl-7-((triethylsilyl)oxy)oct-2-en-5-yn-1-yl)-3-methylenedihydrofuran-2(3*H*)-one (**296**)

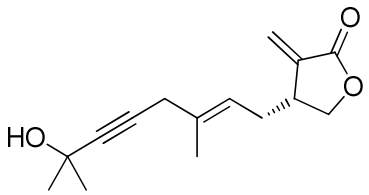


CuI (93 mg, 0.49 mmol) was added to a solution of a alkyne **181** (96.9 mg, 0.49 mmol) and Et_3N (0.068 ml, 0.49 mmol) in DMF (3.5 ml) and Et_2O (0.5 ml) and the reaction mixture was stirred for 1 h at rt (yellow solution), then a solution of allylic bromide **295** (60 mg, 0.24 ml) in Et_2O (1 ml) was added to the reaction mixture and stirred 3 h at rt. The reaction mixture was quenched with sat. aq NH_4Cl (5 mL). The aq layer was extracted with Et_2O (3 × 10 mL) and the combined organic extracts dried (Na_2SO_4), concentrated under reduced pressure and

purified by column chromatography (30 % EtOAc in petrol) to give the alkyne **296** (40.5 mg, 73%) as a yellow oil.

- **R_f**: 0.5 (30% EtOAc in petrol).
- $[\alpha]_D^{23}$ +61.6, *c* 0.35 in $CHCl_3$.
- **IR** (neat): 2981m, 1762s, 1268s, 1167s, 1119w.
- **^{1}H NMR** (500 MHz, $CDCl_3$): 6.29 (d, *J* = 3 Hz, 1 H, $=CH_2$), 5.66 (d, *J* = 2 Hz, 1 H, $=CH_2$), 5.50 – 5.35 (m, 1 H, CH=), 4.43 (dd, *J* = 8, 9 Hz, 1 H, CH_2-O), 3.98 (dd, *J* = 5, 9 Hz, 1 H, CH_2-O), 3.21 – 3.00 (m, 1 H, $=C_q$-C*H*), 2.90 (s, 2 H, ≡C-CH_2), 2.49 – 2.35 (m, 1 H, CH_2), 2.35 – 2.23 (m, 1 H, CH_2), 1.69 (s, 3 H, CH_3), 1.48 (s, 6 H, CH_3), 1.01 – 0.87 (m, 9 H, Si-CH_2-C*H*$_3$), 0.72 – 0.51 (m, 6 H, Si-CH_2).
- **^{13}C NMR** (125 MHz, $CDCl_3$): = 170.7 (CO), 137.9 (*C*$_q$=CH), 134.1(C_q=CH_2), 122.2 (C_q=*C*H), 120.6 (Cq=*C*H_2), 88.3 (C≡), 79.3 (C≡), 70.6 (C_q-O), 66.3 (CH_2-O), 38.7 (CH_2), 33.3 (C_q-CH_2), 32.0 (CH_2), 28.8 (CH_3), 16.5 (CH_3), 7.0 (CH_2), 6.0 (CH_2).
- **LRMS** (ESI): 385.2 (20, M+Na), 625.2 (100); **HRMS** (ESI): M+Na+ found 385.2174; $C_{21}H_{34}O_3NaSi$ requires 385.2175.

(*E*)-4-(7-Hydroxy-3,7-dimethyloct-2-en-5-yn-1-yl)-3-methylenedihydrofuran-2(3*H*)-one (**292**):

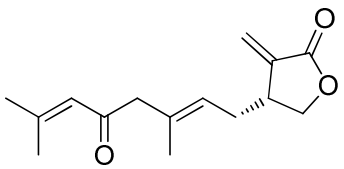


CuI (38 mg, 0.2 mmol) was added to a solution of 2-methylbut-3-yn-2-ol (**176**) (16.8 mg, 0.2 mmol) and Et_3N (0.028 mL, 0.2 mmol) in DMF (0.5 mL) and Et_2O (0.5 mL) and the reaction mixture was stirred for 1 h at rt (yellow solution), then a solution of allylic bromide **295** (24.5 mg, 0.1 mL) in Et_2O (0.5 mL) was added to the reaction mixture and stirred 2 h at rt. The

reaction mixture was quenched with sat. aq, NH_4Cl (5 mL). The aq layer was extracted with Et_2O (3 × 10 mL) and the combined organic extracts dried (Na_2SO_4), concentrated under reduced pressure and purified by column chromatography (40% EtOAc in petrol) to give a propargylic alcohol **296** (15.6 mg, 63%) as a yellow oil.

- ***R*$_f$**: 0.35 (40% EtOAc in petrol).
- $[\alpha]^{23}_D$ +69.6 (*c* 0.25 in $CHCl_3$).
- **IR** (neat): 3439br, 2980w, 1760s, 1269s, 1167w, 1119w.
- **^{1}H NMR** (500 MHz, $CDCl_3$): 6.29 (d, *J* = 2 Hz, 1 H), 5.67 (d, *J* = 2 Hz, 1 H), 5.41 (dt, *J* = 1, 7 Hz, 1 H), 4.43 (t, *J* = 8 Hz, 1 H), 4.00 (dd, *J* = 5, 9 Hz, 1 H), 3.15 (m, 1 H), 2.91 (s, 2 H), 2.47 – 2.37 (m, 1 H), 2.37 – 2.26 (m, 1 H), 2.03 (s, 1 H), 1.69 (s, 3 H), 1.60 (s, 3 H), 1.52 (s, 6 H).
- **^{13}C NMR** (125 MHz, $CDCl_3$): 170.1, 138.0, 134.1, 122.4, 120.4, 88.0, 79.2, 70.6, 65.3, 38.7, 32.2, 31.7, 28.6, 16.6.
- **LRMS** (ESI): 271 (100, M+Na), 519 (60); **HRMS** (ESI): M+Na$^+$ found 271.1305; $C_{15}H_{20}O_3Na$ requires 271.1305.

(+)-Anthecotulide (**4**):



$MoO_2(acac)_2$ (1.4 mg, 0.0044 mmol), $AuCl(PPh_3)$ (2.1 mg, 0.0044 mmol) and AgOTf (1.1 mg, 0.0044 mmol) were added successively to a solution of alkyne **292** (21.0 mg, 0.084 mmol) in toluene (1.5 mL) at 0 °C. The reaction mixture was stirred at rt for 2 h then passed through celite and washed with Et_2O (3.0 mL). Residue was concentrated under reduced

pressure and purified by column chromatography (50% EtOAc in petrol) to give (+)-anthecotulide (**4**)[6] (18.2 mg, 87%) as a yellow oil.

- ***R*$_f$**: 0.30 (50% EtOAc in petrol).
- $[\alpha]^{23}_D$ +81.1 (*c* 0.15, $CHCl_3$); {lit.[139] $[\alpha]^{22}_D$ +76.9 (*c* 0.032, $CHCl_3$)}.
- **IR** (neat): 2912w, 1763s, 1684s, 1618s, 1268m, 1114m.
- **^{1}H NMR** (500 MHz, $CDCl_3$): 6.21 (d, *J* = 2.7 Hz, 1 H), 6.01 (sept, *J* = 1.1 Hz, 1 H), 5.61 (d, *J* = 2.3 Hz, 1 H), 5.15 (dd, *J* = 1.3, 7.3 Hz, 1 H), 4.36 (dd, *J* = 8.4, 9.0 Hz, 1 H), 3.93 (dd, *J* = 5.4, 9.1 Hz, 1 H), 3.08 (dddd, *J* = 2.4, 5.9, 11.4, 13.8 Hz, 1 H), 3.02 (s, 2 H), 2.36 (ddd, *J* = 7.1, 7.1, 14.4 Hz, 1 H), 2.26 (ddd, *J* = 7.3, 7.3, 14.5 Hz, 1 H), 2.08 (d, *J* = 0.9 Hz, 3 H), 1.83 (d, *J* = 0.9 Hz, 3 H), 1.58 (d, *J* = 0.7 Hz, 3 H).
- **^{13}C NMR** (125 MHz, $CDCl_3$): 198.5, 170.8, 156.6, 137.8, 133.6, 123.8, 122.7, 122.4, 70.5, 55.0, 38.6, 32.1, 27.7, 20.7, 16.9.
- **LRMS** (ESI): 271 (100, M+Na), 519 (75); **HRMS** (ESI): $M+Na^+$ found 271.1300; $C_{15}H_{20}O_3Na$ requires 271.1305.

  See ^{13}C and ^{1}H NMR data comparaison of (±)-hydroxyanthecotulide p. 55

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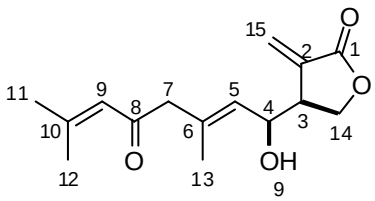
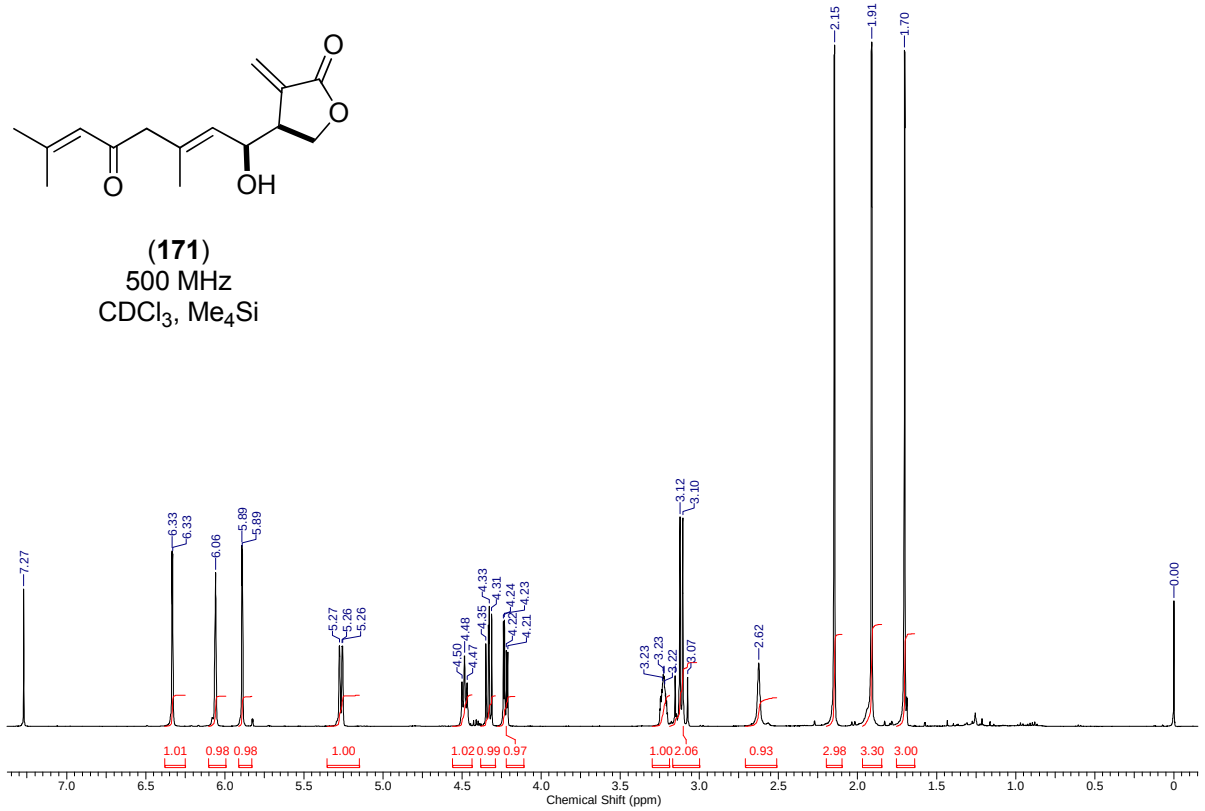
Appendix

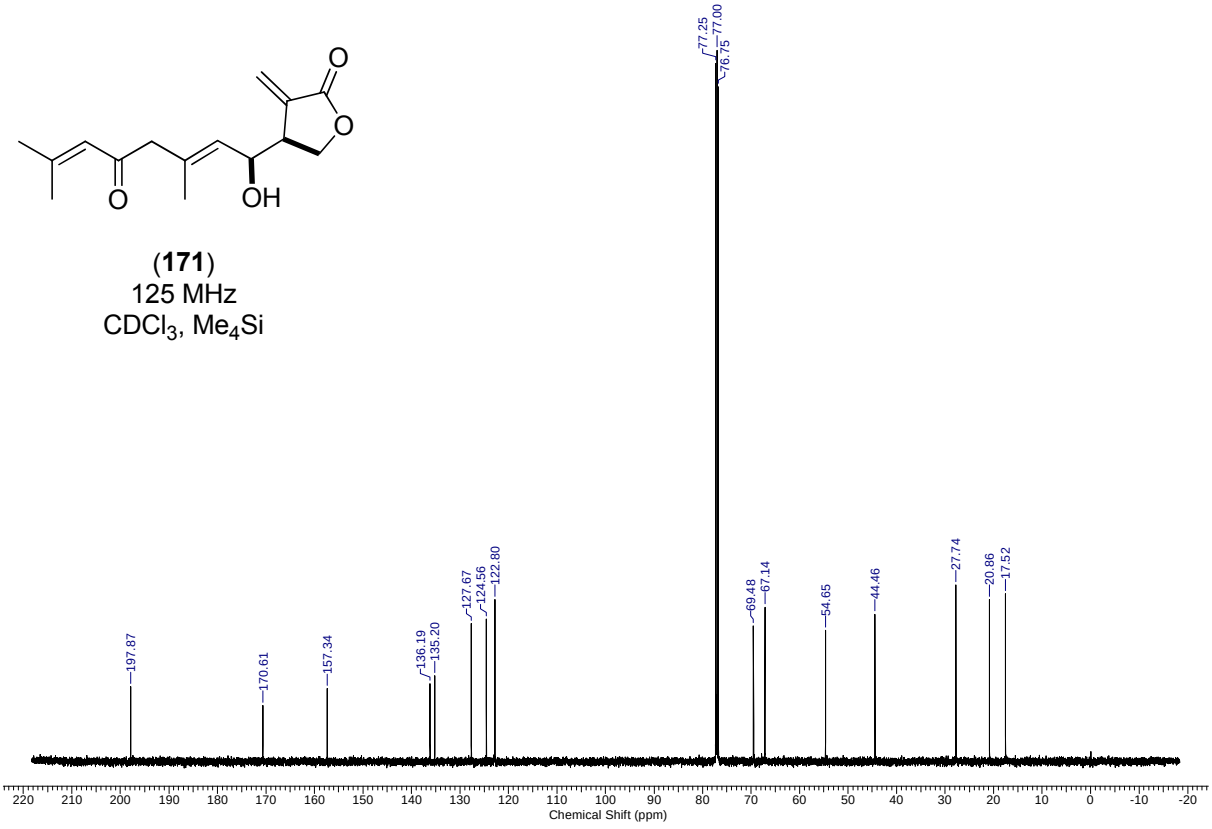
Comparison of Natural and Synthetic NMR data of *syn*-hydroxyanthecotulide (171)



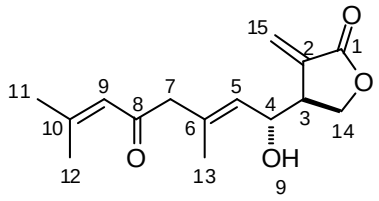
Comparison of Natural and Synthetic NMR data of hydroxyanthecotulide (2)				
atom no.	**^{1}H NMR** of Natural hydroxyanthecotulide (**2**) (500 MHz, $CDCl_3$)	**^{1}H NMR** of Synthetic hydroxyanthecotulide (**171**) (500 MHz, $CDCl_3$)	**^{13}C NMR** of Natural hydroxyanthecotulide (**2**) (500 MHz, $CDCl_3$)	**^{13}C NMR** of Synthetic hydroxyanthecotulide (**171**) (125 MHz, $CDCl_3$)
1	-	-	170.9	170.6
2	-	-	134.3	135.2
3	3.13 m	3.28-3.19, m	44.2	44.5
4	4.41, dd, J = 8.8, 7.8	4.48, t, J = 8.1	69.2	69.5
5	5.23, brd, J = 8.8	5.27. brd, J = 9.1	128.4	127.7
6			135.5	136.2
7a	3.14, d, J = 15.6	3.14, d, J = 14.9	54.4	54.7
7b	3.07, d, J = 15.6	3.09, d, J = 14.9		
8			198.2	197.9
9	6.04 s	6.06 s	122.9	122.8
10			157.5	157.3
11	1.87 s	1.91 s	27.7	27.7
12	2.10 s	2.15 s	20.8	20.9
13	1.63 s	1.70 s	17.5	17.5
14a	4.37, dd, J = 6.9, 4.4	4.33, dd, J = 9.4, 8.1	67.8	67.1
14b		4.23, dd, J = 9.8, 3.8		
15a	6.27, d, J = 2.4	3.66, d, J = 2.1	124.6	124.6
15b	5.77, d, J = 2.4	5.89, d, J = 1.7		

^{1}H and ^{13}C NMR spectra of synthetic *syn*-hydroxyanthecotulide (171)



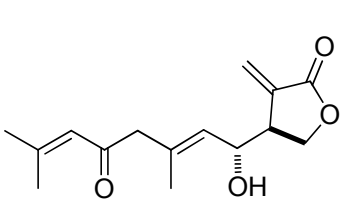


Comparison of Natural and Synthetic NMR data of *anti*-hydroxyanthecotulide (2)

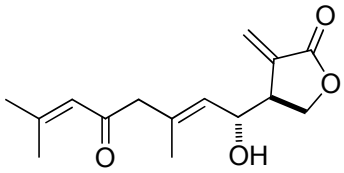


Comparison of Natural and Synthetic NMR data of hydroxyanthecotulide (2)				
atom no.	**1H NMR** of Natural hydroxyanthecotulide (**2**) (500 MHz, $CDCl_3$)	**^{1}H NMR** of Synthetic hydroxyanthecotulide (**2**) (500 MHz, $CDCl_3$)	**13C NMR** of Natural hydroxyanthecotulide (**2**) (500 MHz, $CDCl_3$)	**^{13}C NMR** of Synthetic hydroxyanthecotulide (**2**) (125 MHz, $CDCl_3$)
1	-	-	170.9	170.8
2	-	-	134.3	134.4
3	3.13 m	3.21-3.17, m	44.2	44.3
4	4.41, dd, J = 8.8, 7.8	4.45, t, J = 8.3	69.2	69.4
5	5.23, brd, J = 8.8	5.27, brd, J = 8.6	128.4	128.2
6			135.5	136.3
7a	3.14, d, J = 15.6	3.18, d, J = 15.7	54.4	54.6
7b	3.07, d, J = 15.6	3.11, d, J = 15.7		
8			198.2	197.8
9	6.04 s	6.08 s	122.9	123
10			157.5	157.4
11	1.87 s	1.91 s	27.7	27.8
12	2.10 s	2.14 s	20.8	20.9
13	1.63 s	1.68 s	17.5	17.7
14a	4.37, dd, J = 6.9, 4.4	4.37, dd, J = 6.9, 4.4	67.8	67.8
14b				
15a	6.27, d, J = 2.4	6.33, d, J = 2.6	124.6	124.7
15b	5.77, d, J = 2.4	5.82, d, J = 2.1		

^{1}H and ^{13}C NMR spectra of synthetic *anti*-hydroxyanthecotulide (2)

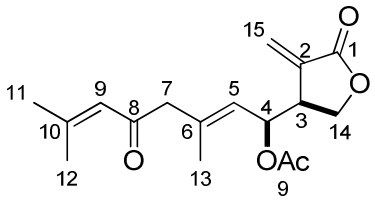


(**2**)
500 MHz
$CDCl_3$, Me_4Si



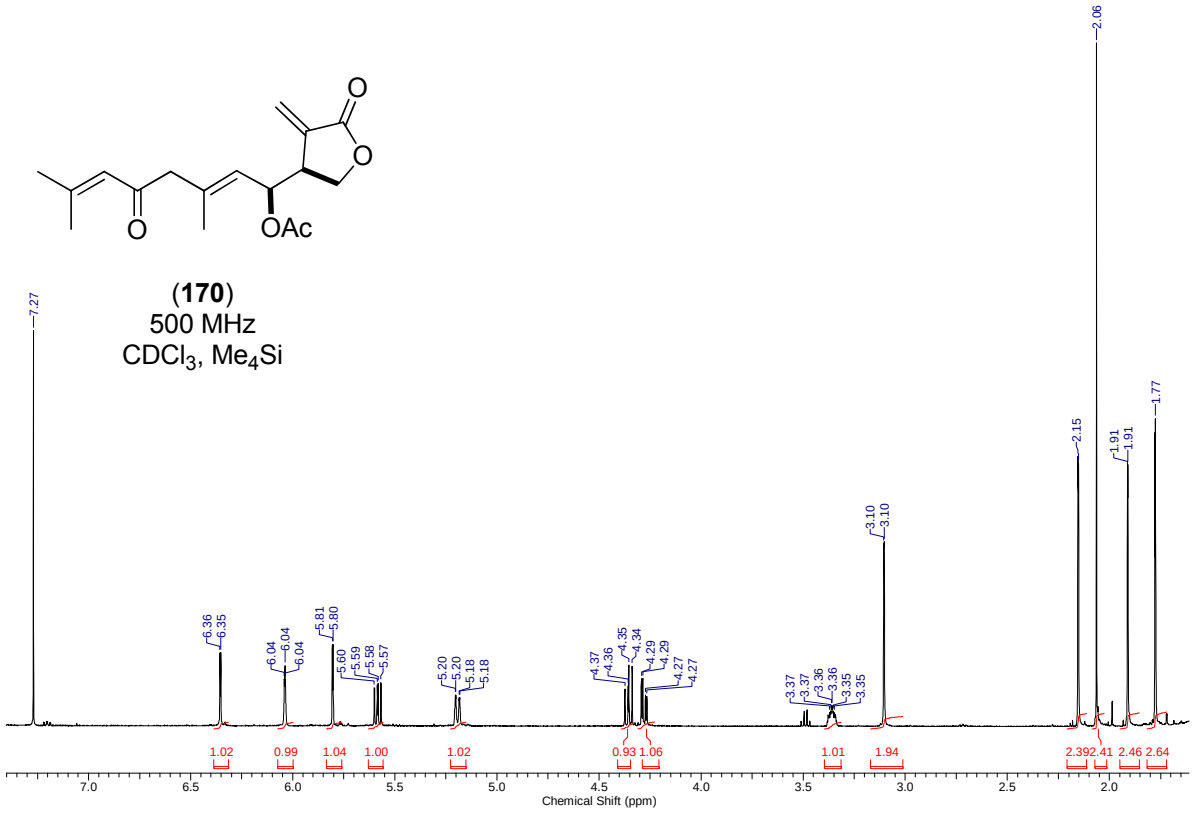
(**2**)
125 MHz
$CDCl_3$, Me_4Si

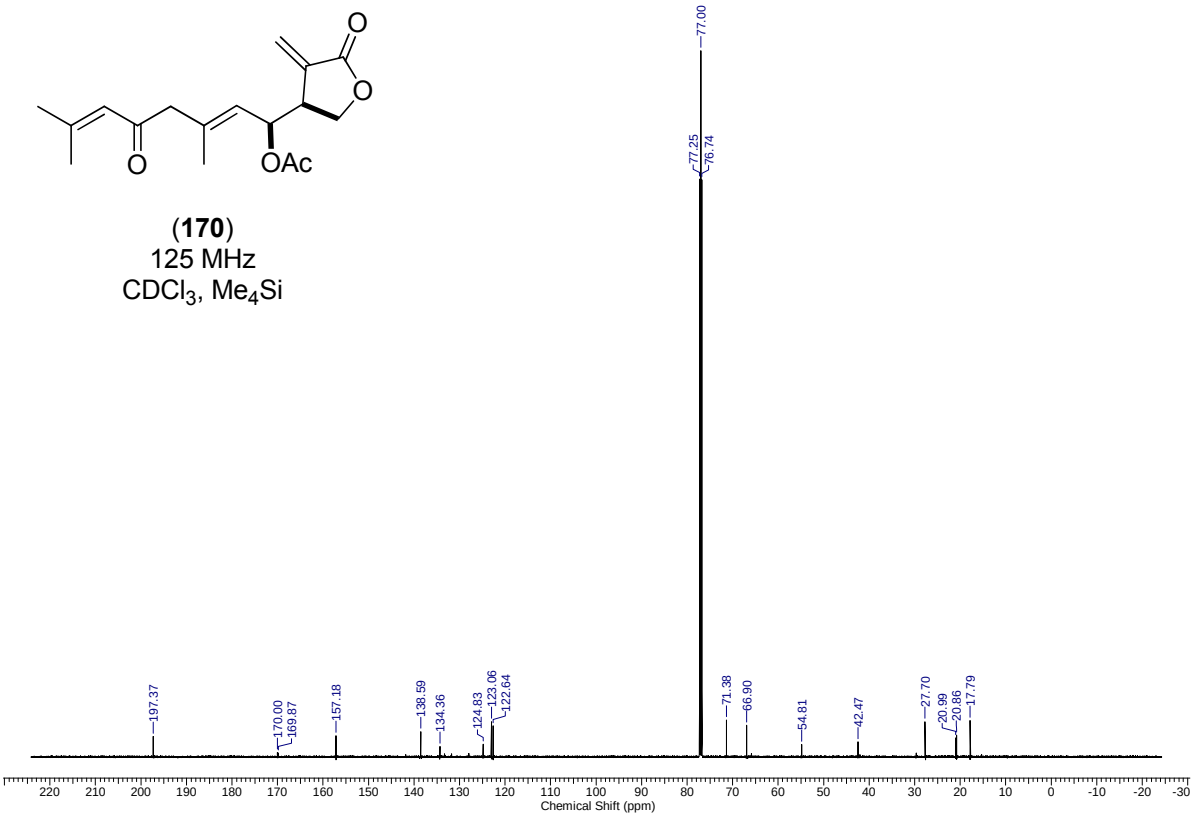
Comparison of Natural and Synthetic NMR data of acetoxyanthecotulide (170)



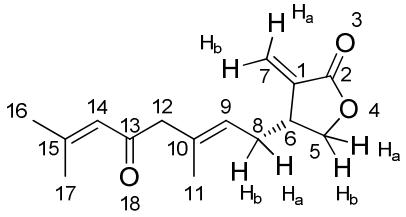
Comparison of Natural[3] and Synthetic NMR data of Acetoxyanthecotulide (**3**)				
atom no.	**^{1}H NMR** of Natural Acetoxyanthecotulide (**3**) ($CDCl_3$, 500 MHz)	**^{1}H NMR** of Synthetic Acetoxyanthecotulide (**170**) ($CDCl_3$, 500 MHz)	**^{13}C NMR** of Natural Acetoxyanthecotulide (**3**) ($CDCl_3$, 125 MHz)	**^{13}C NMR** of Synthetic Acetoxyanthecotulide (**170**) ($CDCl_3$, 125 MHz)
1	-	-	170.9	169.9
2	-	-	135	134.3
7a	3.09	3.1	54.9	54.8
7b				
3	3.59	3.36	42.2	42.5
14a	4.42	4.36	67.8	66.9
14b	4.21	4.28		
15a	6.37	6.36	125.2	124.8
15b	5.89	5.81		
4	5.63	5.58	71.9	71.4
5	5.19	5.19	128.1	123.1
6			138.1	138.5
8			198	197.3
9	6.03	6.04	125.6	122.6
10			157	157.2
11	1.87	1.91	27.8	27.7
12	2.12	2.06	21	21
13	1.78	1.77	15.1	17.8
Ac	2.15	2.15	20.9	20.9
Ac			168	170

^{1}H and ^{13}C NMR spectra of synthetic *syn*-acetoxyanthecotulide (170)



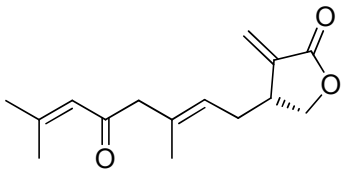


Comparison of Natural and Synthetic NMR data of Anthecotulide (4)

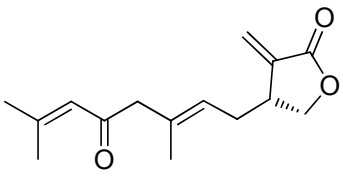


Comparison of Natural[2] and Synthetic NMR data of Anthecotulide (**1**)				
atom no.	**^{1}H NMR** of Natural Anthecotulide (**1**) (500 MHz, $CDCl_3$, Me_4Si)	**^{1}H NMR** of Synthetic Anthecotulide (**1**) (500 MHz, $CDCl_3$, Me_4Si)	**^{13}C NMR** of Natural Anthecotulide (**1**) (125 MHz, $CDCl_3$)	**^{13}C NMR** of Synthetic Anthecotulide (**1**) (125 MHz, $CDCl_3$)
1	-	-	138.1	137.8
2	-	-	170.8	170.8
5a	4.37, dd, *J* = 8.2, 8.9	4.36, dd, *J* = 8.4, 9.0	70.6	70.5
5b	3.91, dd, *J* = 5.5, 8.9	3.93, dd, *J* = 5.4, 9.1		
6	3.15, dddd, *J* = 2.6, 5.3, 10.6, 13.1	3.08, dddd, *J* = 2.4, 5.9, 11.4. 13.8	38.7	38.6
7a	6.13, d, *J* = 2.3	6.21, dd, *J* = 2.7	122.3	122.4
7b	5.64, d, *J* = 2.3	5.61. dd, *J* = 2.3		
8a	2.42, ddd, *J* = 6.7, 6.7, 14.6	2.36, ddd, *J* = 7.1, 7.1, 14.4	32.2	32.1
8b	2.34, ddd, *J* = 7.6, 7.6, 14.6	2.26, ddd, *J* = 7.3, 7.3, 14.5		
9	5.21, br qt, *J* = 7.1, 1.2	5.15, dd, *J* = 7.3, 1.3	124.0	123.8
10	-	-	133.7	133.8
11	1.62, d, *J* = 0.7	1.58, d, *J* = 0.7	16.9	16.9
12	3.00, s	3.02, s	55.1	55.0
13	-	-	198.6	198.5
14	6.02, sept, *J* = 1.1	6.01, sept, *J* = 1.1	123.0	122.7
15	-	-	156.4	156.6
16	2.09, d, *J* = 0.9	2.08, d, *J* = 0.9	20.7	20.7
17	1.88, d, *J* = 1.1	1.82, d, *J* = 0.9	27.7	27.7

^{1}H and ^{13}C NMR spectra of synthetic anthecotulide (4)

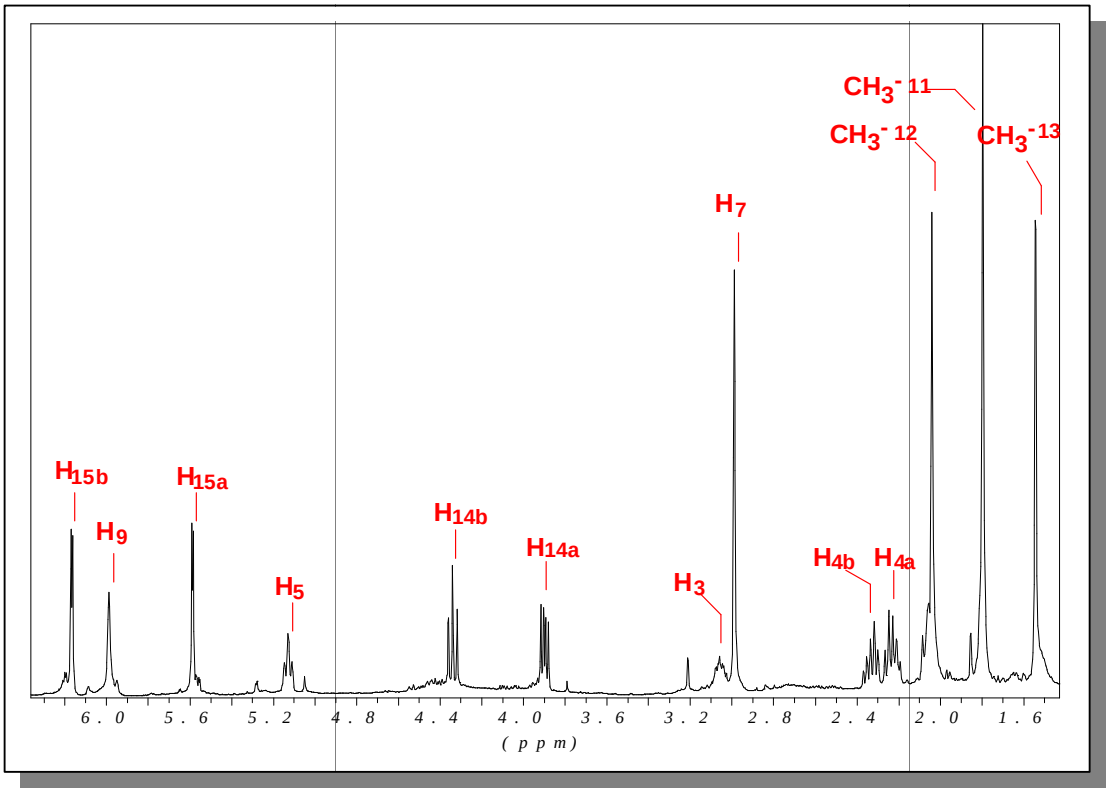


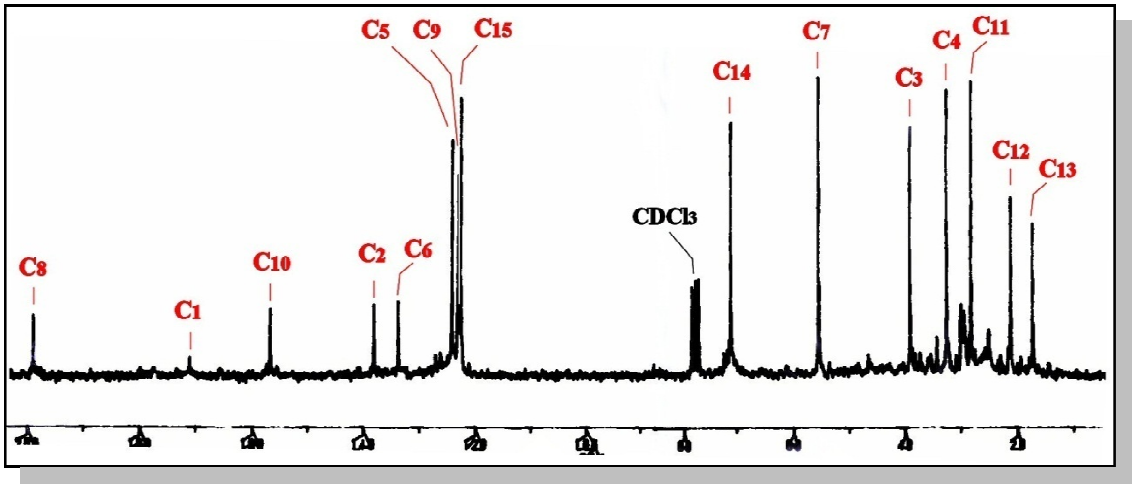
(**4**)
500 MHz
$CDCl_3$, Me_4Si



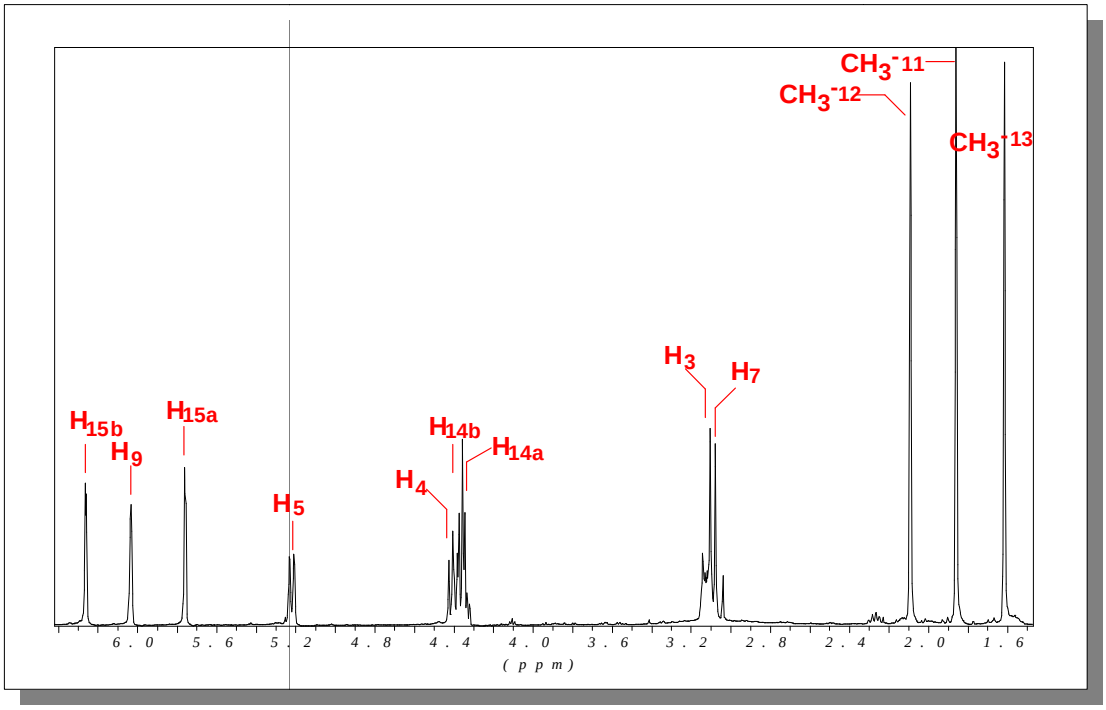
(**4**)
125 MHz
$CDCl_3$, Me_4Si

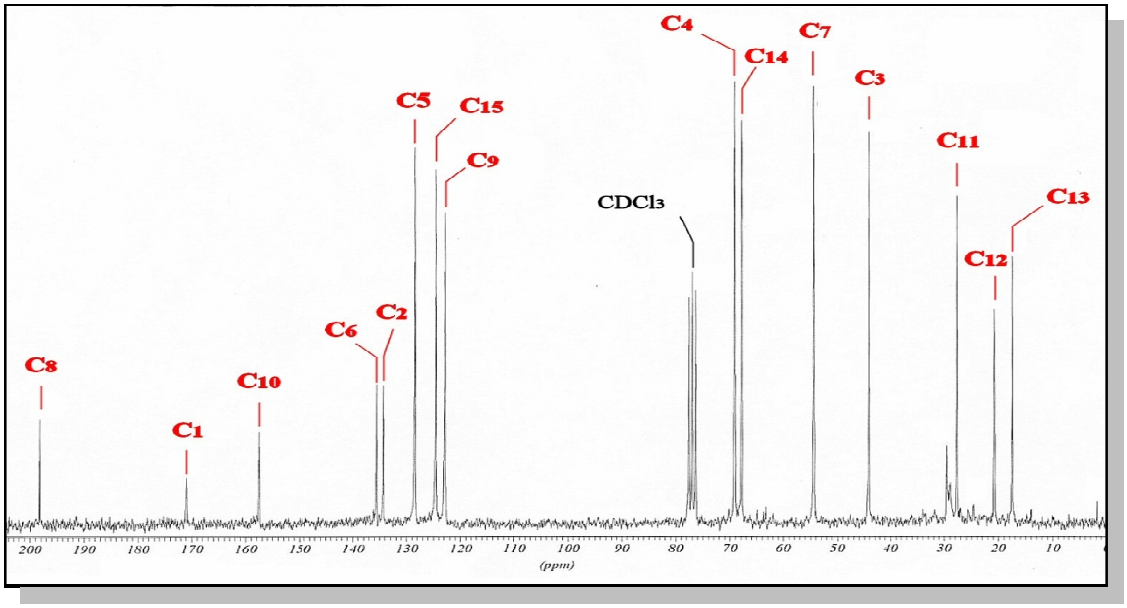
^{1}H and ^{13}C NMR spectra of natural anthecotulide (4) supplied by Dr Skaltsa (university of Athens)[155]



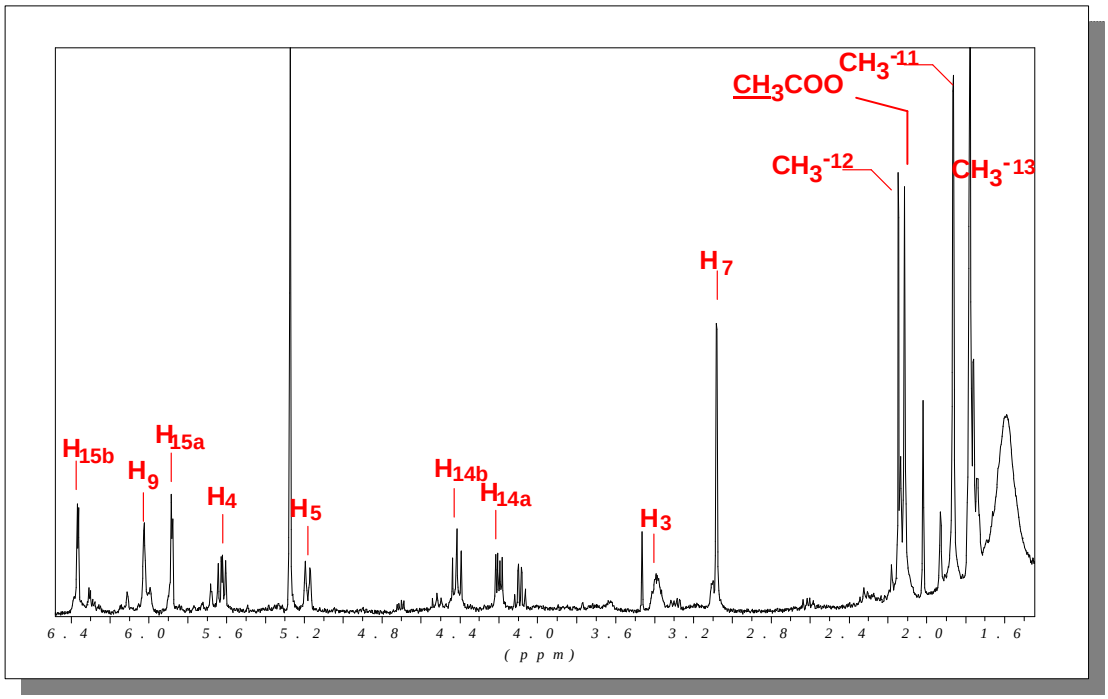


^{1}H and ^{13}C NMR spectra of natural hydroxyanthecotulide (2) supplied by Dr Skaltsa (university of Athens)[155]



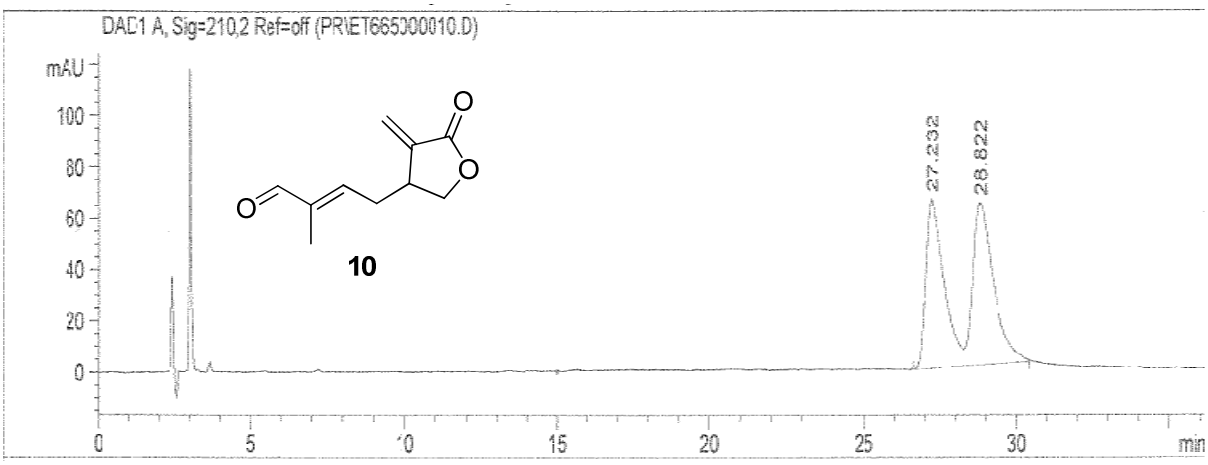


^{1}H spectra of natural acetoxyanthecotulide (3) supplied by Dr Skaltsa (university of Athens)[155]

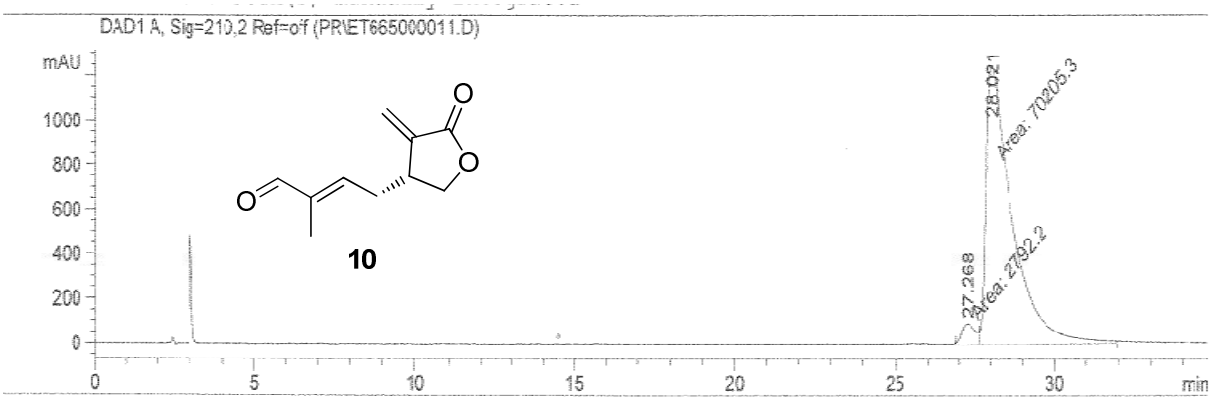


Chiral HPLC data for *E*-α,β-unsaturated aldehyde 293

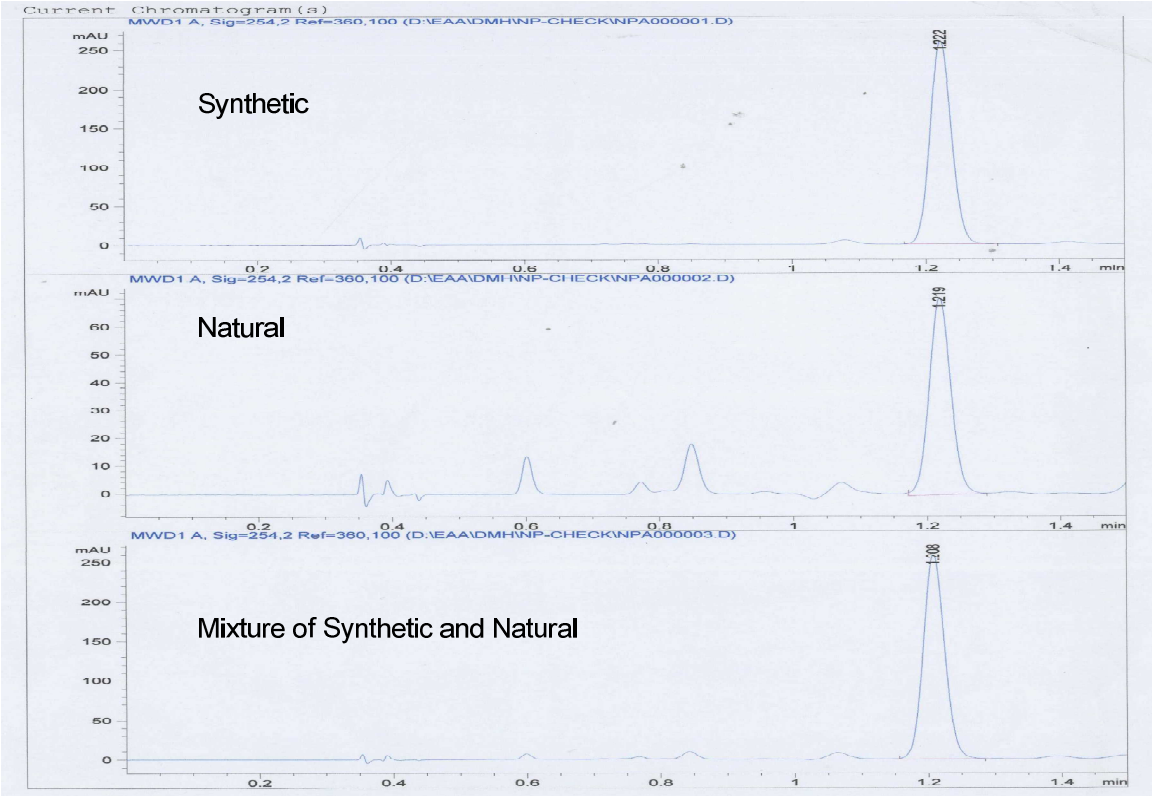
***Rac*-293** (CHIRALPAK IA), 1.3 mL/min, 5% IPA/Hexane) t_R (*S*–): 27.23 min, t_R (*R*–): 28.82 min.



96-4 er (***R*)-293** (CHIRALPAK IA), 1.3 mL/min, 5% IPA/hexane) t_R (*S*–): 27.26 min, t_R (*R*–): 28.02 min.



HPLC comparison between natural product and synthetic anthecotulide (4)



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Stereoselective Synthesis of β-(Hydroxymethylaryl/alkyl)-α-methylene-γ-butyrolactones

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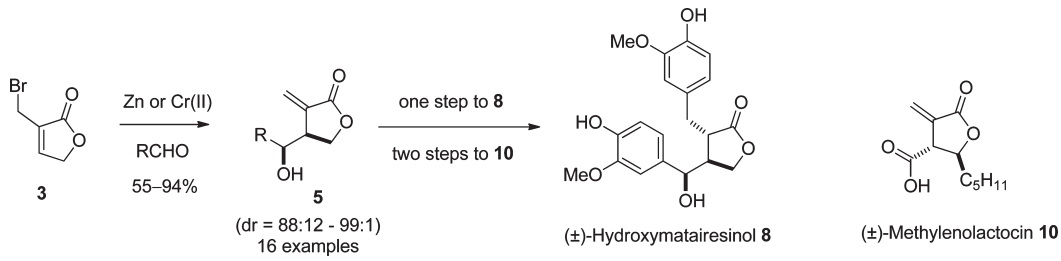
ABSTRACT



Zinc or a chromium(II) source with 3-(bromomethyl)furan-2(5*H*)-one (3) and an aldehyde gives β-(hydroxymethylaryl/alkyl)-α-methylene-γ-butyrolactones 5 in good yields and high diastereoselectivities. The methodology is demonstrated in concise syntheses of (±)-hydroxymatairesinol (8) and (±)-methylenolactocin (10) by subsequent arylboronate conjugate addition and translactonization, respectively.

The α-methylene-γ-butyrolactone motif is found in a large range of natural products, especially sesquiterpene lactones (Figure 1).[1] The presence of the motif is considered to be a major factor in the diverse biological activity observed for these natural products. Consequently, many methods have been developed to access α-methylene-γ-butyrolactones[1] for use in target synthesis and medicinal chemistry[2] programs.

However, at the outset of our studies the allylation method outlined in Scheme 1 to give such systems containing diverse β-hydroxymethyl substitution **5** had not been examined, aside from the work of Liu and co-workers to additionally γ-substituted adducts involving alkyne-derived molybdenum– or tungsten–π-allyl intermediates

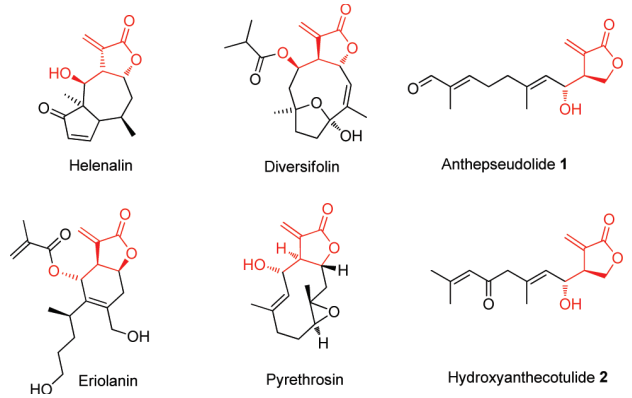


Figure 1. Representative α-methylene γ-butyrolactones.[1]

(**4**, M = MoL_n or WL_n, X = alkyl).[3,4] This substitution pattern is present in several sesquiterpene lactones (e.g., Figure 1), and the method could be of direct utility in syntheses of anthepseudolide (**1**)[5] and the antibacterial

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‡ Eli Lilly and Co. Ltd.

(1) (a) Kitson, R. R. A.; Millemaggi, A.; Taylor, R. J. K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9426–9451. (b) Elford, T. G.; Hall, D. G. *Synthesis* **2010**, 893–907.

(2) (a) Janecki, T.; Blaszczyk, E.; Studzian, K.; Janecka, A.; Krajewska, U.; Rózalski, M. *J. Med. Chem.* **2005**, *48*, 3516–3521. (b) Ramachandran, P. V.; Pratihar, D.; Nair, H. N. G.; Walters, M.; Smith, S.; Yip-Schneider, M. T.; Wu, H.; Schmidt, C. M. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6620–6623.

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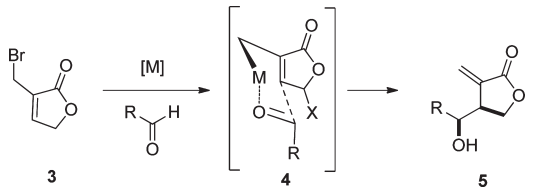
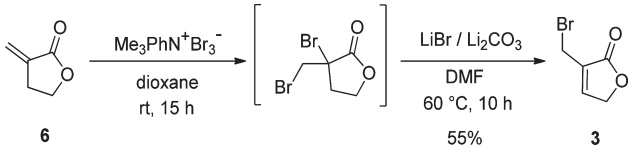
hydroxyanthecotulide (**2**)[6] and analogues.[7] We also viewed alcohols **5** as potentially versatile substrates for conjugate addition and isomerization chemistry, which could lead to other bioactive natural product classes (see later).

Scheme 1. Direct Synthesis of β-(Hydroxymethyl)-α-methylene-γ-butyrolactones **5** from Aldehydes



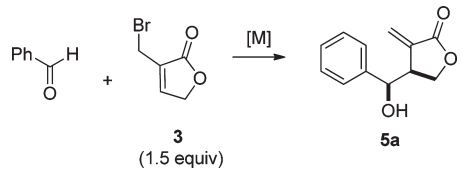
So as to investigate the above chemistry bromolactone **3**, previously accessed in six steps from γ-butyrolactone,[8] was conveniently prepared from commercially available tulipalin (**6**)[9] (Scheme 2). Bromination of **6** with phenyltrimethyl ammonium tribromide, followed by regioselective elimination using $LiBr/Li_2CO_3$ in DMF,[10] gave bromolactone **3** in 55% yield after one purification step.

Scheme 2. Synthesis of Bromolactone **3**



With bromolactone **3** in hand, Barbier-type coupling with benzaldehyde was investigated. Allylic chromium[11] or zinc[12] intermediates (Scheme 1, M = CrL_n or ZnL_n) were considered to have the potential to provide high regio- and stereoselectivity in the C−C bond forming step, together with lactone functional group tolerance. In the event, using the chromium(II) sources $CrCl_2$,[13] $CrCl_3/LiAlH_4$,[14] a catalytic chromium process ($CrCl_3$/Mn/TMSCl),[15] zinc with satd aq NH_4Cl in DMF,[16] or indium in the presence of a Lewis acid,[17] gave in all cases one major diastereoisomer of methylene lactone **5a** by crude ^1H NMR analysis (Table 1).

Table 1. Evalution of Different Allylation Conditions with **3** and Benzaldehyde



entry	conditions	yield of **5a** (%)	dr
1	$CrCl_2$ in DMF (rt, 15 h)	83	97:3
2	$CrCl_3/LiAlH_4$ in THF (rt, 15 h)	68	98:2
3	Cat. $CrCl_3$/Mn/TMSCl/*i*-Pr_2EtN in THF (rt, 15 h)	85	98:2
4	Zn/trace sat. aq NH_4Cl in DMF (rt, 15 h)	83	95:5
5	In/Eu$(OTf)_3$ in sat. aq NH_4Cl (rt, 15 h)	67	97:3

Due to the comparative experimental simplicity of the zinc protocol (Table 1 entry 4),[18] it was decided to evaluate the scope of the allylation process with different aromatic aldehydes under the zinc conditions (Table 2).

The chemistry was found to tolerate electron-rich (entries 4 and 6) and -deficient (entry 7) aromatic aldehydes and the presence of aryl halide (entries 2, 3 and 5), hydroxyl (entry 6), cyano (entry 7), and carbamate (entry 8) functionality. The stereochemistry of the major diastereoisomer **5b** arising from 1-naphthaldehyde (Table 2, entry 1) was established by X-ray crystallographic analysis[18] and is consistent with the transition state indicated in Scheme 1. Also, MOM protection of alcohol **5e** (Table 2, entry 4) gave a MOM ether[18] of established configuration, which has previously been converted into the insecticide

(3) (a) Lin, S.-H.; Chen, C.-C.; Vong, W.-J.; Liu, R.-S. *Organometallics* **1995**, *14*, 1619–1625. (b) Chen, C.-C.; Fan, J.-S.; Shieh, S.-J.; Lee, G.-H.; Wang, S.-L.; Liu, R.-S. *J. Am. Chem. Soc.* **1996**, *118*, 9279–9287. (c) Shiu, L. H.; Wang, S.-L.; Wu, M.-J.; Liu, R. S. *J. Chem. Soc., Chem. Commun.* **1997**, 2055–2062. (d) Chandrasekharam, M.; Liu, R.-S. *J. Org. Chem.* **1998**, *63*, 9122–9124.

(4) During the course of our studies, a single example of this process involving zinc with **3** and a complex chiral aldehyde was reported in a patent: (a) Xu, X.; Yang, H.; Qiao, X.; Xie, L. CN 101481367, 2009; *Chem. Abstr.*, 2009, *151*, 245843. (b) The reaction of zinc with **3** and formaldehyde has also been recently reported: Yang, H. S.; Qiao, X. X.; Cui, Q.; Xu, X. H. *Chin. Chem. Lett.* **2009**, *20*, 1023–1024.

(5) Abou El-Ela, M.; Jakupovic, J.; Bohlmann, F.; Ahmed, A. A.; Seif El-Din, A.; Khafagi, S.; Sabri, N.; El-Ghazouly, M. *Phytochemistry* **1990**, *29*, 2704–2706.

(6) Theodori, R.; Karioti, A.; Rancić, A.; Skaltsa, H. *J. Nat. Prod.* **2006**, *69*, 662–664. Corrigendum: *J. Nat. Prod.* **2009**, *72*, 804.

(7) The stereochemistries of **1** and **2** are currently not known with certainty.

(8) (a) Calderón, A.; de March, P.; el Arrad, M.; Font, J. *Tetrahedron* **1994**, *50*, 4201–4214. See also: (b) Chapleo, C. B.; Svanholt, K. L.; Martin, R.; Dreiding, A. S. *Helv. Chim. Acta* **1976**, *59*, 100–107.

(9) Murray, A. W.; Reid, R. *Synthesis* **1985**, 35–38.

(10) Ando, M.; Wada, T.; Isogai, K. *J. Org. Chem.* **1991**, *56*, 6235–6238.

(11) Hodgson, D. M.; Comina, P. J. In *Transition Metals for Fine Chemicals and Organic Synthesis*, 2nd ed.; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 1, pp 469−481.

(12) Luche, J. L.; Sarandeses, L. A. In *Organozinc Reagents*; Knochel, P., Jones, P., Eds.; Oxford University Press: Oxford, 1999; pp 307−323.

(13) Nishitani, K.; Konomi, T.; Mimaki, Y.; Tsunoda, T.; Yamakawa, K. *Heterocycles* **1993**, *36*, 1957–1960.

(14) Okuda, Y.; Nakatsukasa, S.; Oshima, K.; Nozaki, H. *Chem. Lett.* **1985**, 481–484.

(15) Fürstner, A.; Shi, N. J. *Am. Chem. Soc.* **1996**, *118*, 12349–12357.

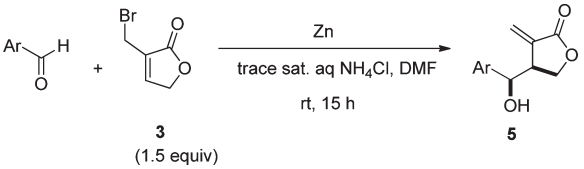
(16) Zinc in THF was very slow, giving only a trace of **5a** after 10 h. Zinc in DMF proceeded to completion, but required prolonged reaction time; the reaction was also accelerated by the addition of $PhCO_2H$ (1 equiv), albeit less efficiently than with NH_4Cl.

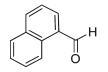
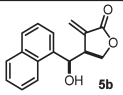
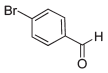
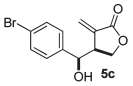
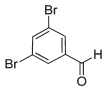
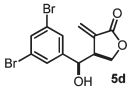
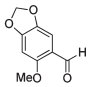
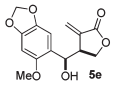
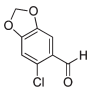
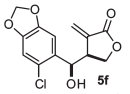
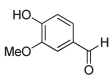
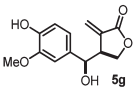
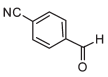
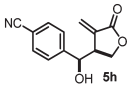
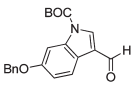
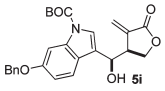
(17) Loh, T.-P.; Cao, G.-Q.; Pei, J. *Tetrahedron Lett.* **1998**, *39*, 1457–1460.

(18) See the Supporting Information for details.

(19) For details of aldehyde preparation see the Supporting Information.

Table 2. Scope of Allylation Using Bromolactone **3** with Zinc and Aromatic Aldehydes



entry	aldehyde	lactone **5**	yield of **5**	dr
1			79%	99:1
2			91%	94:6
3			78%	95:5
4[19]			73%	90:10
5			74%	90:10
6			71%	90:10
7			82%	90:10
8			67%	90:10

phrymarolin II.[20] The stereochemistry of vanillin-derived alcohol **5g** (Table 2, entry 6) was supported by subsequent 1,4-addition[21] of commercially available boronic ester **7**, which resulted in a concise, protecting group-free synthesis of the lignan hydroxymatairesinol (**8**)[22] (Scheme 3). The stereochemistry of **5a** and of the other alcohols in Table 2 was assigned by analogy.

Reduction of diastereoselectivity was observed with nonaromatic aldehydes under the zinc allylation conditions: 83:17 dr (79% yield) with the aliphatic aldehyde docecanal and 55:45 dr (75% yield) with the α,β-unsaturated aldehyde 3-methylbut-2-enal. For such substrates we found that the cat. Cr(II) conditions (Table 1, entry 3) were more effective (Table 3). Excellent drs (98:2–99:1) were uniformly observed, aside from an α,β-unsaturated aldehyde (entry 3). The mild allylation conditions are indicated by the functional group tolerance of cyano, alkenyl iodide, and ketone functionality (entries 5–7) and the viability of a β,γ-unsaturated aldehyde (entry 6).

Scheme 3. Application of Allylation to (±)-Hydroxymatairesinol (**8**)

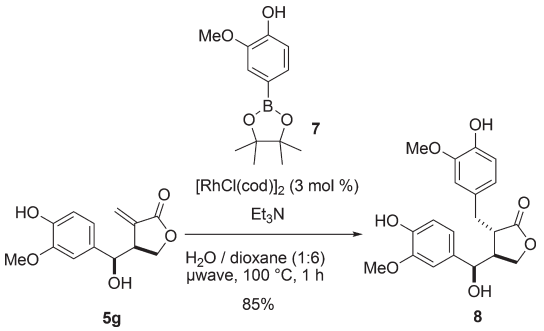
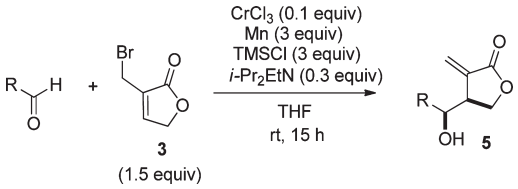
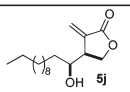
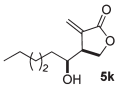
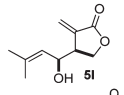
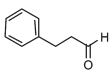
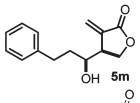
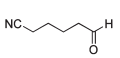
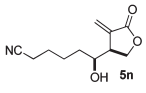
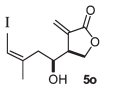
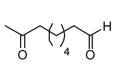
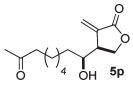


Table 3. Scope of the Allylation of Aliphatic Aldehydes Using Cat. Cr(II) conditions



entry	aldehyde	lactone **5**	yield of **5**	dr
1			94%	99:1
2			93%	99:1
3			55%	88:12
4			75%	99:1
5[19]			65%	99:1
6[19]			56%	98:2
7[19]			70%	99:1

(20) The spectral data were in full accord with the stereochemistry indicated in Table 2, entry 4, and also differed from the previously reported data for the diastereomeric MOM ether: (a) Yamauchi, S.; Yamamoto, N.; Kinoshita, Y. *Biosci. Biotechnol. Biochem.* **2000**, *64*, 2209–2215. (b) Yamauchi, S.; Yamamoto, N.; Kinoshita, Y. *Biosci. Biotechnol. Biochem.* **1999**, *63*, 1605–1613.

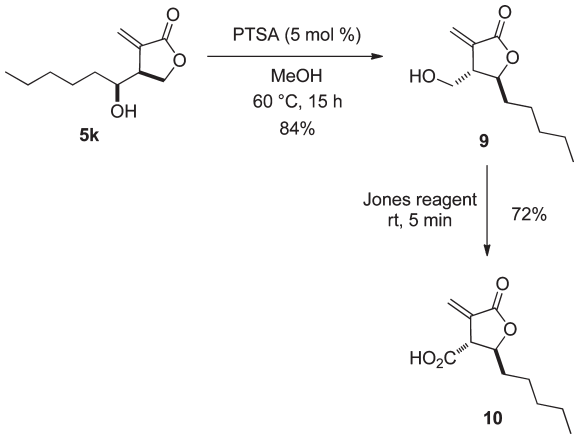
(21) (a) Ito, M.; Osaku, A.; Shiibashi, A.; Ikariya, T. *Org. Lett.* **2007**, *9*, 1821–1824. (b) de la Herrán, G.; Mba, M.; Murcia, M. C.; Plumet, J.; Csákÿ, A. G. *Org. Lett.* **2005**, *7*, 1669–1671.

(22) (a) Freudenberg, K.; Knof, L. *Chem. Ber* **1957**, *90*, 2857–2869. (b) Fischer, J.; Reynolds, A. J.; Sharp, L. A.; Sherburn, M. S. *Org. Lett.* **2004**, *6*, 1345–1348.

That the diastereoselectivity observed for aliphatic aldehydes is the same as found previously with the aromatic examples was supported by spectral comparison of methylene lactone **5j** (Table 3, entry 1) with the literature values[18,23] and by a further transformation of **5k** discussed below.

We also examined acid-catalyzed translactonization as a process to isomerize the β-hydroxymethylene products **5** generated in the above chemistry to *trans* β,γ-disubstituted α-methylenebutyrolactones (e.g., **9**, Scheme 4). The latter substitution pattern is found in many natural products (e.g., Figure 1).[1] Although the generation of primary alcohols from secondary alcohols by this approach has not been previously reported, it is known in a related *trans* β,γ-disubstitued α-methylenebutyrolactone that a less-hindered (Me-substituted) free secondary alcohol is favored (80:20−75:25) over a more hindered (*i*-Pr-substituted) free secondary alcohol at equilibrium.[3a,b] In the event, secondary alcohol **5k** (Table 3, entry 2) was recovered unchanged using the reported conditions (PTSA, CH_2Cl_2, rt, 15 h) for the secondary alcohol equilibration. However, reaction with 5% PTSA in MeOH (65 °C, 15 h) led smoothly to a 4:96 mixture in favor of the known[24] primary alcohol **9** (Scheme 4), which was cleanly isolated in 84% yield. The origin of the thermodynamic preference for primary alcohol **9**[25] may lie in reduction of destabilizing *gauche* interactions present in conformations of the secondary alcohol **5k**.[26] Jones oxidation[24] of primary alcohol **9** completed a short synthesis of the naturally occurring antibacterial and antitumor agent (±)-methylenolactocin (**10**).[3d,24]

Scheme 4. (±)-Methylenolactocin (**10**) by Translactonization



In summary, allylation of aldehyes using 3-(bromomethyl) furan-2(5*H*)-one (**3**) in the presence of zinc or Cr(II) salts provides a regio- and stereocontrolled access to β-substituted α-methylene-γ-butyrolactones. Conjugate addition and translactonization chemistry broaden the utility of the adducts, as illustrated in concise syntheses of (±)-hydroxymatairesinol (**9**) and (±)-methylenolactocin (**10**). Further applications in target synthesis and studies on asymmetric versions of this methodology are currently under investigation.

Acknowledgment. We thank Eli Lilly for funding (to E. P.A.T.) and B. Diseroad (Eli Lilly) for X-ray analysis.

Supporting Information Available. Full experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

Note Added after ASAP Publication. An error in Scheme 3 was corrected in the version reposted April 15, 2011.

(23) Hon, Y.-S.; Hsieh, C.-H.; Chen, H.-F. *Synth. Commun.* **2007**, *37*, 1635–1651. Allylation using the zinc conditions gave **5j** in 79% yield (83:17 dr). The minor diastereomer was determined to be that previously reported (see the Supporting Information).

(24) (a) Hon, Y.-S.; Hsieh, C.-H.; Liu, Y.-W. *Tetrahedron* **2005**, *61*, 2713–2723. (b) Saha, S.; Roy, S. C. *Tetrahedron* **2010**, *66*, 4278–4283.

(25) Submitting primary alcohol **9** to the reaction conditions gave the same 4:96 mixture of **5k**:**9** observed when starting with **5k**.

(26) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: Chichester, 1994; pp 682−684.

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Catalytic Asymmetric Synthesis of (+)-Anthecotulide Using Enyne and Meyer–Schuster Rearrangements

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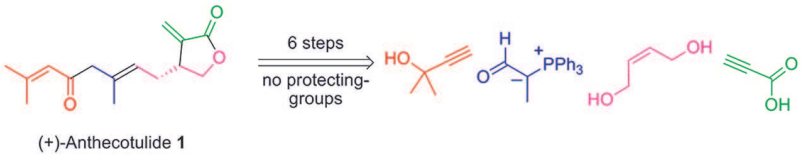
Received September 7, 2011

ABSTRACT



(+)-Anthecotulide **1**

The bioactive sesquiterpene lactone (+)-anthecotulide (1) is synthesized for the first time, in a six-step sequence devoid of protecting groups. The key transformations are a novel Rh(I)-catalyzed asymmetric enyne rearrangement of a terminal alkynyl ester (4), to form the α-methylene-γ-butyrolactone core, and a final-step mild Au(I)-catalyzed Meyer–Schuster rearrangement

Anthecotulide (**1**) is an optically active irregular sesquiterpene lactone first isolated in 1969 from *Anthemis cotula* L. (stinking chamomile).[1] At the time, the structure was assigned from analysis of spectroscopic data. In 2005, a more detailed analysis, which included a NOESY experiment to determine the configuration of the stereogenic double bond, corroborated the original structural assignment.[2] Anthecotulide has attracted interest due to its contact allergen properties[3] (contamination of chamomile preparations by *A. cotula* is to be avoided)[2] and its unusual biosynthesis for a sesquiterpene, involving head-to-middle coupling of geranyl diphosphate and dimethylallyl diphosphate.[4] More recently, anthecotulide demonstrated antibacterial,[5] antimalarial,[6] trypanocidal, and leishmanicidal activity[7] and has been shown to inhibit the activation pathway of the transcription factor NF-*k*B which regulates pro-inflammatory mediators (cytokines, nitric oxide, prostaglandins).[8]

Due to the emerging biological activity profile, and as part of our ongoing interest in the synthesis of α-methylene-γ-butyrolactones,[9] we communicate here the first synthesis of anthecotulide.

In this synthesis we aimed to address the synthetic challenge of assembling the sensitive α-methylene-γ-butyrolactone[10] and deconjugated ketone functionality in an efficient and stereocontrolled manner. Specifically, we envisaged accessing the natural product **1** by a Meyer–Schuster rearrangement from propargylic alcohol **2** (Scheme 1). This alcohol **2** would be derived by Wittig homologation of aldehyde **3**, which was anticipated to be accessible from cycloisomerization of enyne **4**.

So as to examine this chemistry, enyne **4** was first prepared (83% yield) by DCC coupling[11] of commercially available (*Z*)-but-2-ene-1,4-diol (**6**) with propiolic acid (**5**)

† University of Oxford.
‡ Eli Lilly and Co. Ltd.

(1) Bohlmann, F.; Zdero, C.; Grenz, M. *Tetrahedron Lett.* **1969**, 2417–2418.
(2) Meyer, A.; Zimmermann, S.; Hempel, B.; Imming, P. *J. Nat. Prod.* **2005**, *68*, 432–434.
(3) Hausen, B. M.; Busker, E.; Carle, R. *Planta Med.* **1984**, *50*, 229–234.
(4) van Klink, J.; Becker, H.; Andersson, S.; Boland, W. *Org. Biomol. Chem.* **2003**, *1*, 1503–508.
(5) Theodori, R.; Karioti, A.; Rančić, A.; Skaltsa, H. *J. Nat. Prod.* **2006**, *69*, 662–664.
(6) Karioti, A.; Skaltsa, H.; Zhang, X.; Tonge, P. J.; Perozzo, R.; Kaiser, M.; Franzblau, S. G.; Tasdemir, D. *Phytomedicine* **2008**, *15*, 1125–1129.
(7) Karioti, A.; Skaltsa, H.; Kaiser, M.; Tasdemir, D. *Phytomedicine* **2009**, *16*, 783–787.
(8) Vučković, I.; Vujisić, L.; Klaas, C. A.; Merfort, I.; Milosavljević, S. *Nat. Prod. Res.* **2011**, *25*, 800–805.
(9) Hodgson, D. M.; Talbot, E. P. A; Clark, B. P. *Org. Lett.* **2011**, *13*, 2594–2597.

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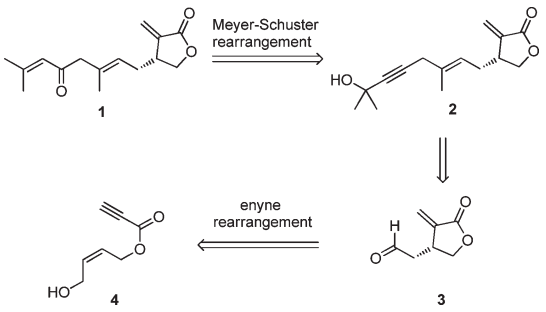
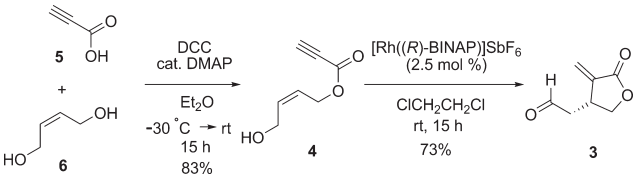
Scheme 1. Retrosynthetic Strategy to Anthecotulide (**1**)



(Scheme 2). Although metal catalyzed Alder-ene reactions of 1,6-enynes have been well-studied,[12] to the best of our knowledge only a single isolated example to form an α-methylene-γ-butyrolactone has been reported, using an achiral ruthenium(I) catalyst ($CpRu(NCCH_3)_3PF_6$).[13]

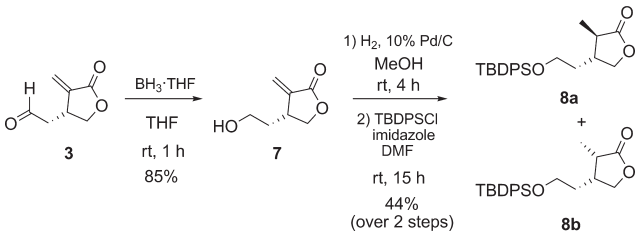
Scheme 2. Synthesis and Cycloisomerization of Enyne **4**



Considering the prospects for asymmetric catalysis, we decided to investigate the synthesis of the α-methylene-γ-butyrolactone core under rhodium(I) catalysis, which was originally developed by Zhang and co-workers with internal alkynes.[14] Using Zhang's conditions ($[Rh(cod)Cl]_2$/*rac*-BINAP/$AgSbF_6$, (0.025:0.05:0.05), $ClCH_2CH_2Cl$, rt, 15 h), enyne **4** gave the desired aldehyde **3**, albeit in low yields (20−30%) which were difficult to reproduce. On the basis that polymerization might be a competitive side reaction, we lowered the reaction concentration from 0.2 to 0.1 M and 0.05 M, but these experiments also gave low yields (23% and 15%, respectively). However, modifying the conditions to those used by Nicolaou and co-workers, where preforming the catalyst [Rh(*rac*)-BINAP)]SbF_6 was found optimal for the synthesis of α-methylene-γ-butyrolactams,[15] gave aldehyde **3** in much improved yield (71%). Finally, using [Rh((*R*)-BINAP)]SbF_6 gave (+)-aldehyde **3** in 73% yield and 96:4 er by chiral HPLC (Scheme 2).[16]

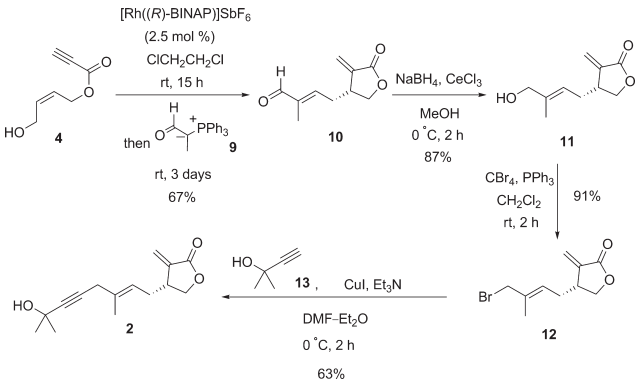
The sense of asymmetric induction in the cycloisomerization above using (*R*)-BINAP was determined by conversion of (+)-aldehyde **3** to the *trans*-lactone **8a**[17] of previously established absolute configuration and comparison of specific rotation values (Scheme 3). Chemoselective reduction of aldehyde **3** using BH_3,[18] followed by hydrogenation of the α-methylene group in lactone **7** and silylation of the resulting primary alcohol, gave a cis−trans mixture of lactones **8** from which *trans*-lactone **8a** could be obtained by careful chromatography. This correlation established that the *R*-configured aldehyde **3** was obtained from enyne **4** when using (*R*)-BINAP, and this corresponds to the same sense of asymmetric induction observed in Zhang's and Nicolaou's studies.[14,15]

Scheme 3. Configuration of Aldehyde (+)-**3** by Conversion to *trans*-Lactone (+)-**8a**



With a catalytic and highly enantioselective synthesis of aldehyde **3** established we examined its conversion to the propargylic alcohol **2** for the projected Meyer−Schuster rearrangement. Structurally related (internal) alkynes have been recently shown to undergo one-pot cycloisomerization−Wittig reaction.[19] In the present case, addition of ylide **9**[20] (1.3 equiv) following the Alder-ene reaction gave the *E*-α,β-unsaturated aldehyde **10** (67% from enyne **4**, Scheme 4).

Scheme 4. Synthesis of Propargylic Alcohol **2**



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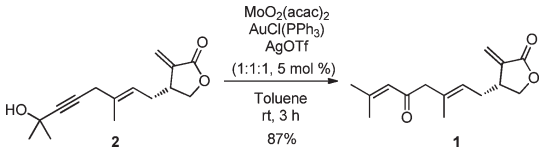
1,2-Reduction of aldehyde **10** with Luche's conditions,[21] followed by an Appel reaction[22] using PPh_3 and CBr_4, gave allylic bromide **12** (79% yield from **10**). Of various procedures examined for the displacement of the allylic bromide **12** by terminal alkynes,[23] conditions developed by White and co-workers were found to work best.[24] Propargylic alcohol **2** was obtained (63%) by addition of the allylic bromide **12** at 0 °C to the alkynylcopper species from alkynol **13**, prepared by mixing with stoichiometric CuI and Et_3N in a 2:1 mixture of Et_2O and DMF.

Mild methods for the conversion of propargyl alcohols into α,β-unsaturated ketones (Meyer–Schuster rearrangements) have recently been developed.[25] Akai and co-workers reported an effective catalytic combination of $MoO_2(acac)_2$ with $AuCl(PPh_3)$–AgOTf, where rearrangement is considered to proceed by [3,3] sigmatropy of an intermediate molybdate which is facilitated by alkyne coordination to an *in situ* generated cationic Au catalyst.[26] Using these conditions propargylic alcohol **2** gave (+)-anthecotulide (**1**) in excellent yield (87%) (Scheme 5). No isomerization of the β,γ-trisubstituted alkene into conjugation with the ketone was observed. The spectroscopic data were in full agreement with those in the literature,[2,16] and the specific rotation of synthetic anthecotulide $[\alpha]^{23}_D$ +81.1 (*c* 0.15, $CHCl_3$) is of comparable magnitude to that reported for the natural product $[\alpha]^{23}_D$ +76.9 (*c* 0.032, $CHCl_3$).[27]

In summary, the first and asymmetric synthesis of (+)-anthecotulide (**1**) has been achieved in six steps from commercially available materials, which additionally establishes the absolute configuration of the natural product as *R*- and provides a strategy for analog synthesis. Aside from its brevity, which stems from only one oxidation level change[28] and the absence of protecting-group chemistry,[29] the synthesis is noteworthy for the first example of an enantioselective enyne cycloisomerization to a α-methylene-γ-butyrolactone and the tolerance of the latter functionality to Au(I)-catalyzed Meyer–Schuster rearrangement.

Scheme 5. Anthecotulide (**1**) by Meyer–Schuster Rearrangement



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Note Added after ASAP Publication. The version published ASAP on October 7, 2011 contained typographical errors in two specific rotations related to Scheme 5. The correct version reposted on October 11, 2011.

Supporting Information Available. Full experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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