UNIVERSITY OF SOUTHAMPTON

FACULTY OF NATURAL AND ENVIRONMENTAL SCIENCES

School of Chemistry

Towards the Total Synthesis of Vibralactone and the Miuraenamides

by

Robert James Heap

Thesis for the degree of Doctor of Philosophy

August 2014

UNIVERSITY OF SOUTHAMPTON

ABSTRACT

FACULTY OF NATURAL AND ENVIRONMENTAL SCIENCES

SCHOOL OF CHEMISTRY

Doctor of Philosophy

TOWARDS THE TOTAL SYNTHESIS OF VIBRALACTONE AND THE MIURAENAMIDES

by

Robert James Heap

This thesis describes the efforts made towards the total synthesis of vibralactone and the miuraenamides. Initially, the attempted synthesis and derivatisation of vibralactone, a pancreatic lipase inhibiting fused bicyclic β-lactone, will be discussed. Vibralactone provides an interesting synthetic challenge not only because of its potent biological activity, but also due to its unique structure when compared to biologically related natural products. Herein, several ring closing metathesis (RCM) and aldol condensation strategies towards vibralactone's cyclopentene ring are presented.

Following diastereoselective addition reactions, metathesis approaches have successfully provided two racemic vibralactone derivatives. A novel auxiliary was subsequently implemented towards a stereoselective formal synthesis of a vibralactone model compound. An alternative aldol condensation approach was then investigated to optimise the synthesis of vibralactone intermediates.

The synthetic approach towards the miuraenamide family is then described. The miuraenamides are macrocyclic depsipeptides which have been shown to possess potent anti-fungal activity. Miuraenamide A has also been shown to stabilise actin filaments. This biological activity makes the miuraenamide family interesting synthetic targets towards the development of novel anti-fungal and anti-cancer therapeutics.

The synthesis towards miuraenamide A, *via* miuraenamide E, is described. The synthesis of the miuraenamide hydrocarbon fragment using stereoselective catalytic procedures was successfully achieved. The remaining peptide fragment was then synthesised using developed amino acid functionalisation and coupling techniques. Finally, optimisation of the union of each of the fragments was investigated, consequently leading to the successful synthesis of a linear, protected, miuraenamide E derivative.

Contents

DECLARATION OF AUTHORSHIP

I, Robert James Heap

declare that the thesis entitled

TOWARDS THE TOTAL SYNTHESIS OF VIBRALACTONE AND THE MIURAENAMIDES

and the work presented in the thesis are both my own, and have been generated by me as the result of my own original research. I confirm that:

- this work was done wholly or mainly while in candidature for a research degree at this University;
- where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;
- where I have consulted the published work of others, this is always clearly attributed;
- where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;
- I have acknowledged all main sources of help;
- where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;
- none of this work has been published before submission.

Signed: ……

Date:……

Acknowledgements

Firstly, I would like to thank Professor Richard Brown for the supervision over the past four years, I am truly grateful for the opportunity to study within your group. Although the projects were at times very frustrating, they were incredibly interesting, brilliantly varied and a joy to work on. I would also like to thank you for the assistance you provided whilst I was seeking a postdoctorate position. Without your support I have no doubt I would not have been as lucky as I was.

My thanks also go to Dr Xavier Franck for the continuous assistance during the PhD, especially at the beginning of the miuraenamide project. You and your group made me feel welcome during my time in your laboratory, allowing me to enjoy the French research experience.

Particular thanks go to Dr Sally Bloodworth, not only for all the feedback on my reports throughout this PhD, but also for the help provided after my masters degree to secure my position within the Brown group.

I would also like to separately thank postdocs Joe and Rob for their corrections to my thesis. Your keen eyes and quick responses have helped finish this PhD. Also, cheers for the karaoke, Joe you rocked it!

My thanks go to all the remaining members of the Brown group and 30/3045 over the past four years, especially (in no particular order); Paul and JB for the metal and ska, Pop for being dirty, Mohammed for Mendeley, Lynda for the effective cake rota, Azzam for the beans, Ian for the walnut cake, Mubina for the mouth, Girth, Zeshan for being halal of a good friend, Chris for making me feel healthy, Alex Leeder for finishing each of my projects so quickly, and of course all the newer and older members of which I do not have to space to mention.

Great thanks to all the people involved with NMR, MS, X-ray crystallography and stores for helping the PhD flow smoothly.

Many thanks to INTERREG, as without their funding this PhD would not have been possible.

Thanks go to Dr Nina Holling for the support she has given over the past 5 years. You have provided me with security in times of hardship, money in times of poorness, direction in times of rehousing, and a severe talking to during times of stupidity. The extent of my appreciation is not justified by these mere words.

My greatest thanks go to my mum, dad, John and Kat. Despite all of the troubles that have occurred in Plymouth since I left, every one of you have been amazingly supportive of me, emotionally and financially, since day one. Your belief in my abilities has driven me to achieve far more than I ever thought I was capable of. I would not be submitting this thesis if it wasn't for all of you making me think I am better than I am.

Abbreviations

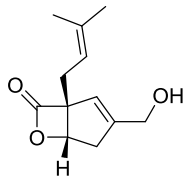
Ac	acetyl
acac	acetylacetonate
ala	alanine
APPI	atmospheric pressure photoionisation
aq.	aqueous
asp	aspartic acid
atm	standard atmosphere
BINAP	(1,1′-binaphthalene-2,2′-diyl)bis(diphenylphosphine)
BINOL	2,2′-dihydroxy-1,1′-dinaphthyl
BMI	body mass index
Bn	benzyl
Boc	*t*-butoxycarbonyl
br	broad
BT	benzotriazole
Bu	butyl
Bz	benzoyl
CAN	ceric ammonium nitrate
Cbz	benzyloxycarbonyl
CI	chemical ionization
cm	centimetre
CM	cross metathesis
COSY	correlation spectroscopy
d	doublet
Da	Dalton
dba	dibenzylideneacetone
DCC	*N*,*N*'-dicyclohexyl-carbodiimide
DEAD	diethyl azodicarboxylate
DEPBT	3-(diethoxyphosphoryl-oxy)-1,2,3-benzotriazin-4(3H)-one
DHP	dihydropyran
$(DHQD)_2PHAL$	hydroquinidine 1,4-phthalazinediyl diether
DIBAL	diisobutylaluminum hydride
DIPA	diisopropylamine
DIPEA	*N*,*N*-diisopropylethyl-amine
DMAP	4-(dimethylamino)-pyridine
DME	dimethoxyethane
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
EDC	1-ethyl-3-(3-dimethyl aminopropyl)-carbodiimide
ED_{50}	50% effective dose
ee	enantiomeric excess
EI	electron impact ionisation
ES	electrospray ionisation
Et	ethyl
et al.	*et alia* (Latin: and others)
eq.	molar equivalent
FDLA	1-fluoro-2,4-dinitrophenyl-5-leucinamide
FT	Fourier transform

g	gram
GC	gas chromatography
gem	geminal
gly	glycine
h	hour
HATU	1-[bis(dimethylamino) methylene]-1H-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate
HBTU	*N*,*N*,*N*′,*N*′-tetramethyl-O-(1H-benzotriazol-1-yl) uronium hexafluorophosphate
his	histidine
HMBC	heteronuclear multiple bond correlation
HMDS	hexamethyldisilazane
HMPA	hexamethylphos-phoramide
HMQC	heteronuclear multiple-quantum correlation
HOBT	hydroxybenzotriazole
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
Hz	hertz
i	iso
IC_{50}	half maximal inhibitory concentration
IPA	isopropyl alcohol
IR	infrared
J	coupling constant
J	joule
Kcal	kilocalorie
K	kilo
L	litre
LC	liquid chromatography
LDA	lithium diisopropylamide
LPA	lysophosphatidic acid
LRMS	low resolution mass spectroscopy
m	milli
m	meter
m (IR)	medium
M	molar
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MeOBIPHEP	(6,6′-dimethoxybiphenyl-2,2′-diyl)bis(diphenyl-phosphine)
MIC	minimum inhibitory concentration
min	minute
MNBA	2-methyl-6-nitrobenzoic anhydride
MOM	methoxymethyl
MRSA	methicillin-resistant *Staphylococcus aureus*
Ms	mesyl
MS	mass spectroscopy
MTPA	methoxy(trifluoromethyl) phenylacetic acid
n	nano
N	normal
NADH	nicotinamide adenine dinucleotide
NBS	*N*-bromosuccinimde
NMM	4-methylmorpholine
NMMO	4-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance

NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
p	para
Pa	Pascal
PEA	phenylethylamine
Ph	phenyl
Piv	pivalate
PL	pancreatic lipase
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
PTSA	*p*-toluenesulfonic acid
Py	pyridine
PyBOP	(benzotriazol-1-yloxy) tripyrrolidinophosphoniu m hexafluorophosphate
q	quartet
quin	quintet
Ra	Raney
RCM	ring closing metathesis
RCEM	ring closing enyne metathesis
ROESY	rotating frame Overhauser effect spectroscopy
RRCM	relay ring closing metathesis
rt	room temperature
s (IR)	strong
s (NMR)	singlet
ser	serine
sxt	sextet
t	tert
t	triplet
TADDOL	2,2-dimethyl-α,α,α′,α′-tetraphenyldioxolane-4,5-dimethanol
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBS	*t*-butyldimethylsilyl
TBTU	*O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate
TES	triethylsilane
Tf	triflate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMAL	tandem Mukaiyama aldol-lactonisation
TMEDA	tetramethyl-ethylenediamine
TMS	trimethylsilyl
Ts	tosyl
TTC	*trans*-2-tritylcyclohexanol
Tyr	tyrosine
T3P	propylphosphonic anhydride
UV	ultraviolet
w	weak
9-BBN	9-borabicyclo[3.3.1]-nonane

1. Introduction

Vibralactone (**1.01**) is a fused β-lactone extracted from *Boreostereum Vibrans* in 2006,[1] and has been shown to be a potent pancreatic lipase inhibitor (**Figure 1.1**). This section of the thesis concerns the Southampton asymmetric approach to vibralactone (**1.01**) and related derivatives, with a broader objective to enhance knowledge in the field of anti-obesity therapeutics.



1.01

Figure 1.1: Structure of vibralactone (**1.01**).

An introduction to the causes and effects of obesity is presented in the following sections, signifying the requirement for medical intervention. Key examples of discontinued obesity pharmaceuticals are introduced to demonstrate the potential of pancreatic lipase (PL) as a therapeutic target. Publications related to PL inhibitor vibralactone will be discussed, including isolation, biosynthesis and synthesis of vibralactone and its derivatives.

Although an array of natural structural types have been shown to affect PL inhibition, a natural β-lactone motif related to vibralactone (**1.01**) has attracted much synthetic interest. A variety of synthetic approaches have been applied to the synthesis of vibralactone and its analogues, and these are overviewed, prior to outlining the Southampton plan for the synthesis of vibralactone.

1.1 Introduction to obesity

Obesity, defined as a BMI (body mass index) of +30 kg/m^2, has become a major contributor to chronic illness and disability.[2] Obesity is caused by a severe imbalance where the energy consumed is greater than the energy expended.[3] This imbalance is normally attributed to the intake of high energy density foods, such as fats (38 kJ/g, compared to 17 kJ/g in carbohydrates).[4] Such imbalances are further exacerbated by sedentary lifestyles, where very low energy expenditure can lead to unhealthy weight gain even with small excesses in calorific intake.[5]

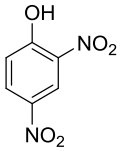
Obesity has been shown to be related to a number of chronic diseases, including; diabetes, hypertension and heart disease, and contributes to more mortality and ill

health worldwide than under nutrition and infectious disease.[6] Since 1980, the number of obese people worldwide has nearly doubled, leading to a figure of nearly 500 million obese adults (20 years and older) alongside ~40 million obese children under the age of 5.[7] This continued increase puts a growing strain on health care systems, and has been estimated to account for 2–6% of all health care costs in a number of developed countries.[8]

Although lifestyle changes to maintain a healthy weight have proven successful in some cases,[9] this method alone is regarded as ineffective[10] due to the inability to sustain these nutritional changes.[11] Complimentary methods for significant and sustained weight loss are therefore required *via* either surgery or pharmacotherapy. Currently, the most effective method for weight loss is bariatric surgery.[12] Such surgical procedures have not only proven effective with weight loss, but have also been related to increased remission rates of type two diabetes.[12,13] Despite these positive observations, surgical patients were no more successful in maintaining weight loss when compared to dieting alone,[14] and eligibility criteria have to be met for surgical treatments, making it unsuitable for certain patients.[15] Also, although the probability of 30 day mortality is classed as low (0.3%), complications such as wound infection, pulmonary events and haemorrhage are much more common, underlining the requirement for the continued development of anti-obesity pharmacotherapy treatments.

1.2 Anti-obesity therapeutics

In the early 1930's, 2,4-dinitrophenol (**1.02**) became the first example of a synthetic anti-obesity drug (**Figure 1.2**).[16] Weight loss was attributed to increased metabolic activity causing fat calories to be dissipated as heat, with suggestions of up to 2–3 pounds a week weight loss.[16] Dinitrophenol use was widespread across the US, with an estimated 100,000 American patients by 1934. However, in 1938 the FDA deemed it too toxic, and removed it from the customer market.[17]

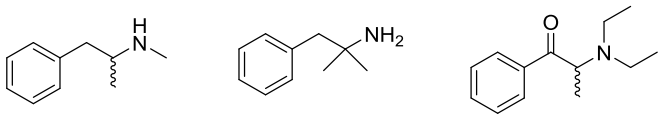


1.02

Figure 1.2: Structure of 2,4-dinitrophenol (**1.02**).

Many alternative drugs have since been used in the treatment of obesity. For example, following the 1947 FDA approval of methamphetamine (**1.03**) for anti-obesity use, a

number of other appetite suppressing derivatives, including phentermine (**1.04**) and diethylpropion (**1.05**), were approved over the next decades (**Figure 1.3**).[18]

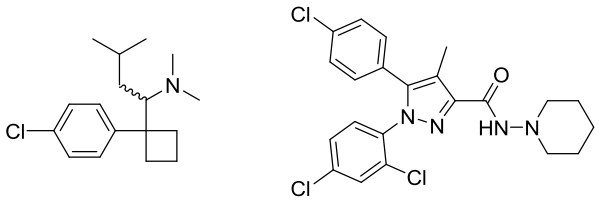


1.03 **1.04** **1.05**

Figure 1.3: Structure of methamphetamine (**1.03**), phentermine (**1.04**) and diethylpropion (**1.05**).

Although amphetamines are still used for the treatment of obesity within America, concerns of increasing amphetamine dependence have led to the restriction to short term use since 1973.[18] Such concerns also led to the banning of amphetamines from the European market since 2000.[19]

More recent FDA approved anti-obesity drugs include sibutramine (**1.06**) and rimonabant (**1.07**) (**Figure 1.4**). Sibutramine (**1.06**), a norepinephrine and serotonin reuptake inhibitor was approved in 1997, showing 10–30% improvement in weight loss maintenance, alongside 4.3% increased weight loss when compared to placebo.[20] Despite these promising results, a study into the effect of sibutramine (**1.06**) on cardiovascular outcomes showed an 11.4% increased chance of serious, nonfatal, cardiovascular event.[21] These results ultimately led to the withdrawal of sibutramine (**1.06**) from the European market in 2010.



1.06 **1.07**

Figure 1.4: Structure of sibutramine (**1.06**) and rimonabant (**1.07**).

A similar development was witnessed with the release of rimonabant (**1.07**). This CB1r antagonist/inverse agonist was shown to produce significant results when compared to placebo in weight loss, lipid concentrations, and insulin resistance.[22] However, a meta-analysis of rimonabant (**1.07**) studies showed patients treated had high rates of psychiatric effects, such as, insomnia, stress and panic attacks.[23] The safety concerns led to the withdrawal of rimonabant (**1.07**) from the US, then European market, by 2009.[19]

These serious side effects raise concerns for classical anti-obesity pharmacotherapy targets, and have led to developments in therapeutic actions on nutrient absorption. These therapies, avoiding any central mechanisms, are becoming promising strategies for modern obesity drugs.[8]

1.3 Pancreatic lipase

Pancreatic lipase (PL) is a gastrointestinal lipolytic enzyme accountable for the hydrolysis of ca. 50–70% of dietary fats.[8] This catalytic hydrolysis converts triglycerides into monoglycerides and fatty acids. These products then form micelles with cholesterol, lysophosphatidic acid (LPA) and bile acids, allowing absorption, where they are resynthesized into triglycerides and stored as fats (**Figure 1.5**).

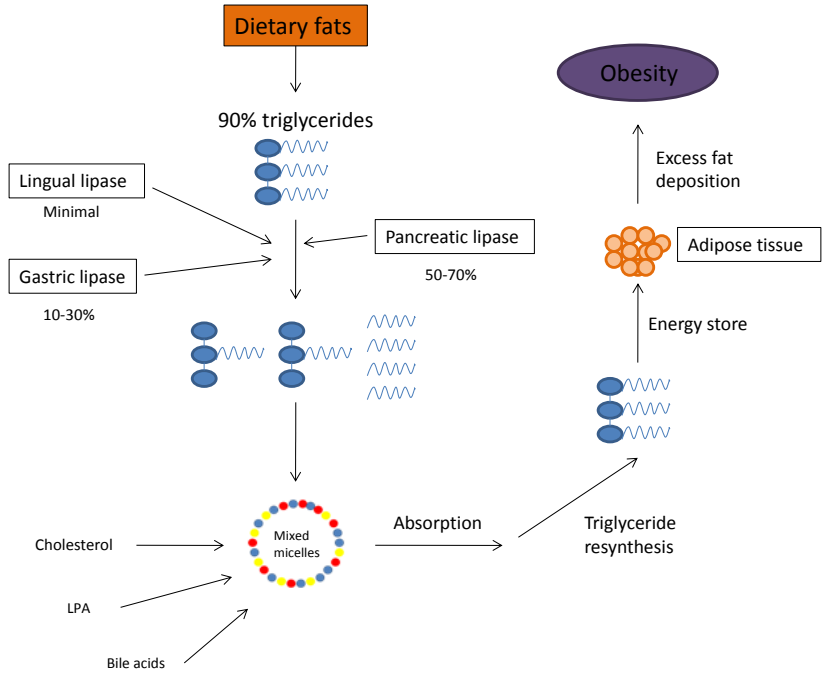
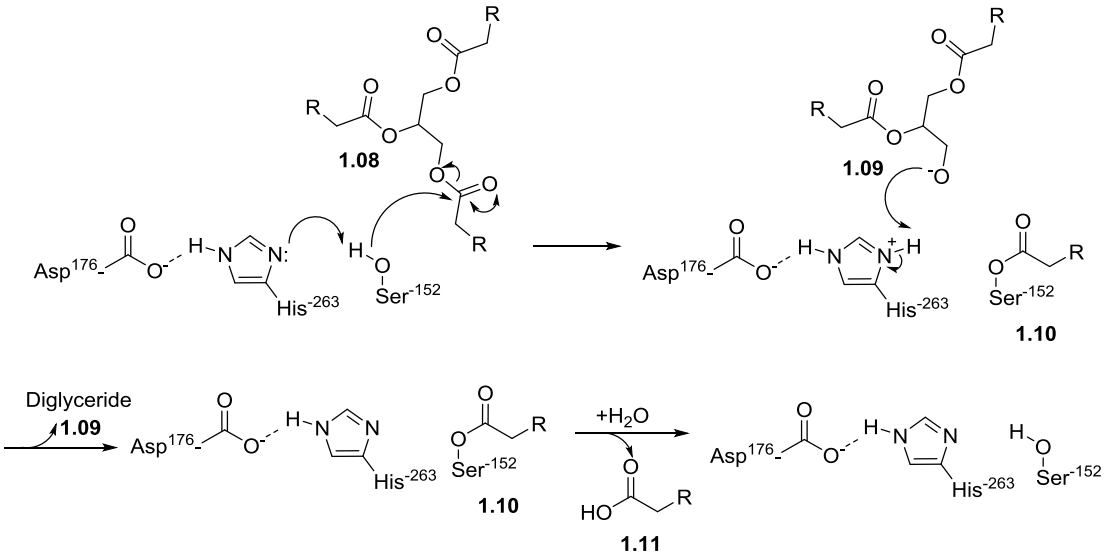


Figure 1.5: Lipolytic processing of triglycerides by pancreatic lipase.

The lipolytic site of PL has been shown to be Ser-152, as part of a catalytic triad with His-263 and Asp-176, analogous to serine protease.[24] The activated serine undergoes a transesterification with the α-ester of the triglyceride (**1.08**), which is then hydrolysed providing the diglyceride (**1.09**) and one fatty acid (**1.11**) (**Scheme 1.1**). This process is repeated on the diglyceride, eventually leading to the absorbable fatty acids and mono-glyceride.



Scheme 1.1: Mechanistic pathway of the hydrolysis of triglycerides (**1.08**) to diglycerides (**1.09**).

This lipolytic process is essential for the absorption of fats, and therefore PL inhibitors can reduce the availability of dietary calories, mimicking reduced food consumption.[25] Consequently, pancreatic lipase inhibition is being exploited for the target of anti-obesity therapeutics. One such approved inhibitor is tetrahydrolipstatin (Orlistat, Roche) (**1.12**), a hydrogenated derivative of natural secondary metabolite lipstatin (**1.13**) (**Figure 1.6**). Tetrahydrolipstatin (**1.12**) has been approved as a PL inhibitor since 1999 [19] and since 2009 has become the only over the counter anti-obesity product (Alli, GSK).[26]

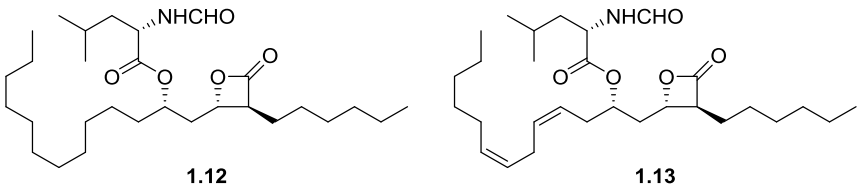


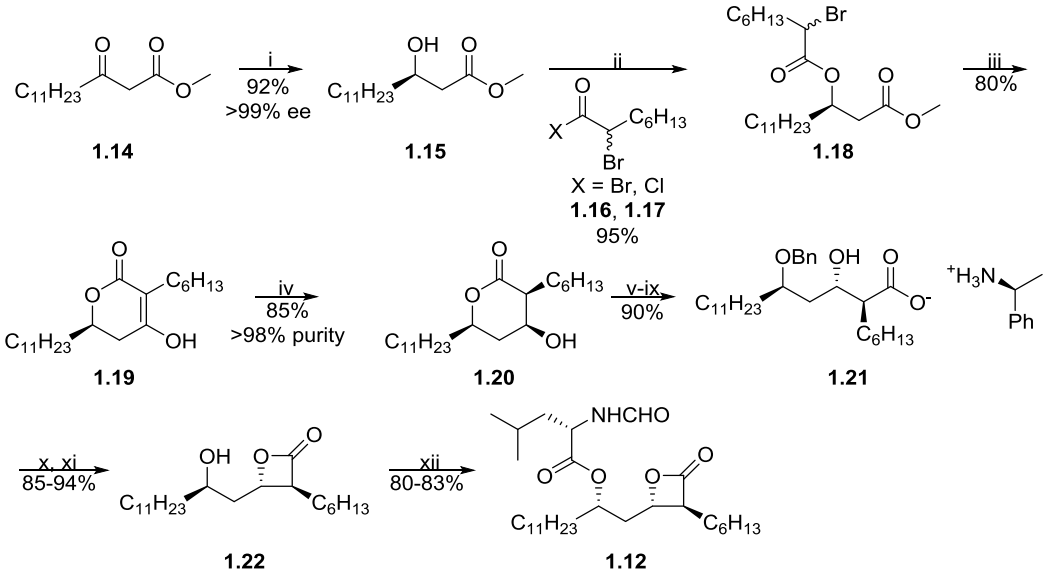
Figure 1.6: Structure of PL inhibitors tetrahydrolipstatin (**1.13**) and lipstatin (**1.13**).

Tetrahydrolipstatin (**1.12**) irreversibly inhibits PL with an IC_{50} of 0.36 μM.[27] The mechanism of inhibition is by covalent modification of the active serine site by acylation with its β-lactone, supported by the dramatic drop in activity in the absence of the β-lactone functionality.[27,28]

Tetrahydrolipstatin (**1.12**) has been shown to improve weight loss with a mean average of 3 kg,[29] whilst lowering fasting blood sugar levels and blood pressure,[30] over 12 months when compared to placebo patients. Although such gastrointestinal side effects as; diarrhoea, flatulence, bloating, abdominal pain, and dyspepsia were noted,[29]

patients reported significantly greater satisfaction with their weight loss medication and programme than placebo patients.[30]

The biological activity of tetrahydrolipstatin (**1.12**) has made it a popular synthetic target. An array of synthetic methods have been applied to its total synthesis including; an *anti* aldol approach,[31] organocatalysed sequential α-aminoxylation/Horner Emmons,[32] and sequential phosphate tethered RCM/CM/hydrogenation pathways.[33] Other noteworthy approaches to related natural products are presented below. The Roche second generation synthesis uses an enantioselective ruthenium hydrogenation, and a diastereoselective Raney nickel hydrogenation (**Scheme 1.2**).[34]

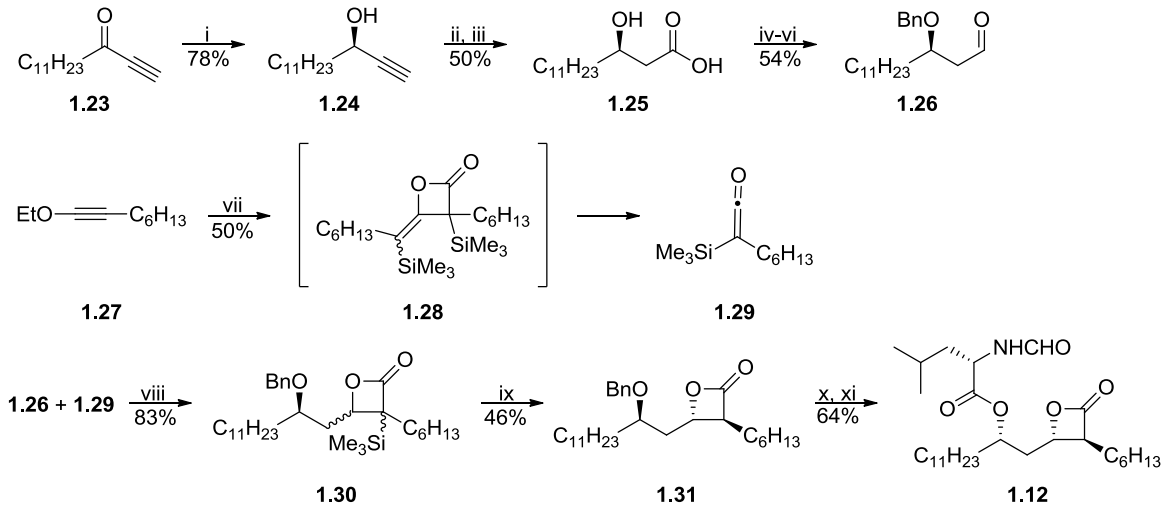


Scheme 1.2: *Reagents and conditions*: i) H_2 (30 bar), [$RuCl_2$((*R*)-MeOBIPHEP)], MeOH. ii) **1.16**, DMAP, K_2CO_3, toluene. iii) *t*-BuMgCl, THF. iv) H_2,Ra-Ni. v) DHP, H^+. vi) NaOH. vii) BnBr, base. viii) H^+, H_2O. ix) (*S*)-PEA purification. x) *p*-TsCl, pyridine. xi) H_2, Pd/C. xii) *N*-formyl-L-leucine, DEAD, PPh_3.

Ruthenium (*R*)-MeOBIPHEP ((*R*)-(+)-(6,6′-Dimethoxybiphenyl-2,2′-diyl)bis(diphenyl-phosphine)) catalysed hydrogenation produced hydroxy-ester **1.15** in high ee. Acylation with acyl bromide **1.16** (commercially available with ca. 3% **1.17**) produced diester **1.18** which was cyclised using *t*-butylmagnesium chloride forming enol **1.19**. Diastereoselective hydrogenation using Raney nickel gave the all *syn*-alcohol **1.20** in high purity. Following protection procedures, crystallisation of the (*S*)-phenylethylamine salt (PEA) **1.21** resolved the single diastereoisomer. Lactonisation followed by deprotection gave lactone **1.22**, which was subsequently coupled with *N*-formyl-L-leucine providing tetrahydrolipstatin (**1.12**) in 41–48% overall yield.

Tetrahydrolipstatin has also previously been synthesised by Kocienski and co-workers at the University of Southampton (**Scheme 1.3**).[35] Ketone **1.23** was enantioselectively

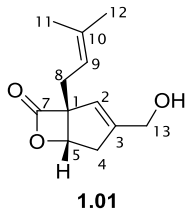
reduced with (*R*)-Alpine-Borane to give alkynol **1.24**, which was subsequently silylated and hydroborated/oxidised, providing hydroxyacid **1.25**. Esterification, benzylation and DIBAL reduction provided the aldehyde intermediate **1.26**. The second fragment **1.29** was synthesised by heating neat alkyne **1.27** with Me_3SiI, forming the tentatively assigned dimer intermediate **1.28**. Subsequent heating under reduced pressure led to ketene **1.29** in 50% yield. Aldehyde **1.26** and ketene **1.29** were then subjected to $BF_3 \cdot OEt_2$, providing a diastereomeric mixture of the cycloadduct **1.30**. Desilylation provided a separable mixture of diastereoisomers by column chromatography, leading to β-lactone **1.31** as a single diastereoisomer. Debenzylation and Mitsunobu esterification with *N*-formyl L-leucine provided tetrahydrolipstatin (**1.12**).



Scheme 1.3: *Reagents and conditions*: i) *R*-Alpine-Borane, 0 °C→rt. ii) *n*-BuLi, THF, -78 °C, then Me_3SiCl, -20 °C→rt, H_2SO_4. iii) dicyclohexylborane, THF, 0 °C, then NaOH, H_2O_2, 40 °C→50 °C. iv) HCl, MeOH, rt. v) benzyltrichloroacetamide, triflic acid, CH_2Cl_2, C_6H_{12}, 10 °C→rt. vi) DIBAL, CH_2Cl_2, -78 °C. vii) Me_3SiI, 70 °C, then 80 °C, 0.5 mm Hg. viii) $BF_3 \cdot OEt_2$, Et_2O, -15 °C→5 °C. ix) TBAF, THF, -80 °C. x) H_2, Pd/C, THF, rt. xi) PPh_3, DEAD, *N*-formyl L-leucine, THF, 0 °C→rt.

1.4 Vibralactone, a natural PL inhibitor

In 2006 vibralactone (**1.01**), a fused β-lactone, was extracted from the culture broth of *Boreostereum Vibrans* (**Figure 1.7**).[1]



1.01

Figure 1.7: Structure of vibralactone (**1.01**).

Vibralactone (**1.01**) was shown to inhibit pancreatic lipase with an IC_{50} of 0.4 μg/mL, making it a potential lead candidate for development of new PL inhibitors. Lui and co-workers[1] were responsible for deducing the chemical structure, using classical methods such as NMR, MS and IR to assign the bicyclic structure. The relative *cis* stereochemistry was tentatively assigned by comparison with literature reports which highlight instability of *trans*-6-oxy-bicyclo[3.2.0]-hept-2-en-7-ones due to the high strain energy of the system. This was supported by MM2 calculations for the *cis* and *trans* steric energies of 34.1 and 68.7 kcal/mol respectively (CS Chem3D Pro). The absolute stereochemistry was assigned using the computational method B3LYP/aug-cc-pVDZ//B3LYP/6-31G(d). Calculated optical rotations of −127.4° and +127.4° were compared to the experimental value of −135.1°, suggesting an absolute stereochemistry of 1*R*,5*S*. The relative and absolute stereochemistry was later confirmed by the first racemic and asymmetric syntheses of vibralactone (**1.01**).[36,37]

1.4.1 Alternative biological applications of vibralactone

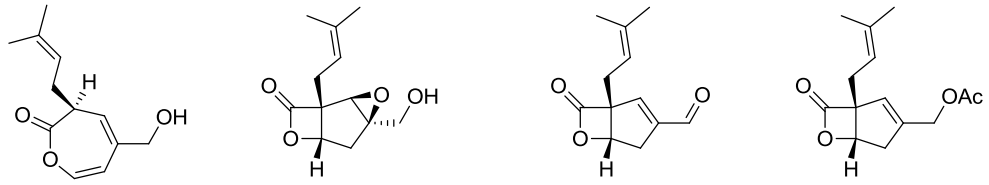
In 2011 vibralactone (**1.01**) was used to probe and label isoforms of the caseinolytic peptidase enzyme.[38] This enzyme has been shown to play a central role in bacterial virulence.[39] Vibralactone analogues were successfully used to study the activity and assembly of these isoforms, subsequently leading to electron microscopic images of the complex porous assembly of these important classes of bacterial enzymes.

Vibralactone's demonstrated ability to bind to the caseinolytic peptidase enzyme could allow further developments of this natural product for the use as an anti-bacterial therapeutic. Sieber *et al.*[40] previously showed a number of natural β-lactones to be inhibitors of this virulence regulator in *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus* (MRSA). Potent examples completely eliminated haemolytic and

proteolytic activity in each of these strains, demonstrating the potential uses of vibralactone analogues beyond those focussed on within this thesis.

1.4.2 Derivatives of vibralactone

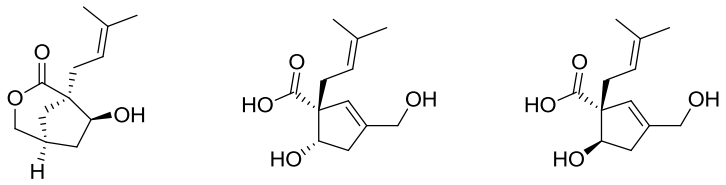
Since the isolation of vibralactone (**1.01**), a number of derivatives have also been isolated from *Boreostereum vibrans*. In 2008 Lui and co-workers[41] reported the extraction of the 4 derivatives; 1,5-secovibralactone (**1.32**), vibralactone B (**1.33**), vibralactone C (**1.34**) and acylated vibralactone (**1.35**) (**Figure 1.8**). Each structure was determined using NMR, IR and MS. The absolute stereochemistry of 1,5-secovibralactone (**1.32**) was tentatively assigned by comparison of optical rotation values obtained from the computational method B3LYP/aug-cc-pVDZ//B3LYP/6-31G*, identifying the *S* configuration. The relative stereochemistry about the epoxide in vibralactone B (**1.33**) was assigned by ROESY experimentation. Surprisingly, no biological data was provided on any of these extracts.



1.32 **1.33** **1.34** **1.35**

Figure 1.8: Structure of 1,5-secovibralactone (**1.32**), vibralactone B (**1.33**), C (**1.34**), and acylated vibralactone (**1.35**).

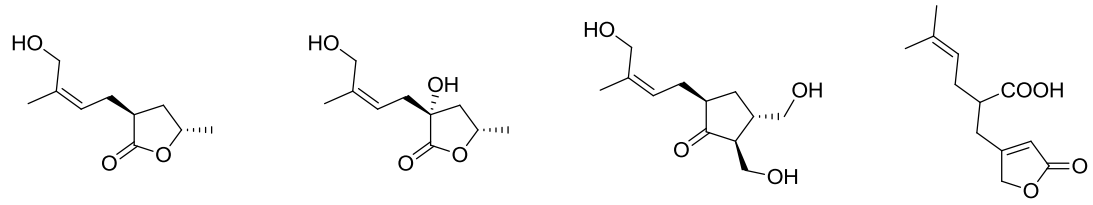
In 2009, 3 more components were isolated,[42] vibralactone D (**1.36**), E (**1.37**) and F (**1.38**) (**Figure 1.9**). X-ray analysis yielded the structure and relative stereochemistry of vibralactone D (**1.36**). The absolute stereochemistry was assigned using the modified Mosher's method.[43] NMR, MS and IR establish the structure of vibralactone E (**1.37**) and F (**1.38**), and the di-MTPA esters of each inferred the secondary hydroxyl groups to be 5*S* and 5*R* respectively. ROESY experiments were used to assign the absolute stereochemistry as 1*R*,5*S* for **1.37**, and 1*R*,5*R* for **1.38**. Each extract's inhibitory effects on the human and mouse 11-β hydroxysteroid dehydrogenases (11β-HSD1 and 11β-HSD2), enzymes accountable for the regulation of intracellular cortisol/cortisone concentrations, were then investigated. These enzymes have been shown to play important roles in insulin resistance, obesity and hypertension.[44] Vibralactone D (**1.36**) showed inhibitory activity with IC_{50} values of; 11β-HSD1 human = 85.7 μM, mouse = 295.2 μM and 11β-HSD2 = 87.1 μM. Vibralactone E (**1.37**) and F (**1.38**) showed weak activity of; 43.6% and 31.2% inhibition of 11β-HSD1, and 37.7% and 24.8% inhibition of μM 11β-HSD2 respectively, each at 150 μM.



1.36 **1.37** **1.38**

Figure 1.9: Structure of vibralactone D (**1.36**), E (**1.37**) and F (**1.38**).

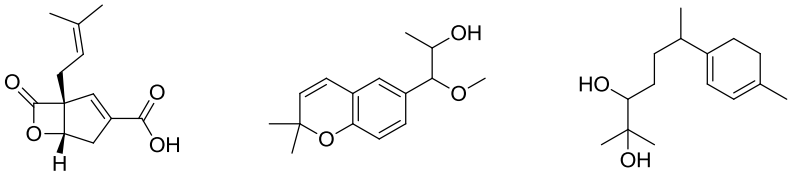
In 2012, another 4 derivatives were described, vibralactone G (**1.39**), H (**1.40**), I (**1.41**) and J (**1.42**) (**Figure 1.10**).[45] The structures of each of these compounds were deduced using MS, IR and NMR spectroscopy. No absolute stereochemical or biological data have been disclosed for these derivatives.



1.39 **1.40** **1.41** **1.42**

Figure 1.10: Structures of vibralactone G (**1.39**), H (**1.40**), I (**1.41**) and J (**1.42**).

Finally, in 2013 Lui's group published the extraction of vibralactone H (**1.43**), along with two novel compounds vibranether (**1.44**) and myrrhlalkyldiol (**1.45**) (**Figure 1.11**).[46] Each structure was established using spectroscopic techniques. These compounds were tested against 6 cancer cell lines, SK-BR-3 breast, SMMC-7721 hepatocellular carcinoma, HL-60myeloid leukaemia, PANC-1 pancreatic cancer, and A-549 lung cancer, although no significant activity was detected (IC_{50} >40 μM).



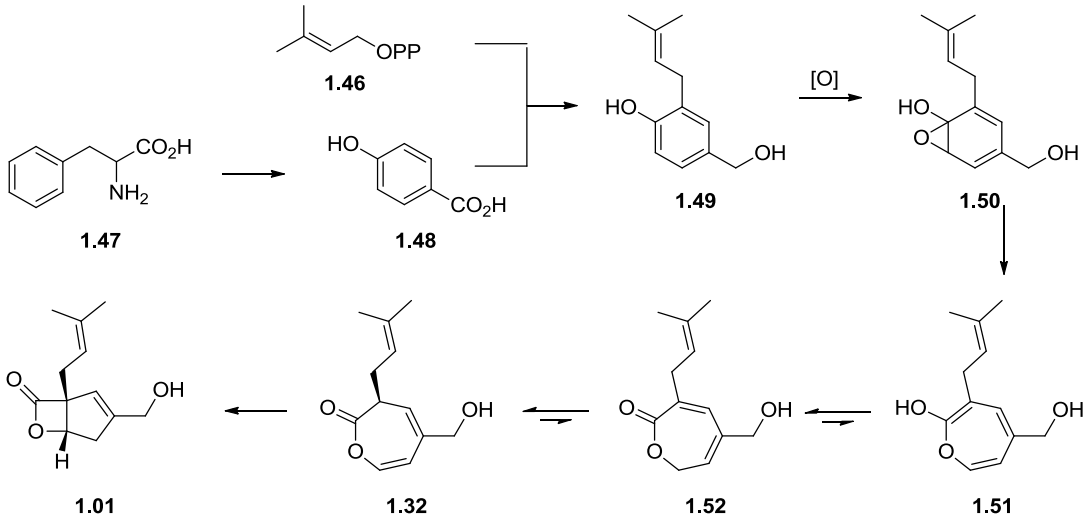
1.43 **1.44** **1.45**

Figure 1.11: Structures of vibralactone H (**1.43**), vibranether (**1.44**) and myrrhlalkyldiol (**1.45**).

1.4.3 Biosynthesis of vibralactone

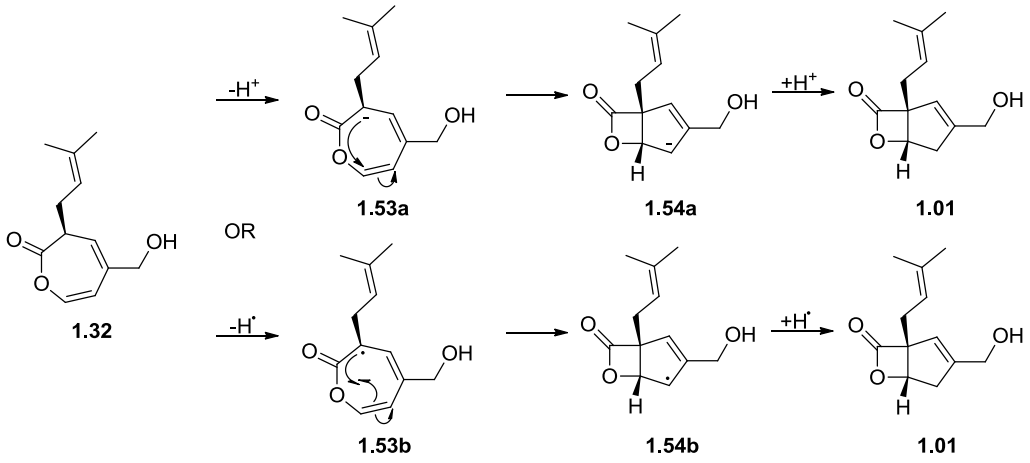
In 2013, Zhao *et al.*[47] established the biosynthetic origin of vibralactone (**1.01**). Derived from phenylalanine (**1.47**), prenylation of hydroxy-acid **1.48** is believed to precede oxidative expansion of the aromatic moiety *via* epoxide intermediate **1.50**. Cyclic

intermediate **1.51** can then tautomerize into the isolated natural product 1,5-secovibralactone (**1.32**).[41] **1.32** then undergoes an intramolecular ring contraction to form the bicyclic structure of vibralactone (**1.01**) (**Scheme 1.4**).



Scheme 1.4: Zhao's proposed biosynthesis of vibralactone (**1.01**).

Two speculative mechanisms for the unusual ring contraction were base induced enolate formation (**1.53a**) followed by nucleophilic ring closure (**1.54a**), or a single electron oxidation α to the carbonyl (**1.53b**), followed by radical cyclisation (**1.54b**) (**Scheme 1.5**).[48]



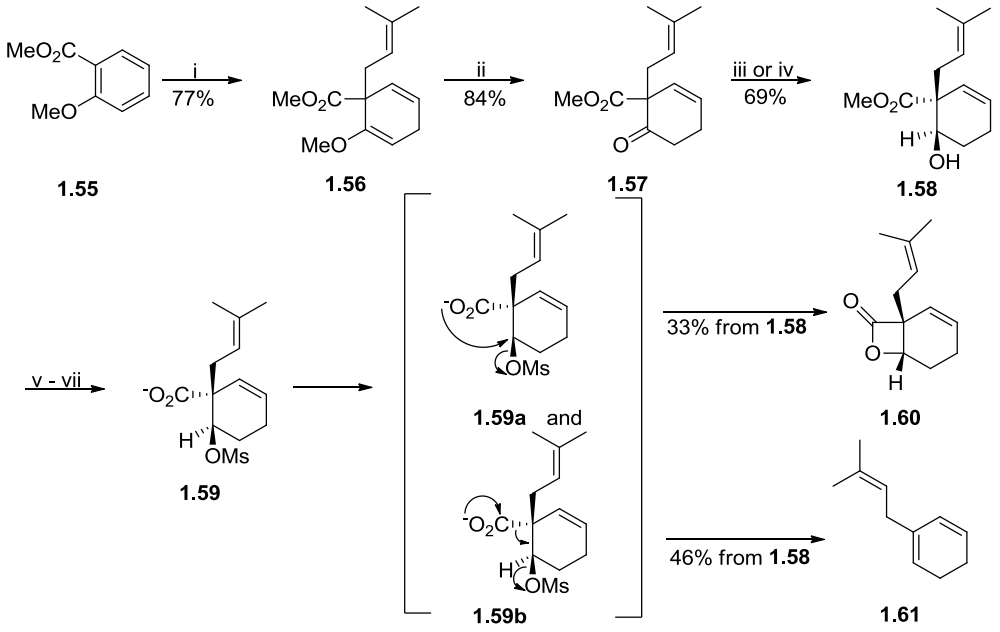
Scheme 1.5: Proposed anionic and radical cyclisation in the biosynthesis of vibralactones fused bicyclic core.

This ring contraction opposes the biosynthetic route proposed by Lui *et al.* where each isolated vibralactone analogue descends from vibralactone (**1.01**).[42,45,41]

1.4.4 Snider's total synthesis of (±)-vibralactone

In 2008, Snider *et al.*[36] reported the first total synthesis of (±)-vibralactone (**1.01**), using an aldol condensation as the key cyclopentene ring-forming step.

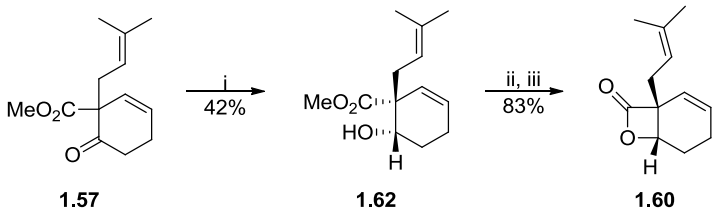
Birch reductive alkylation of methyl methoxybenzoate (**1.55**) gave prenyl derivative (**1.56**), which was subsequently hydrolysed with methanolic HCl, providing β-keto ester (**1.57**). *Trans*-hydroxy ester (**1.58**) was obtained in an optimised yield of 69% by diastereoselective reduction using $Zn(BH_4)_2$ (single diastereoisomer) or $CaCl_2/NaBH_4$ (crude dr. 2:1). Following ester saponification, a Mitsunobu type lactonisation was investigated (**Scheme 1.6**), forming model *cis*-fused β-lactone **1.60**. Hydrolysis of **1.58**, treatment with excess MsCl, followed by hydrolysis at the more activated anhydride position gave carboxylate **1.59**. Spontaneous lactonisation with inversion (**1.59a**) under the reaction conditions gave lactone **1.60** in 33% from **1.58**. Unfortunately, Grob fragmentation (**1.59b**), presumably enhanced by the fixed antiperiplanar configuration of the hydroxyacid,[49] provided triene **1.61** as the major product in 46%.



Scheme 1.6: *Reagents and conditions*: i) a) K, NH_3, *t*-BuOH –78 °C. b) LiI, –78 °C. c) prenyl bromide, –78 °C→25 °C. ii) MeOH, 5% aq. HCl. iii) $NaBH_4$, $CaCl_2$, MeOH. iv) $Zn(BH_4)_2$, Et_2O. v) KOH, MeOH, 60 °C. vi) 3 eq. MsCl, 4 eq. Et_3N, CH_2Cl_2, 0 °C. vii) aq. $NaHCO_3$, THF, 25 °C.

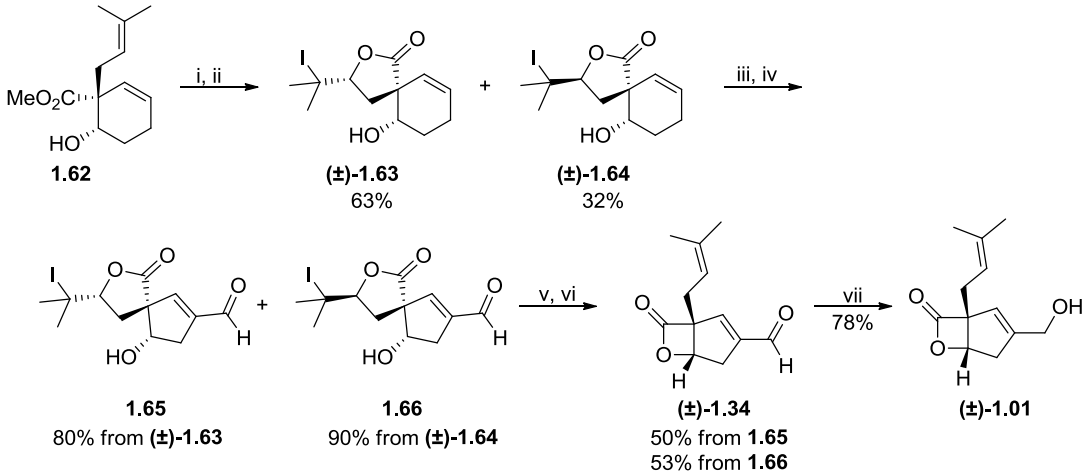
The Grob fragmentation deemed the *trans*-orientated acid **1.59** unsuitable, and therefore lactonisation utilising acid activation was investigated (**Scheme 1.7**). The opposite diastereoselectivity could be obtained from the reduction of ketone **1.57** (3:2 **1.62**:**1.58**) with $Me_4N \cdot BH_4$, providing **1.62** in 42% (alongside 40% of a 1:2 mixture of

1.62:**1.58**, which could be recycled by oxidation to ketone **1.57**). Hydrolysis, followed by treatment with TsCl in pyridine produced model β-lactone **1.60** in 83% from **1.62**.



Scheme 1.7: *Reagents and conditions*: i) $Me_4N \cdot BH_4$, 1:1 THF/MeOH, 25 ˚C. ii) KOH, MeOH, 60 ˚C. iii) *p*-TsCl, pyridine.

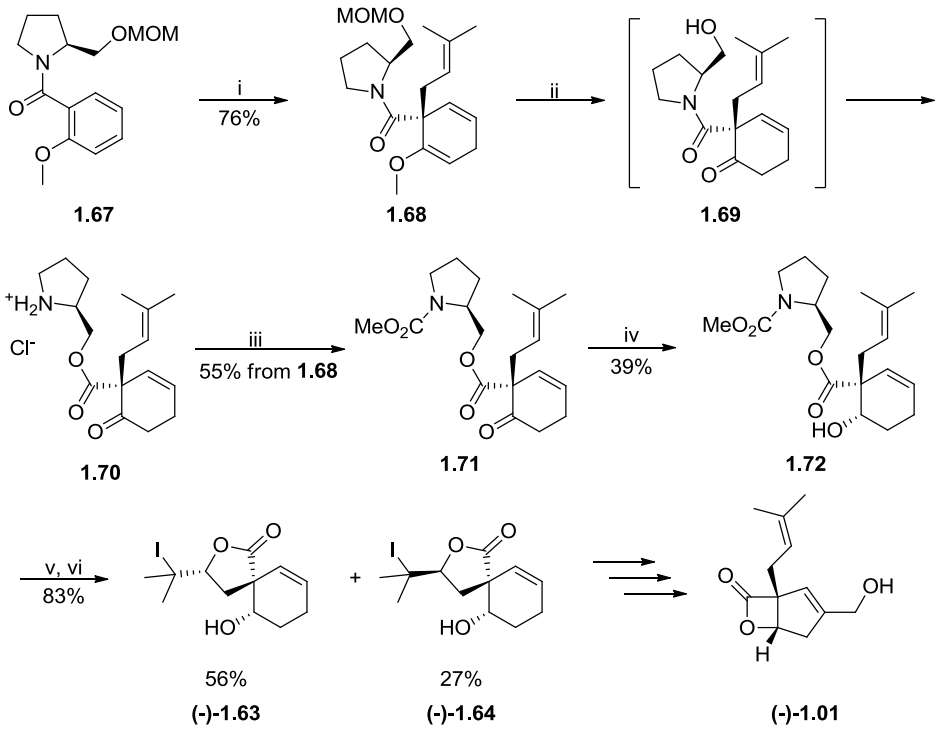
The acid activation approach was then applied to the total synthesis of vibralactone (**1.01**) (**Scheme 1.8**). Following hydrolysis of *cis* hydroxy ester **1.62**, protection of the more electron rich alkene was achieved by iodolactonisation. Treatment with $NaHCO_3$, I_2 and KI give iodolactones **1.63** and **1.64**, which were separated for analytical purposes. X-ray analysis of lactone **1.64** was used to confirm the relative *cis* stereochemistry of hydroxy ester **1.62**. Each isomer was separately ozonised, and following workup, immediately subjected to an intramolecular aldol condensation with $Bn_2NH \cdot TFA$, providing cyclopentenals **1.65** and **1.66**. Each diastereoisomer was then separately deprotected using zinc, then lactonised to provide (±)-vibralactone C (**1.34**). Subsequent aldehyde reduction using $NaBH_4$ gave vibralactone (**1.01**) in 9% over 10 steps.



Scheme 1.8: *Reagents and conditions*: i) KOH, MeOH, 60 ˚C. ii) $NaHCO_3$, I_2, KI, THF, H_2O, 25 ˚C. iii) O_3, 1:1 CH_2Cl_2/MeOH, -78 ˚C, then PPh_3, -78 ˚C→25 ˚C. iv) $Bu_2NH \cdot TFA$, benzene, 25 ˚C. v) Activated Zn, 4:1 THF/HOAc, 0 ˚C. vi) *p*-TsCl, pyridine. vii) $NaBH_4$, 100:1 DME/H_2O.

1.4.5 Snider's total synthesis of (–)-vibralactone

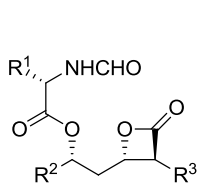
Snider *et al.* subsequently applied their approach to the enantioselective synthesis of (–)-vibralactone (**1.01**) (**Scheme 1.9**).[37] Birch reductive alkylation of 2-methoxymethoxymethylpyrrolidine 2-methoxybenzamide (**1.67**) provided cyclohexadiene **1.68** as a single diastereoisomer. MOM deprotection provided **1.69** which successively rearranged forming ammonium ester **1.70**. Subsequent treatment with methyl chloroformate gave carbamate **1.71**. Keto-reduction using $Me_4N \cdot BH_4$ in MeOH provided a 3:2 mixture of *cis*-**1.72**:*trans*-**1.72**, giving 39% of *cis*-**1.72** after purification (along with 45% of a 1:3 mixture of *cis*-**1.72**:*trans*-**1.72**, which could be recycled by oxidation to ketone **1.71** with Dess-Martin periodinane). Hydrolysis and iodolactonisation provided diastereoisomers (–)-**1.63** and (–)-**1.64** as single enantiomers. The absolute stereochemistry of iodolactone (–)-**1.64** was confirmed by X-ray analysis. The reaction sequence then mirrored the racemic synthesis of (±)-vibralactone (**1.01**),[36] leading to (–)-vibralactone (**1.01**) in 4.8% over 11 steps.

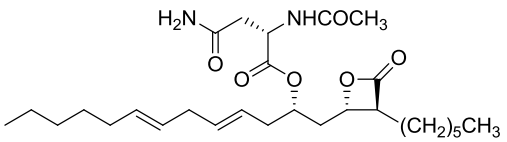


Scheme 1.9: *Reagents and conditions*: i) a) K, NH_3, *t*-BuOH –78 °C. b) prenyl bromide, –78 °C→25 °C. ii) MeOH, 10% aq. HCl, microwave, 60 °C. iii) $NaHCO_3$, $ClCO_2Me$, CH_2Cl_2. iv) $Me_4N \cdot BH_4$, MeOH, 25 °C. v) MeOH, 3.5 M aq. KOH, 60 °C. vi) $NaHCO_3$, I_2, KI, THF, H_2O, 25 °C.

1.5 Related natural β-lactone PL inhibitors and their syntheses

Since 1978, there have been many structurally similar PL inhibitors extracted from microbial sources. Each of these contain the same motif of a branched (*S*,*S*)-β-lactone, with (*S*)-branching *N*-functionalised amino acids (**Figure 1.12**).





Esterastin **1.79** 0.2 ng/mL (hog PL)

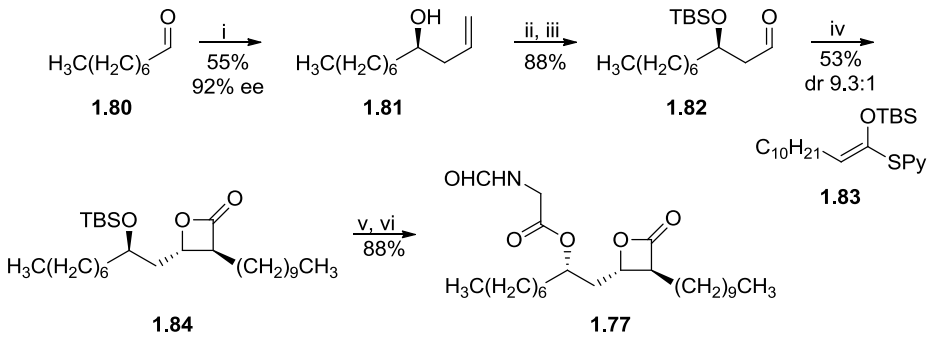
Name		R^1	R^2	R^3	IC_{50}
Lipstatin	**1.13**	$CH_2CH(CH_3)_2$	$(CH_2CHCH)_2(CH_2)_4CH_3$	$(CH_2)_5CH_3$	0.14 μM (porcine PL)
Valilactone	**1.73**	$CH(CH_3)_2$	$(CH_2)_4CH_3$	$(CH_2)_5CH_3$	0.14 ng/mL (hog PL)
Panclicin A	**1.74**	CH_3	$(CH_2)_6CH_3$	$(CH_2)_7CH(CH_3)_2$	2.9 μM (porcine PL)
Panclicin B	**1.75**	CH_3	$(CH_2)_6CH_3$	$(CH_2)_9CH_3$	2.6 μM (porcine PL)
Panclicin C	**1.76**	H	$(CH_2)_6CH_3$	$(CH_2)_7CH(CH_3)_2$	0.62 μM (porcine PL)
Panclicin D	**1.77**	H	$(CH_2)_6CH_3$	$(CH_2)_9CH_3$	0.66 μM (porcine PL)
Panclicin E	**1.78**	H	$(CH_2)_6CH_3$	$(CH_2)_{11}CH_3$	0.89 μM (porcine PL)

Figure 1.12: Naturally occurring β-lactone PL inhibitors.

Due to their biological potential, a number of groups have undertaken stereoselective syntheses of these natural products, and the varying synthetic approaches are presented below.

1.5.1 The Romo approach

In 1997, Romo and Yang published the first enantioselective synthesis of panclicin D (**1.77**),[50] using a diastereoselective tandem Mukaiyama aldol-lactonisation (TMAL) (**Scheme 1.10**). The first stereogenic centre was installed using a Brown allylation[51] of *n*-octanal (**1.80**) with *d*-*B*-allyldiisopinocampheylborane (^{d}Ipc2-Ball^a), providing homoallylic alcohol **1.81** in 92% ee. Alcohol protection and ozonolysis provided TMAL precursor **1.82**. This aldehyde (**1.82**) was subjected to TMAL with thioacetal **1.83**, giving β-lactone **1.84** with a dr of 9.3:1. Following alcohol deprotection, each diastereoisomer could be separated, and a Mitsunobu reaction with *N*-formylglycine provided (–)-panclicin D (**1.77**) in 20% yield over 6 steps from *n*-octanal.

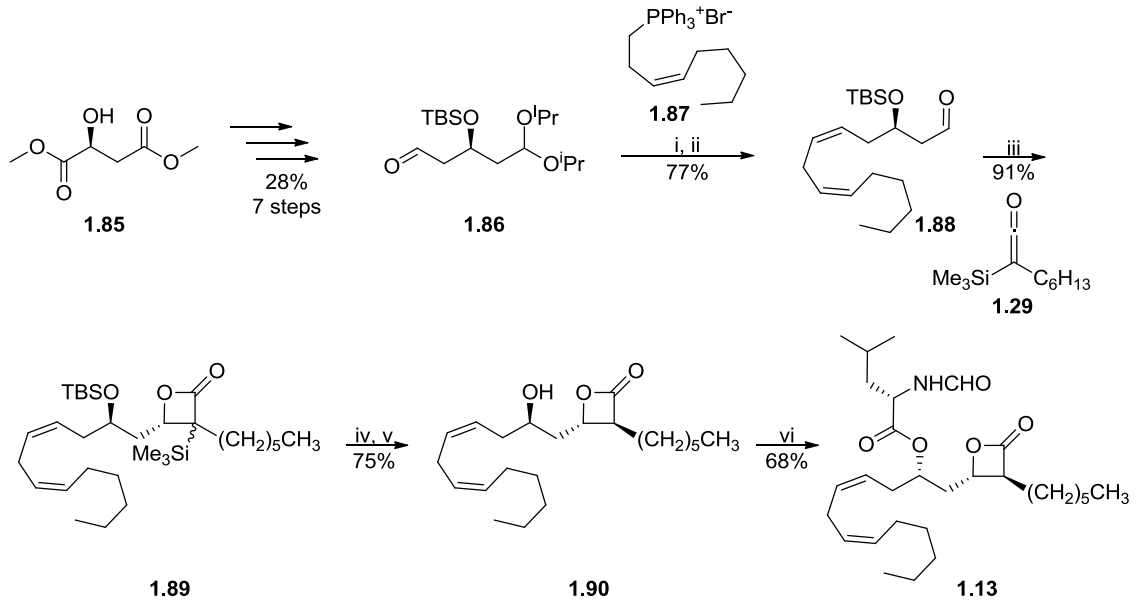


Scheme 1.10: *Reagents and conditions*: i) *d-B*-allyldiisopinocampheylborane. ii) TBSCl, imidazole. iii) O_3, then Me_2S, Et_3N. iv) **1.83**, $ZnCl_2$. v) 48% aq. HF. vi) *N*-formylglycine, DIAD, PPh_3.

The Romo group also more recently applied this approach to the synthesis and derivatisation of tetrahydrolipstatin (**1.12**) and valilactone (**1.73**),[52] although an enantioselective Noyori reduction replaced the Brown allylation when installing the initial stereocentre.

1.5.2 The Kocienski approach

Alongside their synthesis of tetrahydrolipstatin (see section 1.3), Kocienski *et al*. have applied similar diastereocontrol to the only total synthesis of lipstatin (**1.13**),[53,54] using a [2+2] cycloaddition for the formation of the β-lactone (**Scheme 1.11**). From dimethyl-(*S*)-malate (**1.85**), regioselective reduction, followed by suitable functionalisation and homologation provided aldehyde **1.86** in 7 steps. **1.86** was subsequently subjected to a Wittig reaction with **1.87**, forming *cis*-dienal **1.88**. [2+2] cycloaddition with silylketene **1.29** provided a mixture of the 4 inseparable lactone diastereoisomers (**1.89**). Silyl ether deprotection followed by *C*-silyl deprotection afforded separable diastereoisomers, allowing isolation of the required *anti-trans* lactone **1.90**. Mitsunobu reaction with *N*-formyl L-leucine provided (–)-lipstatin (**1.13**).

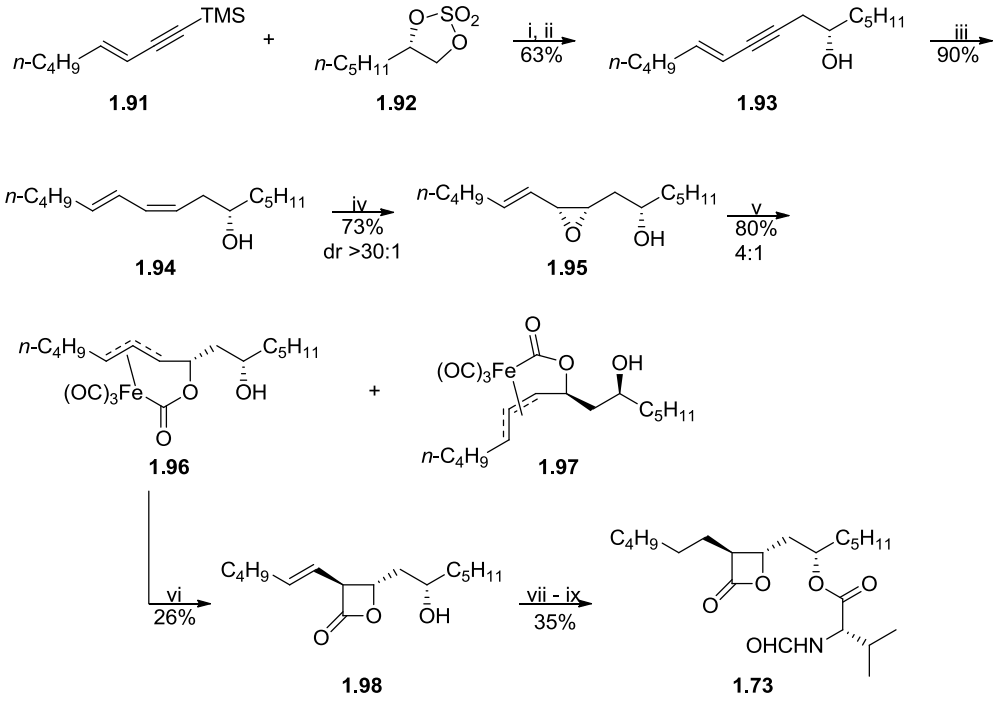


Scheme 1.11: *Reagents and conditions*: i) a) **1.87**, $NaN(SiMe_3)_2$, THF, –30 °C→rt. b) aldehyde **1.86**, –90 °C→rt. ii) TsOH, THF, H_2O, Δ. iii) **1.29**, $EtAlCl_2$, Et_2O, –45 °C→–20 °C. iv) 40% aq. HF, MeCN, 0 °C. v) TBAF, THF, –90 °C. vi) *N*-formyl L-leucine, DEAD, PPh_3, THF.

Kocienski *et al*. later applied this diastereoselective [2+2] cycloaddition to the synthesis of panclicins A–E (**1.74**–**1.78**),[55] substituting the lengthy synthesis of the appropriate alcohol from malate derivative **1.85**, with the enantioselective Noyori reduction of an appropriate β-ketoester.

1.5.3 The Ley approach

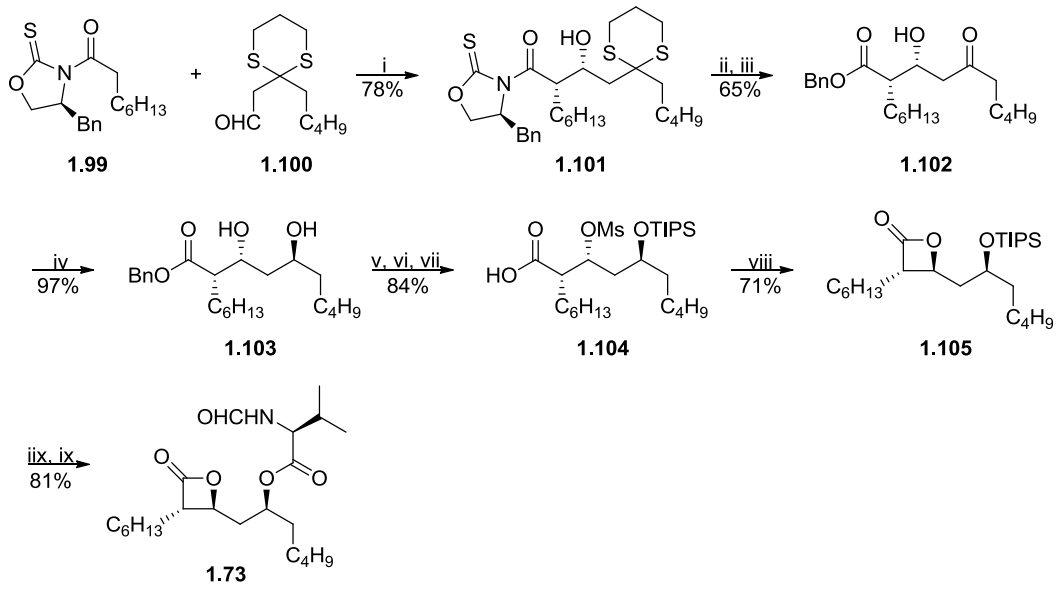
In 1991, Ley reported an alternative approach to valilactone (**1.73**), using an iron catalysed carbonyl insertion (**Scheme 1.12**).[56,57] Cyclic sulfate **1.92** was coupled with silylacetylene **1.91** leading to (*S*)-alcohol **1.93**, which was reduced providing *cis*-alkene **1.94**. Homoallylic alcohol **1.94** was then regio and diastereoselectively epoxidised using $VO(acac)_2$, providing a dr of >30:1. Epoxide **1.95** was subsequently treated with diiron nonacarbonyl providing a separable mixture of the two insertion complexes **1.96** and **1.97**. **1.96** was treated with ceric ammonium nitrate, providing β-lactone **1.98**. Esterification with N-Cbz-L-valine, followed by hydrogenation then formylation, gave (–)-valilactone (**1.73**).



Scheme 1.12: *Reagents and conditions*: i) MeLi, THF, 3 h, 0 ˚C→rt. ii) 20% H_2SO_4. iii) Zn(Cu/Ag), MeOH, H_2O, 50 ˚C. iv) $VO(acac)_2$, *t*-BuOOH, CH_2Cl_2, 0 ˚C→rt. v) $Fe_2(CO)_9$, THF. vi) CAN, EtOH, rt. vii) *N*-Cbz L-valine, DCC, CH_2Cl_2, 0 ˚C, then DMF, DMAP, rt. viii) H_2, Pd/C, THF. ix) AcOCHO, CH_2Cl_2.

1.5.4 The Wu approach

More recently, Wu *et al.*[58] demonstrated an aldol-based approach to valilactone (**1.73**) (**Scheme 1.13**). A diastereoselective *syn* aldol was undertaken between substrates **1.99** and **1.100** using $TiCl_4$, providing the 'Evans'[59] enantiomer **1.101**. Auxiliary removal and deprotection provided ketone **1.102** which was diastereoselectively reduced with $Me_4N \cdot BH(OAc)_3$ producing *anti*-diol **1.103**. Regioselective alcohol protection, reduction and alcohol activation gave acid **1.104**, which upon lactonisation with inversion provided *trans*-lactone **1.105**. TIPS deprotection and coupling with (*S*)-*N*-formyl-L-valine provided valilactone (**1.73**).

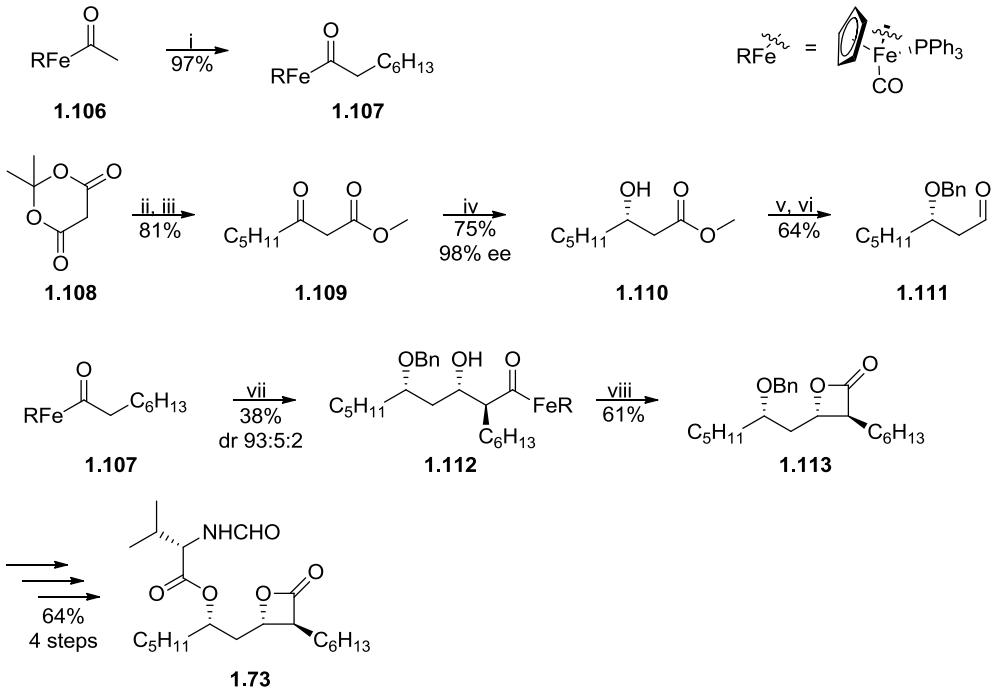


Scheme 1.13: *Reagents and conditions*: i) $TiCl_4$, TMEDA, CH_2Cl_2, 0 ˚C. ii) BnOH, DMAP, CH_2Cl_2, rt. iii) I_2, $NaHCO_3$, acetone, H_2O, 0 ˚C. iv) $Me_4N \cdot BH_4(OAc)_3$, AcOH, MeCN, -15 ˚C. v) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 ˚C. vi) MsCl, Et_3N, CH_2Cl_2, 0 ˚C. vii) $Pd(OH)_2$, H_2, EtOAc, MeOH, rt. viii) K_2CO_3, THF, rt. iix) HF.pyridine, THF, rt. ix) DCC, DMAP, *N*-formyl L-valine, CH_2Cl_2, rt.

1.5.5 The Davies approach

Davies *et al*.[60] have also described an aldol approach to valilactone (**1.73**), using an iron auxiliary **1.107**, derived from the ethanal derivative **1.106** (**Scheme 1.14**). The Davies group previously devised a means of kinetic resolution of the acyl auxiliary **1.106**.[61]

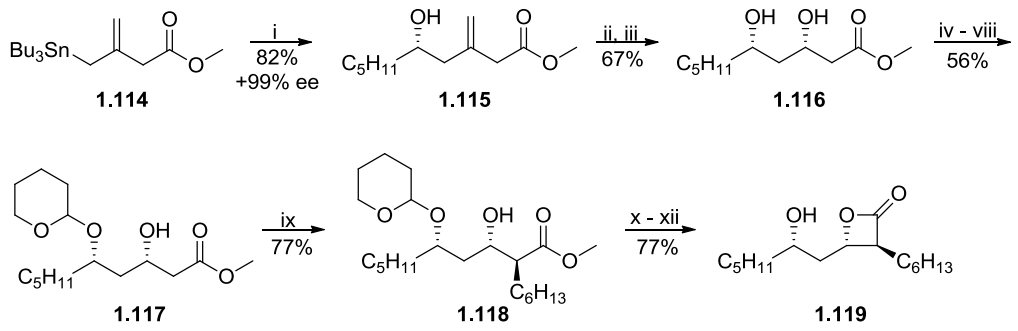
Acylation of Meldrum's acid (**1.108**), followed by decarboxylation in MeOH provided β-ketoester **1.109**. Noyori hydrogenation afforded hydroxyester **1.110** in 99% ee, which was protected and reduced giving aldehyde **1.111**. Aldehyde **1.111** was then subjected to an aldol reaction with iron complex **1.107**, using $AlEt_2Cl$ as the Lewis acid, providing *anti*-diastereocontrol (**1.112**). Auxiliary removal and in situ lactonisation provided β-lactone **1.113**, which was then converted to valilactone (**1.73**) by benzyl deprotection, coupling with *N*-Cbz-L-valine, hydrogenation and *N*-formylation. This approach was also applied to the synthesis of tetrahydrolipstatin (**1.12**) within the same paper.



Scheme 1.14: *Reagents and conditions*: i) BuLi, THF, –78 ˚C then $C_6H_{13}I$, THF, –78 ˚C→rt. ii) $C_5H_{11}COCl$, pyridine, CH_2Cl_2. iii) MeOH, Δ. iv) Ru[(*S*)-BINAP]Cl_2, H_2 (100 atm), EtOH, rt. v) Benzyltrichloroacetimidate, CF_3SO_3H, 2:1 cyclohexane/CH_2Cl_2, rt. vi) DIBAL, –78 ˚C. vii) a) BuLi, THF, –78 ˚C. b) Et_2AlCl, –40 ˚C. c) **1.111**, –98 ˚C then MeOH. viii) Br_2, CH_2Cl_2, –78 ˚C then Et_3N, –78 ˚C→rt.

1.5.6 The Mineeva approach

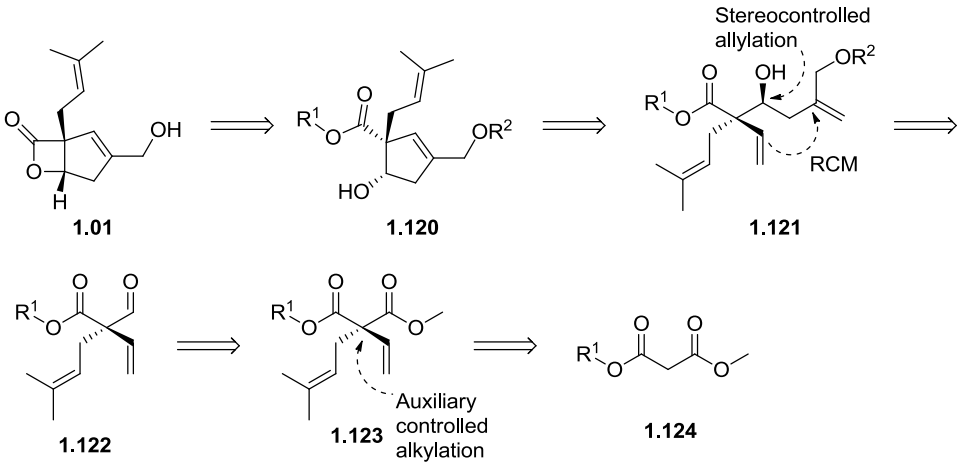
The most recently published approach to the β-lactone pancreatic lipase inhibitors was a formal synthesis of valilactone (**1.73**) reported by Mineeva (**Scheme 1.15**).[62] Allyl stannane **1.114** was reacted with hexanal under Keck conditions ((*R*)-BINOL, Ti(O*i*-Pr)$_4$) providing chiral homoallylic alcohol **1.115** in +99% ee. Ozonolysis, followed by *syn*-selective reduction with $NaBH_4$/Ti(O*i*-Pr)$_4$ provided *syn*-diol **1.116**. Following extended protection group manipulation, a diastereoselective alkylation of alcohol **1.117** provided intermediate **1.118** (no dr was provided). Ester hydrolysis, and lactonisation followed by acid deprotection completed the formal synthesis of valilactone (**1.73**).



Scheme 1.15: *Reagents and conditions*: i) $C_5H_{11}CHO$, (*R*)-BINOL, $Ti(O\textit{i}\text{-}Pr)_4$, CH_2Cl_2. ii) O_3, CH_2Cl_2 then PPh_3.iii) $Ti(O\textit{i}\text{-}Pr)_4$, $NaBH_4$, THF. iv) TsOH, PhH. v) TBSCl, imidazole, CH_2Cl_2. vi) Et_3N, MeOH. vii) DHP, PPTS, CH_2Cl_2. viii) TBAF, THF. ix) LDA, $C_6H_{13}Br$, THF. x) NaOH, MeOH, H_2O. xi) *p*-TsCl, pyridine. xii) PPTS, MeOH.

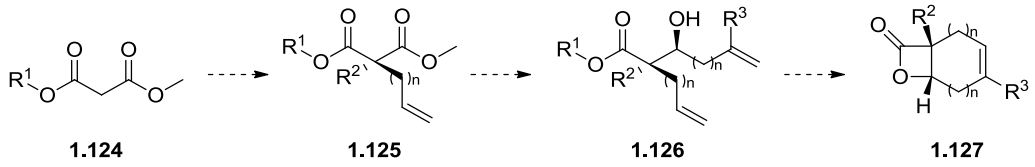
1.6 The Southampton approach to vibralactone

The distinct chemical structure of vibralactone (**1.01**) when compared to related pancreatic lipase inhibitors makes it a very interesting synthetic target. The approach described in this thesis was initially focussed around use of ring closing metathesis for the construction of vibralactone's cyclopentene ring (**Scheme 1.16**). As described by Snider *et al*.,[36,37] it is known that for subsequent lactonisation to be successful, the *cis* hydroxy ester **1.120** is required, and thus we can deduce the required stereochemistry of triene **1.121**. This RCM precursor (**1.121**) was envisioned to be formed by a stereoselective allylation of aldehyde **1.122** which could be derived from vinylic malonate **1.123**. From simple malonate starting materials (**1.124**), suitable alkylation and elimination procedures could be applied in the synthesis of the vinyl-prenyl malonate **1.123**. It was proposed that the absolute stereochemistry of this vinylic intermediate (**1.123**) could be controlled by application of a novel cyclohexyl chiral auxiliary recently developed within the Brown laboratory in Southampton.



Scheme 1.16: The Southampton synthetic plan for vibralactone (**1.01**), using an RCM.

The outlined synthesis plan was intended to be applicable to the derivatisation of vibralactone (**1.01**). As shown with tetrahydrolipstatin (**1.12**), minor structural modifications can aid the drug-like characteristics of a compound, and so we were keen to allow such adaptations to our total synthesis (**Scheme 1.17**). Modifications to the prenyl functionality could be easily achieved by use of varying electrophiles (R^2). Use of varying chain lengths of alkenes in place of the vinyl functionality would allow ring expansion (**1.125**). This ring expansion could also be achieved varying the allyl chain length (**1.126**). Extending the ring size from either functionality would allow migration of the alkene about the ring. Finally, changing functionalities to the allyl group would allow alterations to be made to the methyl alcohol functionality (R^3).

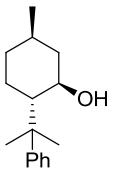


Scheme 1.17: Extending the Southampton approach to vibralactone analogues.

Each of these variations could be readily accommodated in the proposed synthesis of vibralactone (**1.01**) when compared to the previous Snider synthesis.[36,37] If successful, a number of derivatives could be prepared and biologically assessed for inhibition of PL.

1.6.1 Introduction to TTC

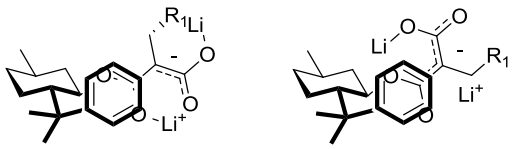
The asymmetric formation of quaternary β-dicarbonyls using auxiliary control was first reported by Fukumoto in 1989.[63] In this report, the asymmetric induction of malonic half esters was induced under the control of 8-phenylmenthol (**1.128**) (**Figure 1.13**).[64]



1.128

Figure 1.13: Structure of (–)-8-phenylmenthol (**1.128**).

This auxiliary has since been used in the substitution of similar substrates towards the synthesis of enantiopure quaternary fluorinated centres,[65] pyrazolinones [66] and amino acids.[67] In 1991, Ihara *et al*.[68] suggested two anionic conformations, **1.129a** and **1.129b**, which account for the observed selectivity's of alkylation for 8-phenylmenthol malonic acid half esters (**Figure 1.14**). In the more thermodynamically favourable conformation A (**1.129a**), when R=H, the auxiliary blocks the approach of the electrophile from the *si* face, leading to preferential substitution from the *re* face. When R≠H though, in conformation A (**1.129a**) the R group restricts the electrophilic approach from the *re* face, inhibiting the substitution. In *trans* conformation B (**1.129b**), although the auxiliary is blocking approach from the *si* face, the R group is orientated in such a way that the electrophile can approach from the *re* face. From these models, it can be presumed that increased steric bulk implemented by the auxiliary should lead to increased selectivity.

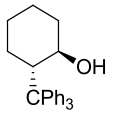


1.129a
Conformation A

1.129b
Conformation B

Figure 1.14: Dianion conformers (**1.129a** and **1.129b**) proposed by Ihara for the diastereoselective alkylation with 8-phenylmenthol.

An auxiliary currently under investigation within our laboratory is *trans*-2-tritylcyclohexanol (TTC) (**1.130**), first synthesised in 1968 by Peddle (**Figure 1.15**).[69]

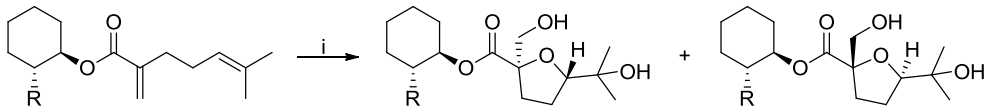


(+)-1.130

Figure 1.15: Structure of (+)-TTC (**1.130**).

This auxiliary was employed by Brown and Al Hazmi in the synthesis of (+)-linalool oxide (**Scheme 1.18**).[70] TTC (**1.130**) and 6 other auxiliary's were compared for their

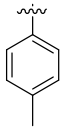
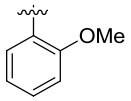
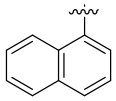
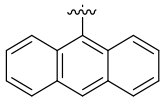
ability to impart diastereoselectivity to the permanganate oxidative cyclisation of a 1,5-dienoate system (**1.131**), with the diastereoselectivity obtained using TTC (**1.131g**) far surpassing the other cyclohexyl auxiliaries investigated (**Table 1.1**).



1.131a-g **1.132a-g** **1.133a-g**

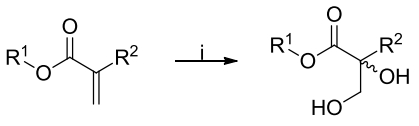
Scheme 1.18: *Reagents and conditions:* i) $NaMnO_4$, AcOH, acetone/phosphate buffer (**Table 1.1**).

Table 1.1: Results of Al Hazmi's oxidative cyclisation of dienes **1.131a–g** using cyclohexyl auxiliaries.

Entry	**R**	Yield[a] (%)	dr (**122**:**123**)
1 (**1.131a**)		56	1:1
2 (**1.131b**)		89	1.03:1
3 (**1.131c**)		95	1.08:1
4 (**1.131d**)		69	1.75:1
5 (**1.131e**)		82	1.32:1
6 (**1.131f**)		99	1.79:1
7 (**1.131g**)		61	32.3:1

a) Yield given is for purified isolated compounds.

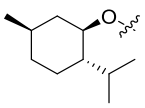
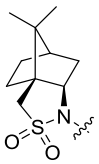
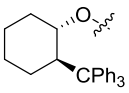
TTC (**1.130**) was later applied to a diastereoselective dihydroxylation by Brown and Watkin (**Scheme 1.19**).[71] When compared to (−)-menthol (**1.134a**) and (−)-10,2-camphorsultam (**1.134b** and **c**) for the dihydroxylation of the same acrylate derivatives, improved diastereoselectivities were once again achieved with TTC (**1.134d** and **e**) (**Table 1.2**).



1.134a-e **1.135a-e**

Scheme 1.19: Auxiliary controlled dihydroxylation of **1.134**. *Reagents and conditions*: OsO_4, NMO, citric acid, *t*-BuOH, H_2O.

Table 1.2: Diastereoselectivities observed for different auxiliaries in diastereoselective dihydroxylations of acrylate ester derivatives

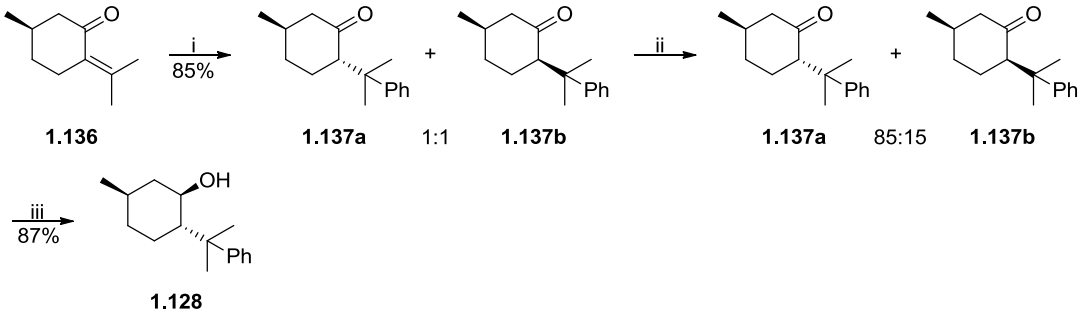
R^1	R^2	Yield[a] (%)	dr
	Me (**1.134a**)	92%	2:1[72]
	H (**1.134b**) Me (**1.134c**)	83 87	4:1 14:10
	H (**1.134d**) Me (**1.134e**)	93% 74%	4:1 12:1

a) Yield given is for purified isolated compounds

Although diastereoselective alkylations of malonic derivatives using the auxiliary 8-phenylmenthol (**1.128**) have proven successful in natural product synthesis,[68] the selectivity imparted by this auxiliary has proved modest (key examples are provided for comparison within the results and discussion). The generally superior results obtained from both the above investigations suggest that TTC (**1.130**) could serve to improve stereoinduction in malonate alkylation reactions, with application towards the synthesis of vibralactone (**1.01**).

1.6.2 Resolution of 8-phenylmenthol, a comparison with TTC

The resolution of (–)-8-phenylmenthol (**1.128**) can be achieved in 3 steps from optically pure (+)-pulegone (**1.136**), as described by Corey (**Scheme 1.20**).[64] A copper mediated 1,4-addition with phenylmagnesium bromide provides a 1:1 mixture of **1.137a** and **1.137b**. Equilibration with KOH provides an 85:15 mixture in favour of the *trans* isomer **1.137a**. This mixture is then reduced with sodium, providing a separable mixture of alcohols, which after column chromatography affords (–)-8-phenylmenthol (**1.128**) in 74% yield.



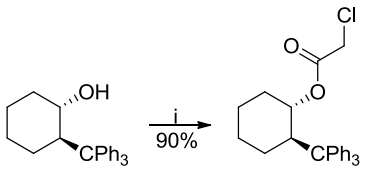
Scheme 1.20: *Reagents and conditions*: ii) PhMgBr, CuCl. ii) KOH, EtOH. iii) Na, *i*-PrOH, toluene, reflux.

The resolution of (+)-8-phenylmenthol (**1.128**) can be achieved using (–)-pulegone (**1.136**). Unfortunately, although this unnatural enantiomer is commercially available, it is very expensive (1 mL, £136.50, SigmaAldrich). Corey has described a synthesis of this enantiomer from (+)-pinane in 4 steps,[73] extending the synthesis of (+)-8-phenylmenthol (**1.128**) to seven steps from expensive starting materials.

Within both the Al Hazmi[70] and Watkin[71] studies, a resolution method allowing the isolation of either enantiomer of TTC (**1.130**) in +99% ee was developed. Each enantiomer can be obtained in 3 synthetic steps from cheap commercially available cyclohexene oxide, with an intermediate resolution step. This resolution strategy further demonstrates TTC's (**1.130**) synthetic utility as a malonate alkylation chiral auxiliary. During the current studies towards vibralactone (**1.01**), this resolution was repeated, and therefore is discussed in more detail within the results and discussion section of this thesis.

1.6.3 Absolute stereochemistry of TTC

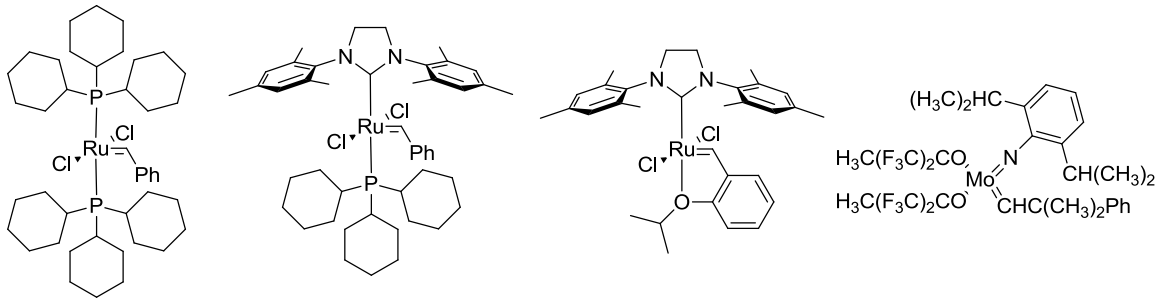
In his thesis, Watkin also reported the determination of the absolute stereochemistry of (–)-TTC to be (1*S*,2*R*)-2-tritylcyclohexan-1-ol ((–)-**1.130**) by X-ray crystallography of chloro derivative **1.138**, (**Scheme 1.21**).



Scheme 1.21: *Reagents and conditions*: i) Chloracetyl chloride, DMAP, Et_3N, CH_2Cl_2.

1.7 Metathesis catalysts

Throughout this section of the thesis, 4 distinct metathesis catalysts have been used. Grubbs' catalyst 1st generation (**1.139**) (refereed in the text as Grubbs' 1), Grubbs' catalyst 2nd generation (**1.140**) (referred in the text as Grubbs' 2), Hoveyda-Grubbs' catalyst 2nd generation (**1.141**) (Hoveyda-Grubbs' 2) and Schrock's catalyst (**1.142**).



1.139 **1.140** **1.141** **1.142**

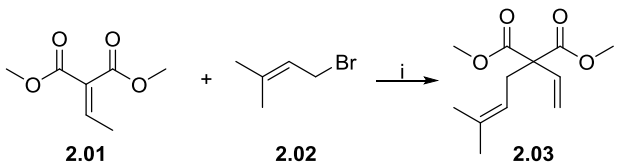
Figure 1.16: Structure of metathesis catalysts.

2. Results and discussion

As no earlier synthetic studies towards vibralactone had been undertaken within our group, a racemic synthesis was initially embarked upon. If successfully achieved, it was believed that implementation of auxiliary **1.130** should provide a means to access enantiomerically enriched vibralactone.

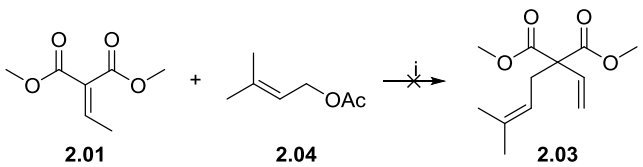
2.1 Synthesis of a vinyl malonate derivative

Preliminary interests focussed on the synthesis of vinyl malonate **1.123** (**Scheme 1.16**) where R^1 = Me (**2.03**). Few generalised methods for the synthesis of vinyl malonates have been published.[74-76] Although many individual examples are present within the literature, poor substrate scope,[77,78] the use of heavy metals[74] and harsh reaction conditions[79] rendered most protocols unsuitable for the synthesis of **2.03**. We initially investigated a deconjugative alkylation using dimethyl ethylidenemalonate (**2.01**) with prenyl bromide (**2.02**) (**Scheme 2.1**). Dimethyl ethylidenemalonate (**2.01**) was obtained commercially in the first instance, although it can be prepared from dimethyl malonate *via* Knoevenagel condensation.[80] The deconjugative alkylation of **2.01** with **2.02**, by adaptation of Herrmanns proceedure,[81] unfortunately provided an in inseparable mixture of products. Although vinyl malonate **2.03** was later confirmed to have been formed, a 60% mass recovery of impure material, alongside reports of poor results from similar alkylidene malonates,[82,83] led us to abandon this protocol.



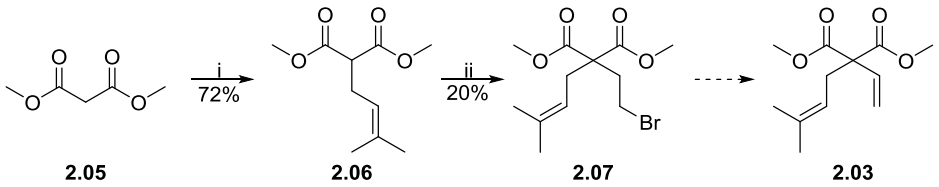
Scheme 2.1: Reagents *and conditions*: i) *n*-BuLi, DIPA, HMPA, THF, -78 °C.

We next attempted an alternative approach to this concise method. In 2003, Mori *et al*.[84] used a Tsuji-Trost reaction for the allylation of alkylidene malonates with allyl acetates. We applied this method using prenyl acetate (**2.04**) as the allyl functionality (**Scheme 2.2**), but unfortunately in our hands no conversion to vinyl malonate **2.03** was observed.



Scheme 2.2: *Reagents and conditions* i) Pd_2dba_3, PPh_3, LDA, DMF, 0 ˚C→rt.

Brunce *et al*. presented a generalised route to install the vinyl functionality by E2 elimination of ethyl bromides.[76] The broad substrate scope and synthetic simplicity made it an attractive route to the required malonate **2.03**. We therefore investigated this route by first prenylating dimethyl malonate (**2.05**), which occurred uneventfully (**2.06**) (**Scheme 2.3**). Alkylation with dibromoethane was first attempted using the procedure described by Brunce *et al*.[76] Unfortunately only starting material was obtained from the reaction mixture, presumably caused by the sensitivity of dibromoethane alkylations to steric effects.



Scheme 2.3: *Reagents and conditions* i) NaH, prenyl bromide (**2.02**), THF, 0 ˚C→rt; ii) NaH, dibromoethane, THF, rt.

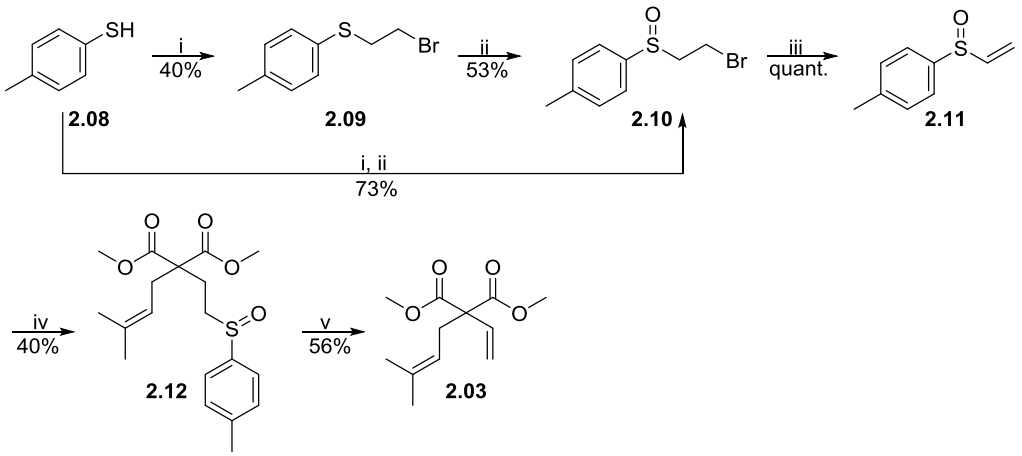
Varying the reaction conditions for this alkylation led to a modest optimised yield of only 20% of **2.07** (**Table 2.1**). Since undertaking this study, Cienfuegos *et al*.[85] have reported a 55% yield for the same alkylation.

Table 2.1: Optimisation results and conditions for the reaction alkylation of **2.05**.

Bromide eq.	NaH eq.	Temp.	Time	Yield
1.1	1.1	rt	18 h	30% conv.
1.1	2	rt	18 h	n/a
1	1.4	reflux	5 h	50% conv.
1	1.4	42 ˚C	18 h	20% isolated

The yield we obtained was obviously insufficient for the second step of the synthesis and so we focussed our attention towards introducing the vinyl group by sulfoxide elimination. Although this approach generally requires fairly harsh reaction conditions, it has proven successful in the formation of a number of vinyl malonate derivatives.[86,87]

Thiotoluene **2.08** was alkylated with dibromoethane, providing thioether **2.09** which proved difficult to isolate due to its instability during column chromatography. Oxidation of crude **2.09** with *m*-CPBA was therefore undertaken, providing bromo sulfoxide **2.10** in 73%. Alkylation of prenyl malonate **2.06** with **2.10** gave very poor results, and so Michael acceptor **2.11** was synthesised as an alternative alkylating agent in quantitative yield. The Michael addition between malonate **2.06** and vinyl sulfoxide **2.11** provided the sulfoxide elimination precursor **2.12** in an un-optimised yield of 40% (**Scheme 2.4**).



Scheme 2.4: *Reagents and conditions* i) *t*-BuOK, *t*-BuOH, dibromoethane, reflux; ii) *m*-CPBA, CH_2Cl_2, rt; iii) NaOH, H_2O, rt; iv) **2.06**, NaH, THF, 0 °C→rt; v) toluene, μw, 130 °C.

With sulfoxide **2.12** in hand, we investigated the *syn* elimination (**Table 2.2**). 18 h reflux in toluene provided no conversion, and so extended reaction times were investigated. Although increased conversions were observed, the reaction times proved impractical. Increased reaction temperatures were then implemented, providing much faster conversions. Unfortunately, this increase in conversion was also matched with increased degradation, and a modest isolated yield of 28% of **2.03** was the best result obtained.

Table 2.2: Initial optimisation of the sulfoxide elimination of **2.12**.

Solvent	Temp.	Time (h)	Additive	Yield
Toluene	100 °C	18	n/a	0% conv.
Toluene	Reflux	36	$NaHCO_3$	40% conv.
Toluene	Reflux	40	NaOAc	45% conv.
Xylene	Reflux	4	n/a	50% conv.
Xylene	Reflux	19	n/a	28% isolated

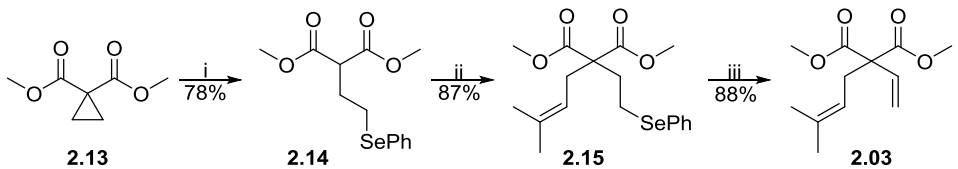
These results strongly suggested that the temperature required for conversion and degradation of **2.12**/**2.03** are very similar. This relationship was investigated using a flow reactor, allowing much more accurate temperature control. Reaction times were limited to 2 h, and temperatures of 120, 130 and 140 °C were implemented (**Table 2.3**). The results showed an optimum ratio between conversion and degradation could be obtained at ca. 130 °C. This method was then repeated in a microwave reactor to allow extended reaction times, successfully providing a 56% yield of vinyl malonate **2.03** after 250 min, giving a 16% overall yield from dimethyl malonate (**2.05**).

Table 2.3: Temperature study for the sulfoxide elimination of **2.12**.

Reactor	Temp. (°C)	Time	Solvent	Yield
Flow	120	2 h	Toluene	<5% conv.
Flow	130	2 h	Toluene	30% conv.
Flow	140	2 h	Toluene	Degradation
Microwave	130	200 min	Toluene	87% conv.
Microwave	130	250 min	Toluene	56% isolated

As this *syn*-elimination procedure proved successful, we aimed to optimise the overall yield whilst maintaining the elimination process. We achieved this by use of a selenoxide elimination. Selenoxide eliminations are known to generally occur spontaneously at rt.[88] If an efficient route to selenide **2.15** could be achieved (**Scheme 2.5**), the reduced reaction temperature should maintain the integrity of the starting material/product.

Adapting a procedure from Kocienski *et al.*[89] commercially available cyclopropylmalonate **2.13** was selenated with PhSeSePh in the presence of $NaBH_4$ (**Scheme 2.5**). Alkylation with prenyl bromide subsequently provided selenoxide elimination precursor **2.15** in good yield. Treatment with H_2O_2 gave the selenoxide which eliminated *in situ* providing vinyl malonate **2.03** in 60% over 4 steps, a 44% increase when compared to the sulfoxide approach.

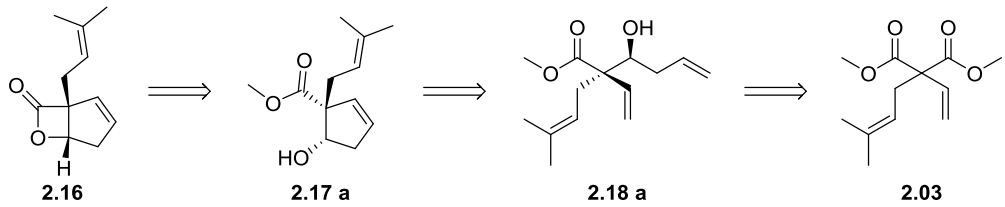


Scheme 2.5: *Reagents and conditions*: i) PhSeSePh, $NaBH_4$, MeOH, rt; ii) NaH, prenyl bromide (**2.02**), THF, rt; iii) H_2O_2, THF, rt.

Pleased with the optimised route to **2.03**, we next investigated a model system towards vibralactone (**1.01**).

2.2 Racemic synthesis of a vibralactone model system by RCM

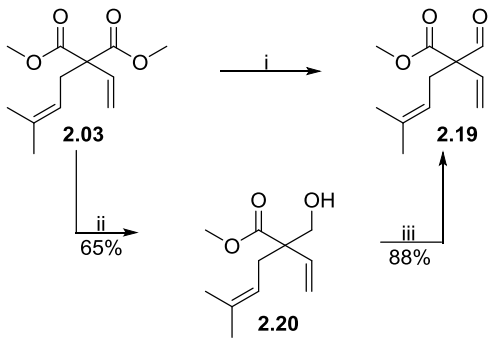
At this stage of the project, it was considered that a model system could provide important information regarding the viability of the proposed route to vibralactone. We aimed to simplify the target, and the proposed allylation and RCM procedures, by removing the hydroxymethyl functionality present within vibralactone (**1.01**), leading to model compound **2.16**. The proposed synthesis plan commenced from the previously synthesised vinyl malonate **2.03** (**Scheme 2.6**).



2.16 **2.17 a** **2.18 a** **2.03**

Scheme 2.6: Retrosynthesis of vibralactone model **2.16** from vinyl malonate **2.03**.

The synthesis of aldehyde **2.19** was initially achieved using DIBAL to selectively reduce malonate **2.03**. Although this reagent sometimes provides modest yields for the mono-reduction of malonates,[90] it provides a direct route to the required mono-aldehyde **2.19**. When applied to malonate **2.03** a mixture of aldehyde **2.19** and over-reduced products were obtained (**Scheme 2.7**). Although formation of these side products could be suppressed by careful temperature control, they proved very difficult to separate by column chromatography and Kugelrohr distillation. These time consuming purifications, coupled with aldehyde **2.19**'s instability, prevented the isolation of analytically pure aldehyde **2.19** by DIBAL reduction of **2.03**.

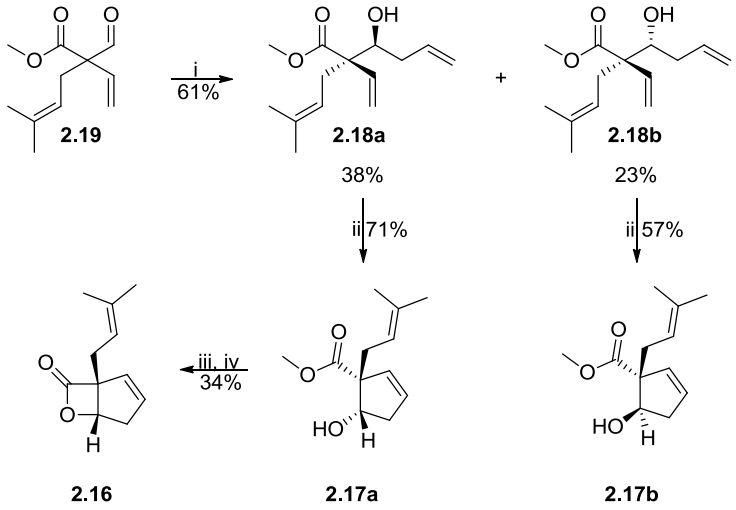


2.03 **2.19** **2.20**

Scheme 2.7: *Reagents and conditions*: i) DIBAL, CH_2Cl_2, –78 °C. ii) Li(*t*-BuO)$_3$AlH, THF, –78 °C→rt. iii) DMP, CH_2Cl_2, rt.

A two-step procedure was therefore undertaken. Li(O-*t*-Bu)$_3$AlH has been shown to be highly selective to the mono-reduction of malonates to mono-alcohols, due to the stability and steric bulk of the intermediate aluminate.[91] Malonate **2.03** was treated with Li(O-*t*-Bu)$_3$AlH, providing alcohol **2.20** in 65% yield after 3 days (**Scheme 2.7**). Although reaction times can be reduced if the reaction is heated, Ayers[91] showed this to be unsuitable for methyl esters due to over reduction, and so this was not applied to **2.03**. Dess–Martin oxidation was then undertaken, proceeding with good yield. Although analytically pure aldehyde **2.19** could be achieved *via* alcohol **2.20**, the time consuming reduction was later avoided by taking the crude aldehyde, obtained from DIBAL reduction, forward into the next reaction.

Allylation of aldehyde **2.19** was then undertaken using allyl Grignard, providing homoallylic alcohols **2.18a** and **2.18b** which could be separated by column chromatography (dr **a**:**b** ~1.2:1 from the crude ^{1}H NMR spectrum) (**Scheme 2.8**). RCM of each of these allylated products proceeded smoothly with Grubbs' 2 (**1.140**), providing **2.17a** and **2.17b** in good yield.



Scheme 2.8: *Reagents and conditions*: i) Allylmagnesium bromide, Et_2O, -78 °C→rt. ii) Grubbs' 2 (**1.140**), CH_2Cl_2, rt. iii) NaOH, MeOH, 60 °C. iv) TsCl, pyridine 0 °C→-5 °C.

Once cyclised, NOE experiments were used to establish the relative stereochemistry of each of the RCM products (**Figure 2.1**).

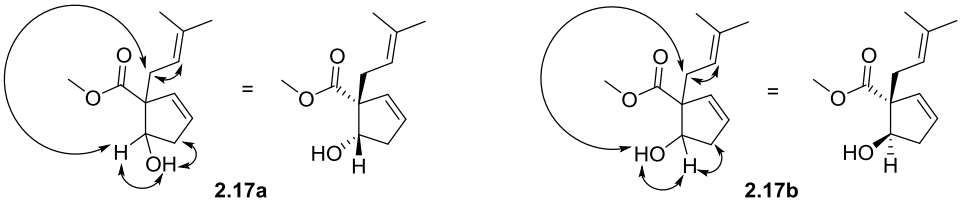
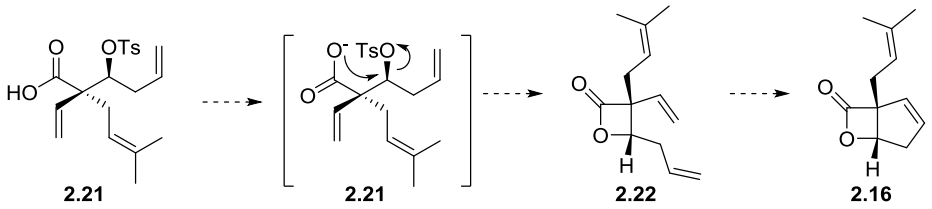


Figure 2.1: NOE analysis obtained for compound **2.17a** and **2.17b**.

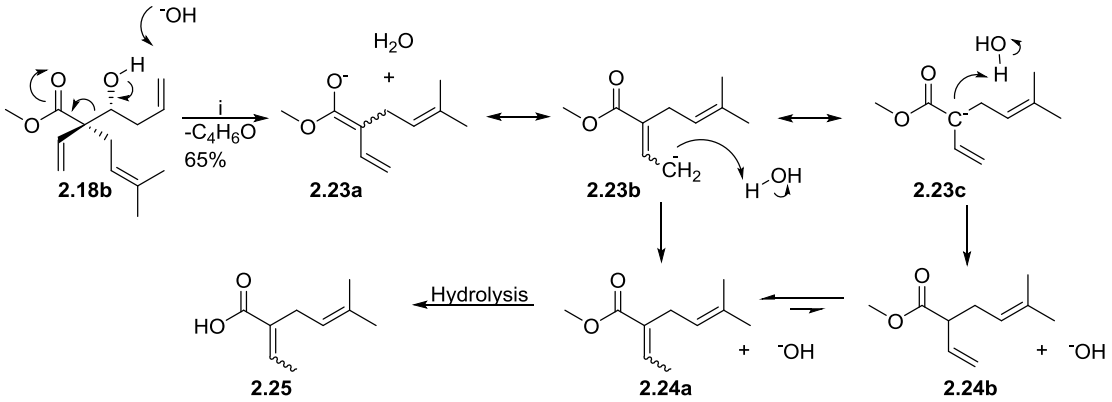
Based on the work by Snider *et al*.[36,37] hydrolysis of *syn* hydroxy-ester **2.17a**, followed by lactonisation using the procedure described by Adam *et al*.,[92] successfully provided racemic model **2.16** in 34% yield (**Scheme 2.8**). The modest yield obtained for the bicyclic lactone is believed to be due to its volatility. Further optimisation should easily be achieved with careful future purification attempts. Despite being un-optimised, this validated the use of RCM for the derivatisation of vibralactone (**1.01**).

We next investigated the applicability of *anti* diastereoisomer **2.17b** to the synthesis of model **2.16** by lactonisation with inversion. Based on the aforementioned work by Snider *et al*.,[36,37] it was assumed Mitsunobu type lactonisation on *anti* cyclopentene **2.17b** would lead to undesired Grob fragmentation. We envisaged that this fragmentation may be suppressed by using an acyclic derivative **2.21**, where there is no fixed antiperiplanar relationship between the two eliminating groups.[49] If successful, RCM could be undertaken as a final step leading to model compound **2.16** (**Scheme 2.9**).



Scheme 2.9: Lactonisation with inversion approach to vibralactone from **2.21**.

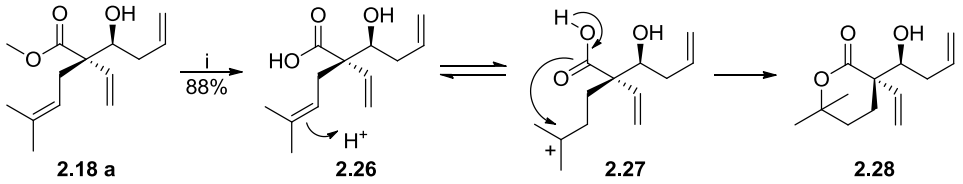
Hydrolysis of diastereoisomer **2.18b** was therefore attempted, initially using NaOH. Unfortunately, hydrolysis was unsuccessful, and acid **2.25** was formed instead, presumably caused by retro-aldol followed by hydrolysis (**Scheme 2.10**).



Scheme 2.10: Retro-aldol mechanism leading to diene **2.25**. *Reagents and conditions*; i) NaOH, MeOH, rt.

To avoid deprotonation of the alcohol, we attempted an acid promoted hydrolysis of **2.18b**. This once again proved unsuccessful, leading to lactone **2.28** in 88% yield (**Scheme 2.11**).

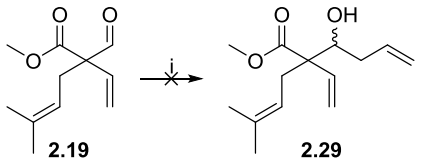
This lactone is likely to have formed by cycloisomerisation of hydrolysis product **2.26**.[93] It was therefore considered that the *anti* diastereomer was not applicable in this synthesis of vibralactone, and attention should focus on developing a stereocontrolled allylation.



2.18 a **2.26** **2.27** **2.28**

Scheme 2.11: Hydrolysis/lactonisation mechanism leading to lactone **2.28**. *Reagents and conditions*: i) HCl, H_2O, 65 °C.

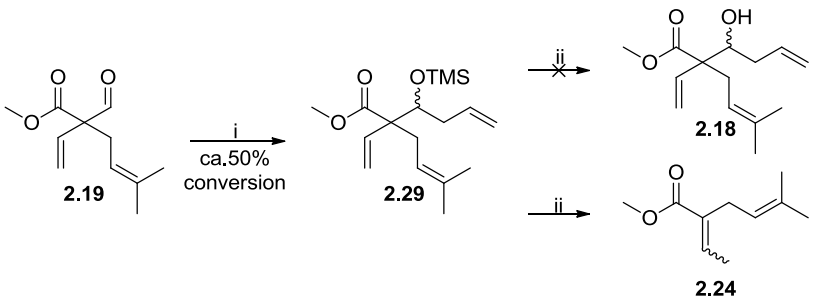
The lack of diastereocontrol witnessed during the addition with allyl Grignard suggested the α-substituents were too similar to induce substantial diastereoselectivity. We therefore initially considered using chiral reagents for a stereoselective allylation of aldehyde **2.19**. Use of TADDOL as a ligand in asymmetric allylation was first described in 1992 by Hafner and co-workers,[94] and since then has been effective in a number of total syntheses.[95,96] In particular, it has been used for the enantioselective allylation of 1,3-dicarbonyls where other enantioselective allylations failed.[97] We therefore applied this enantioselective allylation to aldehyde **2.19** (**Scheme 2.12**). Unfortunately, in our hands no allylated product **2.29** was retrieved from the reaction. Instead, a complex mixture of diastereoisomers of an unknown compound was obtained. Identification of this compound was not achieved, although the complexity of the crude mixture led us to investigate alternative procedures.



2.19 **2.29**

Scheme 2.12: *Reagents and conditions*: i) TADDOL, CH_2=$CHCH_2MgBr$, 0 °C, then **2.19** – 78 °C.

We next attempted a BINOL/TiF_4 catalysed allylation reported by Carreira and co-workers, using allyl silanes.[98] After 2 days, no conversion was observed, although after a prolonged reaction time standing in the fridge (21 days) ca. 50% conversion was achieved (**Scheme 2.13**).



Scheme 2.13: *Reagents and conditions*: i) (*S*)-Binol, TiF_4, allyltrimethylsilane, CH_3CN, CH_2Cl, 0 ˚C. ii) TBAF, THF, 0 ˚C→rt.

Regrettably, after attempted desilylation by treatment with TBAF, crude data strongly suggested degradation to the retro aldol product **2.24** had again occurred (**Figure 2.2**).

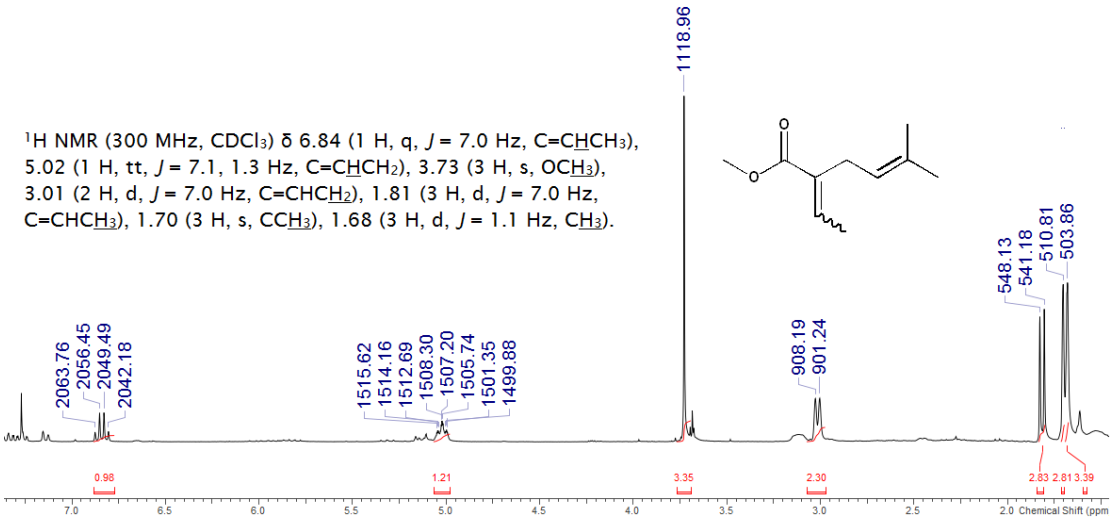
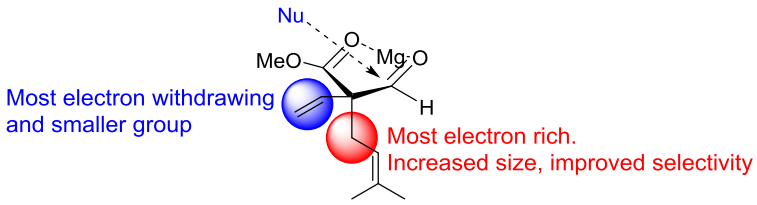


Figure 2.2: ¹H NMR data showing retro-aldol product **2.24**.

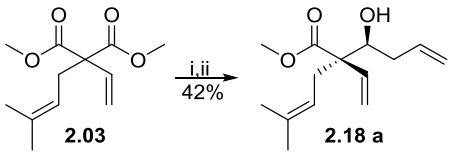
Although optimisation of this reaction was feasible, we became aware of an alternative diastereoselective approach. In 2012 Linclau and co-workers reported a diastereoselective allylation of prochiral 1,3-dialdehydes using $MgBr_2$ chelation with allyltin reagents.[99] A flattened boat model was presented to explain the high diastereocontrol witnessed from these addition reactions. Application of the same model to aldehyde **2.30** (**Figure 2.3**) places the more electron-withdrawing vinyl group in the pseudoequatorial position, whilst the more electron-rich α-substituent resides in the pseudoaxial position. The pseudoaxial orientation of the prenyl group should prevent nucleophilic approach from the *re*-face. In the case of aldehyde **2.30**, diastereoselectivity, in the desired sense, should be enhanced by the pseudoequatorial group being smaller than that of the pseudoaxial group.



2.30

Figure 2.3: Flattened boat model for the diastereoselective allylation of aldehyde **2.30**.[99]

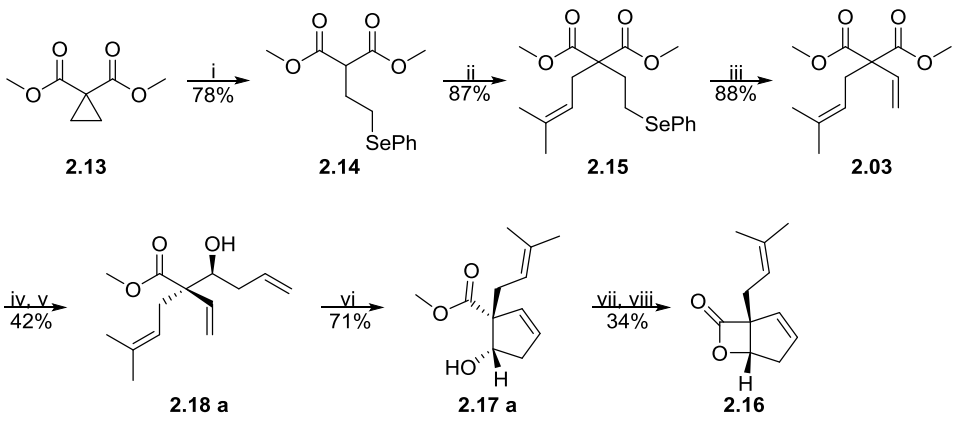
After applying this method to aldehyde **2.19** we were delighted to obtain a highly diastereoselective addition in favour of the desired stereoisomer **2.18a** (dr **2.18a**:**2.18b** ~15:1, ^{1}H NMR), and an acceptable isolated yield of 42% (**Scheme 2.14**). The diastereoselectivity of related allylation reactions was later found to be greatly influenced by reaction temperature. Careful addition of reactants is expected to further improve the dr of this reaction to match those later obtained. The fair yield is believed to have been caused by degradation during purification. Crude analysis of each of the presented allylation reactions suggest much higher yields could be achieved. Based on evidence from earlier reactions, it is suggested that retro-aldol during column chromatography may play a role in the observed degradation. This proposal is supported by later observations of increased stability of allylation products where substituents other than vinyl are present.



2.03 **2.18 a**

Scheme 2.14: *Reagents and conditions*: i) DIBAL, CH_2Cl_2, -78 ˚C. ii) $MgBr_2 \cdot OEt_2$, allyltributyltin, CH_2Cl_2, -78 ˚C→-25 ˚C.

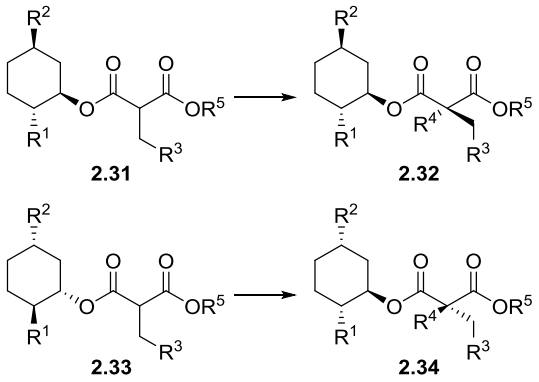
The highly diastereoselective reduction-allylation sequence completed the synthesis of model compound **2.16**, obtaining 6% yield over 8 steps (**Scheme 2.15**).



Scheme 2.15: *Reagents and conditions*: i) PhSeSePh, $NaBH_4$, MeOH, rt; ii) NaH, prenyl bromide (**2.02**), THF, rt; iii) H_2O_2, THF, rt. iv) DIBAL, CH_2Cl_2, -78 ˚C. v) $MgBr_2 \cdot OEt_2$, allyltributyltin, CH_2Cl_2, -78 ˚C→-25 ˚C. vi) Grubbs' 2 (**1.140**), CH_2Cl_2, rt, vii) NaOH, MeOH, 60 ˚C. viii) *p*-TsCl, pyridine, 0 ˚C→-5 ˚C.

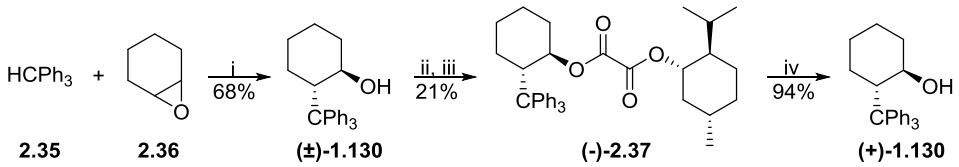
2.3 Enantioselective synthesis of the vibralactone model system by RCM

The next objective was to develop an enantioselective synthesis of model compound **2.16** using a bulky cyclohexyl chiral auxiliary, TTC (**1.130**), recently developed in our laboratory. As previously mentioned, in 1991 Ihara *et al.*[68] suggested two anionic conformations **1.129a** and **1.129b**, which account for the observed selectivity's of alkylation for 8-phenylmenthol malonic acid half esters (**Figure 1.14**). Based on the Ihara model, the same sense of stereoselectivity would be expected from 8-phenylmenthol (**1.128**) and TTC (**1.130**), where the 1*R*,2*S*-cycloheyl auxiliary (**2.31**) provides the *R*-quaternary centre (R^5=H/Me, $R^3 \neq H$ and is higher priority than R^4) (**2.32**), whilst the 1*S*,2*R*-cyclohexyl auxiliary (**2.33**) provides the *S*-quaternary centre (**2.34**) (**Scheme 2.16**).



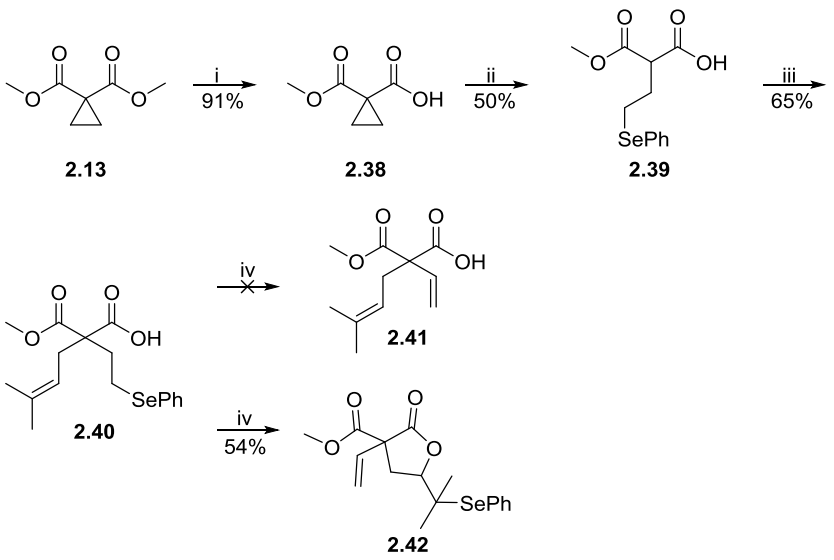
Scheme 2.16: Alkylation diastereoselectivity expected from the Ihara model.[68]

Based on the Ihara model, we inferred that (1*R*,2*S*)-2-tritylcyclohexanol ((+)-TTC) (**1.130**) would provide the correct *R*-stereochemical outcome for the newly formed quaternary centre (R^5 = Me/H, R^3 has higher priority than R^4) (**2.32**). (±)-TTC (**1.130**) was subsequently synthesised and resolved using a method previously developed within the Brown laboratory, providing (+)-TTC (**1.130**) in +99% ee (**Scheme 2.17**).[71] Thus, opening of cyclohexene oxide (**2.36**) with lithiated $HCPh_3$ (**2.35**) provided the racemic auxiliary (**1.130**). Coupling of (±)-TTC (**1.130**) with (+)-menthol using oxalyl chloride provided a mixture of oxalate diastereoisomers (**2.37**). These diastereoisomers were then refluxed in MeOH, before filtering and washing the filter cake with hot MeOH, providing the enriched filtrate and filter cake. After repeating this 5 times with the filter cake, a de >99% was indicated by chiral HPLC. Hydrolysis of (–)-oxylate derivative **2.37** gave (+)-TTC (**1.130**) in 94% yield. Although the collected enantioenriched filtrate ((+)-**2.37**) could have potentially been resolved further as to increase the yield beyond 21% (Watkin obtained a 33% yield in >99% ee of **2.37**), this was not undertaken in the first instance in the interest of time.



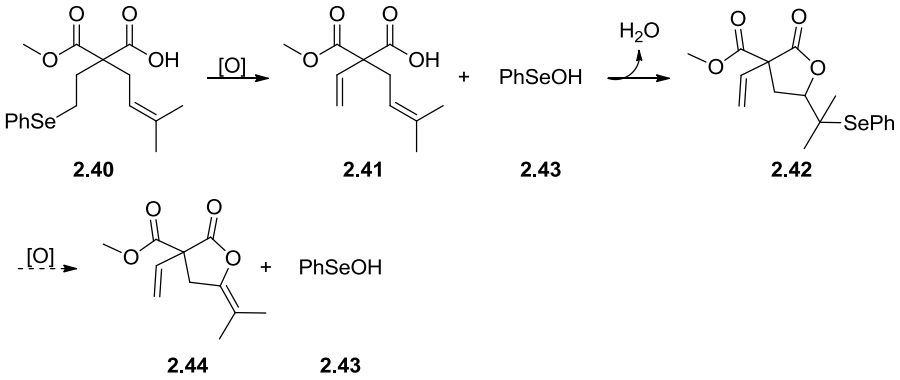
Scheme 2.17: *Reagents and conditions*: i) *n*-BuLi, THF, –78 °C→rt. ii) Oxalyl chloride, (+)-menthol, CH_2Cl_2, 0 °C→rt, then **1.130**, pyridine, CH_2Cl_2, rt. iii) Hot methanol resolution. iv) KOH, MeOH, H_2O, 65 °C.

Fukumoto and co-workers have previously described an increase in reactivity and diastereoselectivity when alkylating mono-malonic acids under auxiliary control, compared to diester derivatives.[65] We were therefore interested in investigating whether the mono-acid was suitable for our approach. In the first instance, this was investigated without auxiliary (+)-**1.130** as to simplify analysis and minimise material losses (**Scheme 2.18**). Cyclopropyl malonate **2.13** was monohydrolysed, selenated and alkylated as previously undertaken, providing prenyl malonic acid **2.40** in fair yield. The selenoxide elimination was then attempted, but no vinyl malonate **2.41** was obtained. Instead, the seleno-lactone **2.42** was isolated as a mixture of diastereoisomers in 54% yield. Confirmation of the seleno-lactone structure was achieved by separation of a small quantity of a single diastereoisomer.



Scheme 2.18: *Reagents and conditions*: i) NaOH, H_2O, 0 °C→rt. ii) PhSeSePh, DMF, rt. iii) *n*-BuLi, DIPA, prenyl bromide (**2.02**), THF, -78 °C→rt. iv) H_2O_2, THF, rt.

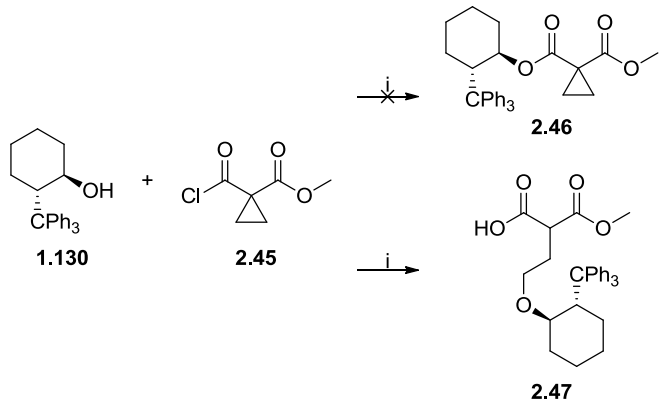
Selenenic acid (**2.43**) additions to alkenes have previously been described, although oxidative elimination has followed in the synthesis of allylic ethers.[100] The use of 1 equivalent of H_2O_2 in the selenoxide elimination prevented this second elimination, which would lead to diene **2.44** (**Scheme 2.19**).



Scheme 2.19: Proposed synthetic pathway leading to lactone **2.42** with one equivalent of oxidant.

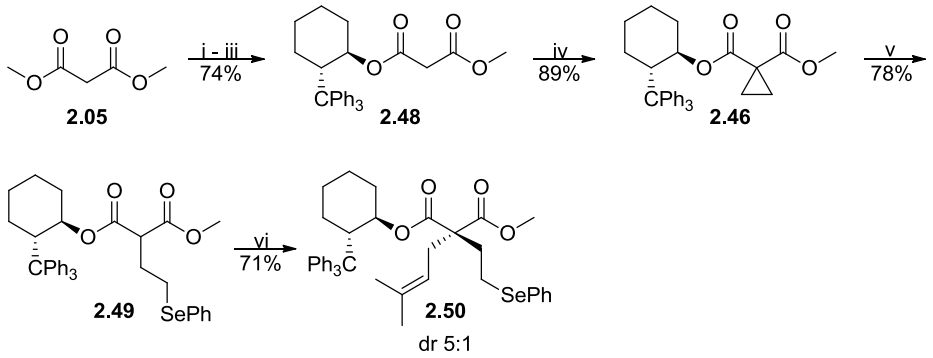
To avoid this unwanted selenolactonisation, we decided to use the diester functionality in the asymmetric approach to model compound **2.16**. Although scavengers for the PhSeOH (**2.43**) could have been used during the selenoxide elimination, it was decided the use of the diester function would provide simplified synthetic procedures to progress our investigation towards later stage intermediates. We therefore subsequently applied the developed route to the asymmetric synthesis of model compound **2.16**. Initial attempts to install the auxiliary onto cyclopropyl malonate **2.45**

proved unsuccessful (**Scheme 2.20**). Crude ^{1}H NMR suggested the formation of diastereoisomers, presumably caused by cyclopropyl ring opening (**2.47**).



Scheme 2.20: *Reagents and conditions*: i) DMAP, Et_3N, CH_2Cl_2, reflux.

We therefore began the asymmetric synthesis from dimethyl malonate (**2.05**). Mono hydrolysis, acid chloride formation followed by treatment with (+)-TTC (**1.130**) in the presence of Et_3N and DMAP provided diester **2.48** in good yield. The cyclopropyl ring was then installed with dibromoethane and K_2CO_3 in 89%, and then selenated as previously described, giving **2.49** as a mixture of diastereoisomers (**Scheme 2.21**), which was subsequently diastereoselectively prenylated.



Scheme 2.21: *Reagents and conditions*: i) KOH, MeOH, 65 °C. ii) Oxalyl chloride, DMF, CH_2Cl_2, rt. iii) **1.130**, DMAP, Et_3N, CH_2Cl_2, reflux. iv) Dibromoethane, K_2CO_3, TBAB, DMF, 50 °C. v) PhSeSePh, $NaBH_4$, MeOH, reflux. vi) *n*-BuLi, DIPA, prenyl bromide (**2.02**) THF, –78 °C→rt.

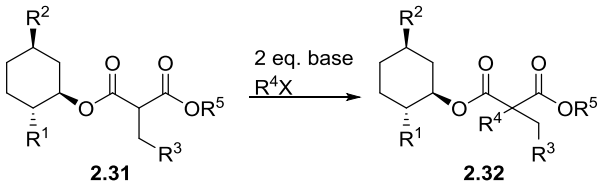
Although the highest dr achieved in the prenylation of **2.49** was 7:1 (^{1}H NMR) (**Table 2.4**), a dr of 5:1 is presented within the experimental. This scaled reaction providing a dr of 5:1 was the only reaction purified separately, as optimisation reactions were combined prior to purification. Further optimisation of the alkylation reaction is required to further increase the dr, possibly by using non-coordinating bases to further promote the required *trans* transition state.

Table 2.4: Optimisation results for the alkylation of **2.49**.

Base	Solvent	Temp.	dr[a]
NaH	THF	0 °C→rt	4:1
NaH	THF	-78 °C	7:1
LiHMDS	THF	-78 °C	6:1
LDA	THF	-78 °C	7:1
LDA	Et_2O	-78 °C	5.5:1

a) Complete conversion was noted in each reaction (crude ^{1}H NMR). Reaction mixtures were combined prior to purification of **2.50**.

The diastereoselective prenylation of TTC-malonate **2.49** provided similar results to those achieved when using 8-phenylmenthol malonic half esters, described by Ihara *et al*. (**Scheme 2.22**, **Table 2.5**).[63,68] Although 8-phenylmenthol (**1.128**) provided increased diastereoselectivities when sterically demanding alkyl groups (R^3) and electrophiles (R^4) were used (**Table 2.5** entries 3-5), we were delighted to achieve comparable results with TTC (**1.130**) without thorough optimisation, and without the need to have the malonic acid functionality.[65]



2.31 **2.32**

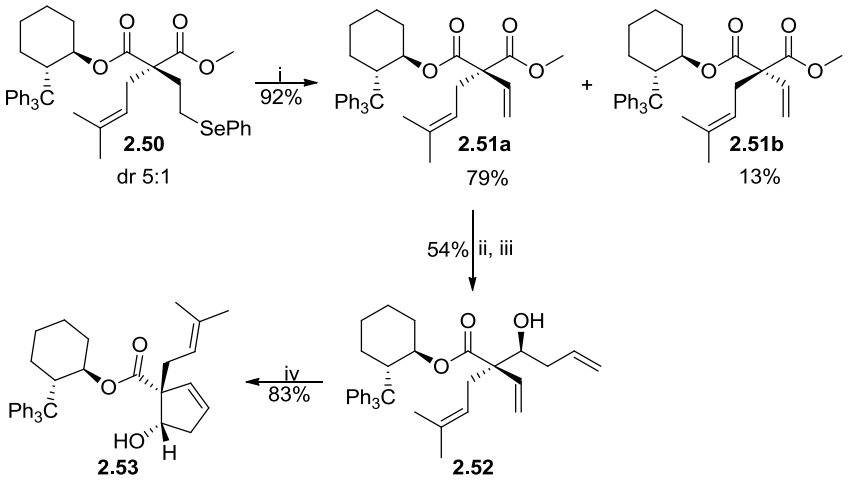
Scheme 2.22: Generalised diastereoselective alkylation of malonate half-esters, under cyclohexyl auxiliary control (**Table 2.5**).[63,68]

Table 2.5: Previously reported examples of malonate half-ester alkylations under auxiliary control.

Entry	R^1	R^2	R^3	R^4	R^5	R:S
1	$C(CH_3)_2Ph$	Me	H	Et	H	4:1[63]
2	$C(CH_3)_2Ph$	Me	H	*i*-Pr	H	4:1[63]
3	$C(CH_3)_2Ph$	Me	H	$PhCH_2$	H	12:1[63]
4	$C(CH_3)_2Ph$	Me	H	2-$MeOPhCH_2$	H	16:1[63]
5	$C(CH_3)_2Ph$	Me	Ph	Me	H	15:1[68]
6	$C(CH_3)_2Ph$	Me	CH_2CH_3	Me	H	5:1[68]

It is worthy of note that during the course of this PhD, Park *et al*.[101,102] have published the results of elegant studies regarding the asymmetric alkylation of unsymmetrical malonates, forming chiral quaternary centres. In these papers, the group applied phase transfer catalysis to the alkylation, achieving up to 97% ee.

The diastereoisomers of **2.50** proved difficult to separate by column chromatography, and so they were taken forward as a mixture (**Scheme 2.23**). Treatment with H_2O_2 provided the selenoxide elimination products **2.51a** and **2.51b**, which were then easily separated by column chromatography, providing diastereoisomer **2.51a** in good yield. The major isomer **2.51a** was then reduced with DIBAL. It is worthy of note that in this case the aldehyde displayed increased stability and could be successfully purified, although overall increased yields were obtained when it was taken forward crude. Diastereoselective allylation with allyltributyltin provided a single allylated diastereoisomer **2.52** (crude ^{1}H NMR) in 54% yield (alongside 18% recovered **2.51a**). RCM was then successfully applied leading to cyclopentene **2.53** in 83% yield, a 12% increase when compared to the racemic derivative in half of the reaction time.



Scheme 2.23 *Reagents and conditions*: i) H_2O_2, THF, rt. ii) DIBAL, CH_2Cl_2, –78 °C. iii) $MgBr_2 \cdot OEt_2$, allyltributyltin, CH_2Cl_2, –78 °C→–25 °C. iv) Grubbs' 2 (**1.140**), CH_2Cl_2, rt.

X-ray analysis of **2.53** confirmed the relative stereochemistry of the major diastereoisomer obtained from the auxiliary controlled alkylation to be that predicted by the Ihara mode (**Figure 2.4**).[68] Furthermore, the desired relationship between the two newly created stereogenic centres was confirmed to be that required for the synthesis of vibralactone (**1.01**).

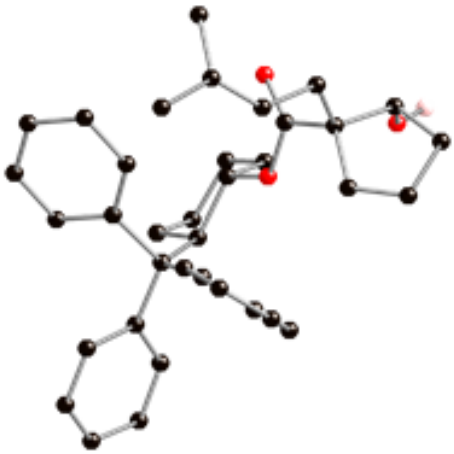
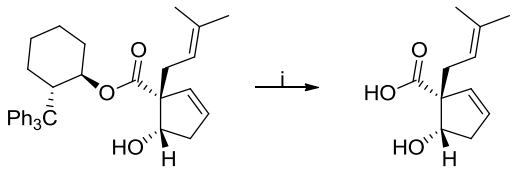


Figure 2.4: X-Ray crystal structure of **2.53**.

Removal of the auxiliary was then investigated. Unfortunately, due to the quantity of **2.53** obtained from the above sequence, none of acid **2.54** was isolated. In this investigation, though, a number of methods were applied, including; KOH, NaOH, $LiOH/H_2O_2$ and NaOMe. In each case no conversion was noted, except when using a refluxing 0.3 M solution of KOH in $MeOH/H_2O$ (**Scheme 2.24**). These conditions mimic those applied to the synthesis of (+)-TTC (**1.130**) from oxalate **2.37** (**Scheme 2.17**). During the KOH mediated hydrolysis of **2.53**, TLC and NMR analysis of the crude reaction mixture both suggested hydrolysis was successful, and thus these conditions are expected to provide hydroxyacid **2.54** once **2.53** is synthesised in appropriate quantities.



2.53 **2.54**

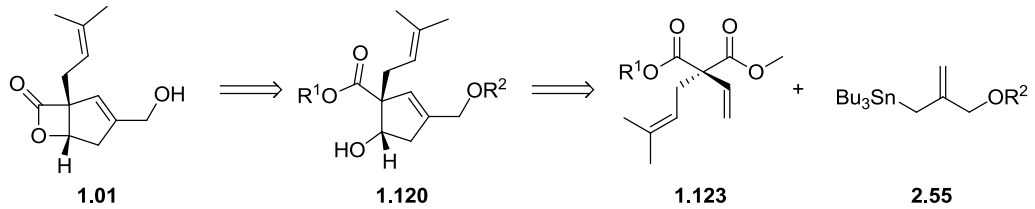
Scheme 2.24: *Reagents and conditions*: i) KOH, MeOH, H_2O, 65 ˚C.

Despite not isolating acid **2.54**, the obtained analysis suggested the successful application of auxiliary **1.130** in the formal enantioselective synthesis of model **2.16**.

2.4 Synthetic studies towards racemic vibralactone by RCM

With the racemic and enantioselective model studies in place, our objective was to extend the developed methods to the synthesis of vibralactone (**1.01**), where a

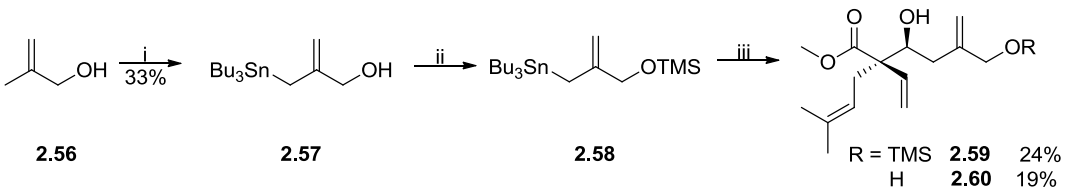
hydroxymethyl-substituted allyltin reagent **2.55** replaces allyltributyltin to install the disubstituted alkene (**Scheme 2.25**).



1.01 **1.120** **1.123** **2.55**

Scheme 2.25: Retrosynthesis of vibralactone (**1.01**) from malonate **1.123** and tin reagent **2.55**.

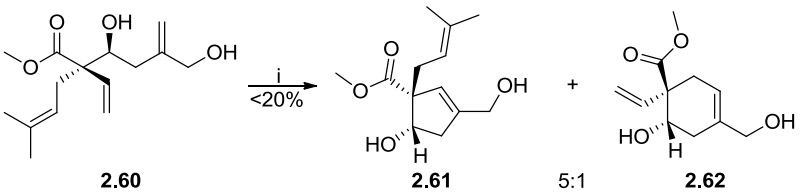
Propenyltin precursor **2.57** was synthesised from methallyl alcohol (**2.56**) and tributyltin chloride. Following TMS protection, the diastereoselective allylation procedure was applied using the tin reagent **2.58** and aldehyde **2.19**, providing homoallylic alcohol **2.59** as a single diastereoisomer (crude ^{1}H NMR) (**Scheme 2.26**). The poor yield was thought to have been caused by the previously observed retro-aldol, alongside deprotection of the TMS group on the column. This was supported by the isolation of diol **2.60** in 19% yield when repeating the same allylation procedure (**Scheme 2.26**).



2.56 **2.57** **2.58**

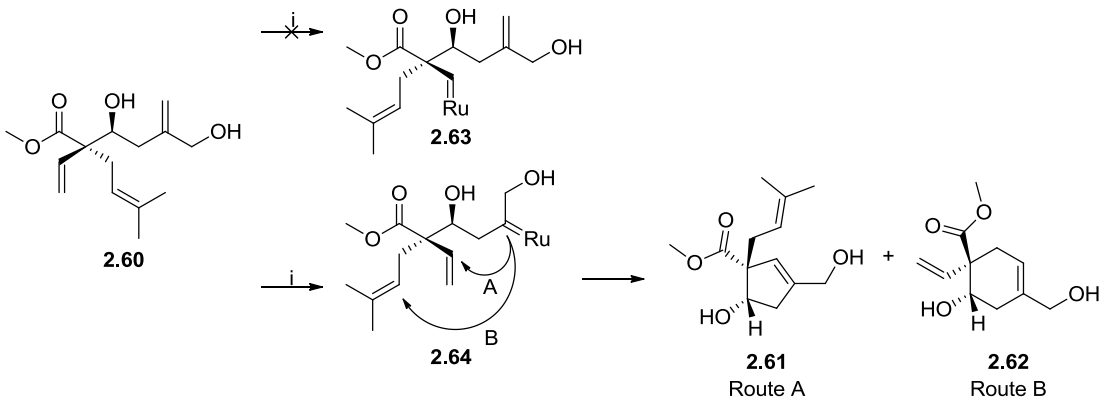
Scheme 2.26: *Reagents and conditions*: i) *n*-BuLi, TMEDA, Bu_3SnCl, Et_2O, THF, 0 °C→rt. ii) TMSCl, pyridine, THF, 0 °C. iii) $MgBr_2 \cdot OEt_2$, aldehyde **2.19**, –78 °C→–25 °C.

Diol **2.60** was subjected to a number of RCM procedures. At rt for 18 h in the presence of Grubbs' 2 (**1.140**), ca. 20% conversion was obtained. When refluxed in CH_2Cl_2 for 3 days in the presence of Grubbs' 2 (**1.140**) (10 mol %), ~20% conversion was once again observed. Following column chromatography of the refluxed reaction mixture, RCM product **2.61** was obtained as a 5:1 mixture (**2.61**:**2.62**) with a second product. Although separation of these intermediates was unsuccessful, the data obtained strongly support the formation of the alternative metathesis product **2.62** (**Scheme 2.27**).



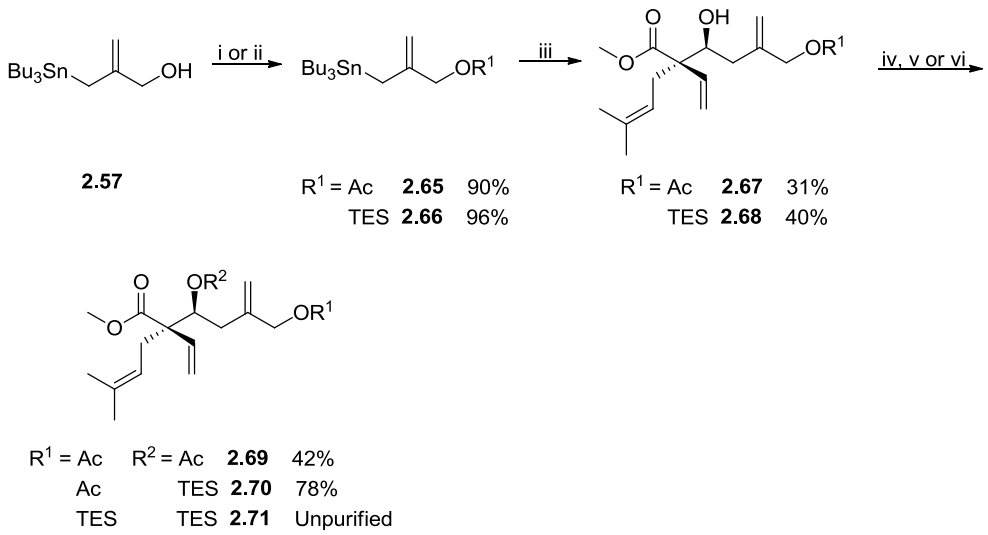
Scheme 2.27: Cyclisation products obtained from RCM of triene **2.60**. *Reagents and conditions*: i) Grubbs' 2 (**1.140**), CH_2Cl_2, reflux.

Cyclisation product **2.62** suggests initiation of the metathesis takes place at the disubstituted alkene rather than the monosubstituted, accounted for by the two possible routes of cyclisation (A + B) from intermediate **2.64** (**Scheme 2.28**). *Gem*-disubstituted alkenes are known to be less reactive to ruthenium catalysts when compared to mono-substituted,[103] and thus the initiation selectivity must be due to the steric hindrance caused by the allylic quaternary centre present in triene **2.60**. The relatively unreactive site of initiation accounts for the higher reaction temperatures required for conversion of this intermediate when compared to model compound **2.18a**.



Scheme 2.28: Two cyclisation pathways resulting from the initiation at the *gem*-disubstituted alkene. *Reagents and conditions*: i) Grubbs' 2 (**1.140**), CH_2Cl_2, reflux.

Optimisation studies were therefore attempted to increase the yield of the RCM for triene **2.60** (**Table 2.6**). During this initial study, unsurprisingly,[103] Grubbs' 1 (G1) (**1.139**) proved ineffective (Entry 3). Using the more reactive Grubbs' 2 (G2) (**1.140**) system, poor conversions were witnessed at rt (Entry 1), while extended heating increased degradation (Entry 2). This degradation primarily stopped us from using higher boiling point solvents than CH_2Cl_2 during cyclisation attempts. Primary alcohols have previously been shown to degrade Grubbs' catalysts by formation of hydride species,[104-106] and so a number of protected intermediates were synthesised (**Scheme 2.29**) and investigated (**Scheme 2.30**, **Table 2.6**). Various protecting groups were applied to establish whether steric and electronic effects influenced the RCM.



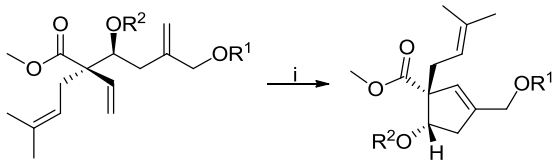
Scheme 2.29: *Reagents and conditions*: i) AcCl, Et_3N, CH_2Cl_2, 0 ˚C. ii) TESCl, Et_3N, CH_2Cl_2, 0 ˚C. iii) Aldehyde **2.19**, $MgBr_2 \cdot OEt_2$, −78 ˚C→−40 ˚C. iv) AcCl, DMAP, Et_3N, CH_2Cl_2, 0 ˚C. v) TESOTf, Et_3N, CH_2Cl_2, 0 ˚C→rt. vi) TESCl, Et_3N, DMAP, CH_2Cl_2, 0 ˚C→rt.

Table 2.6 shows the derivatives and conditions attempted for the RCM of the intermediates of general structure **2.72** (**Scheme 2.30**). Protection of the primary alcohol with TMS (**2.59**) and Ac (**2.67**) groups provided no noticeable improvements to the RCM when compared to diol **2.60**, with low conversion and degradation once again preventing isolation of the cyclopentene products **2.73a** and **2.73b** (Entries 4–6). The use of Hoveyda-Grubbs' 2 (H-G 2) (**1.141**) catalyst also proved ineffective (Entry 7). As retro-aldol had previously caused degradation of intermediates similar to **2.59**, **2.60** and **2.67**, we next investigated whether protection of the secondary alcohol would improve stability to the reaction conditions, preventing degradation during RCM. Unfortunately, when diprotected intermediate **2.71** was heated in CH_2Cl_2 (Entry 8), no conversion was noted, demonstrating the adverse effects of sterics near the *gem*-disubstituted alkene to the success of the RCM.

Next, higher temperatures were implemented using microwave heating for the RCM of mono (**2.68**) and diprotected (**2.71**) derivatives. Although improved conversions could be achieved in shortened reaction times for the mono-protected derivative **2.68** (Entries 9–11), this was matched with substantial degradation, once again preventing isolation. Unfortunately, despite the large increase in temperature, no substantial conversion could be achieved with the diprotected derivative **2.71** (Entry 12).

A final attempt was undertaken using Schrock's catalyst (S1) (**1.142**), as this catalyst has been shown to be much more reactive towards *gem*-disubstituted alkenes.[103] Unfortunately, Schrock's catalyst (**1.142**) proved ineffective for the RCM of **2.69** and

2.70, and despite extended reaction times, no conversion to **2.73e** and **2.73f** was noted (Entry 13 and 14).



2.72 **2.73**

Scheme 2.30: Attempted RCM reactions of trienes of general structure **2.72**. *Reagents and conditions*: i) **Table 2.6**.

Table 2.6: Attempted RCM reaction conditions of protected triene diols of general structure **2.72**.

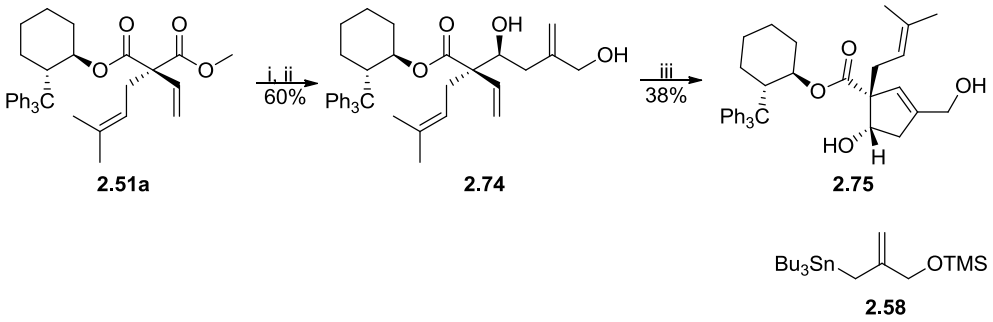
Entry	R^1/R^2	Sol	Temp	Cat. (mol%)	Time	Conv.[a] (product)	Degradation
1 (**2.60**)	H/H	CH_2Cl_2	rt	G2 (10)	18 h	~20% (**2.61**)	Minor
2 (**2.60**)	H/H	CH_2Cl_2	Reflux	G2 (10)	3 days	~20% (**2.61**)	Major
3 (**2.60**)	H/H	CH_2Cl_2	Reflux	G1 (10)	4 days	0% (**2.61**)	n/a
4 (**2.59**)	TMS/H	CH_2Cl_2	rt	G2 (10)	3 days	~10% (**2.73a**)	n/a
5 (**2.59**)	TMS/H	CH_2Cl_2	Reflux	G2 (20)	2 days	~30% (**2.73a**)	Moderate
6 (**2.67**)	Ac/H	CH_2Cl_2	Reflux	G2 (20)	24 h	<10% (**2.73b**)	Moderate
7 (**2.67**)	Ac/H	CH_2Cl_2	Reflux	H-G2 (10)	36 h	<20% (**2.73b**)	Minor
8 (**2.71**)	TES/TES	CH_2Cl_2	Reflux	G2 (10)	3 days	~20% (**2.73d**)	Minor
9 (**2.68**)	TES/H	CH_2Cl_2	100 °C (μw)	G2 (20)	1 h	~50% (**2.73c**)	Moderate
10 (**2.68**)	TES/H	CH_2Cl_2	100 °C (μw)	G2 (20)	1.5 h	n/a (**2.73c**)	Major
11 (**2.68**)	TES/H	CH_2Cl_2	80 °C (μw)	G2 (10)	6 h	~30% (**2.73c**)	Moderate
12 (**2.71**)	TES/TES	CH_2Cl_2	100 °C (μw)	G2 (5)	3 h	<20% (**2.73d**)	Minor
13 (**2.69**)	Ac/Ac	C_6H_6	rt	S1 (10)	24 h	0% (**2.73e**)	0%
14 (**2.70**)	Ac/TES	C_6H_6	rt	S1 10)	7 days	0% (**2.73f**)	0%

a) Conversion estimated by crude ^{1}H NMR

The difficulty in achieving RCM with the racemic methyl ester derivatives, described above, redirected our aims towards the enantioselective synthesis of vibralactone. It was previously noted in the model system that the TTC (**1.130**) esters had generally performed better, and in particular the RCM had been more efficient.

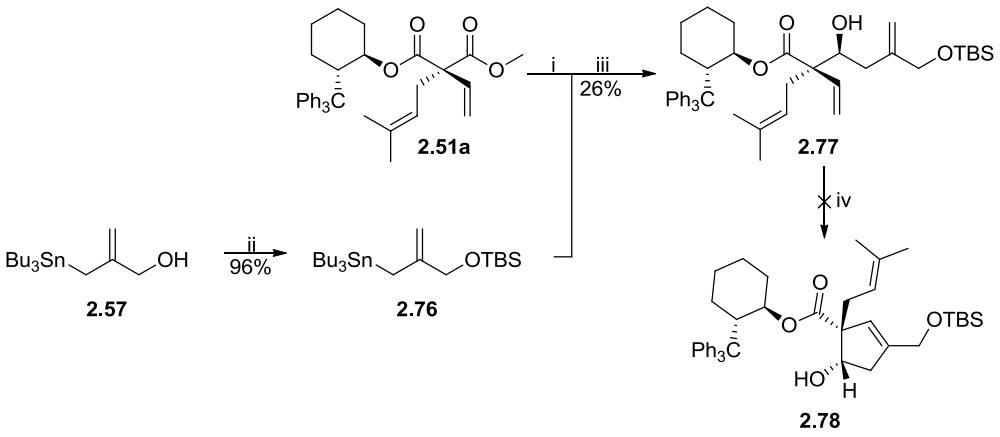
2.5 Towards an Enantioselective synthesis of vibralactone by RCM

We next undertook a brief investigation into the asymmetric synthesis of vibralactone by RCM. During the model study, increased yields were met with reduced reaction times for RCM when the auxiliary was in place. We were therefore keen to see if this was also the case in the fully functionalised triene precursor. Reduction of **2.51a** followed by allylation with TMS protected **2.58** provided diol **2.74** in 60% yield and as a single diastereoisomer, following deprotection during column chromatography (**Scheme 2.31**). **2.74** was then subjected to Grubb's 2 (**1.140**) in CH_2Cl_2 under reflux overnight, and to our delight, cyclopentene **2.75** was obtained in 38% yield.



Scheme 2.31: *Reagents and conditions*: i) DIBAL, CH_2Cl_2, –78 °C. ii) $MgBr_2 \cdot OEt_2$, tin reagent **2.58**, CH_2Cl_2, –78 °C→–25 °C. iii) Grubb's 2 (**1.140**), CH_2Cl_2, reflux.

Although a promising initial result, this proved to be the best yield we were able to achieve, and of a level unsuitable for completion of the total synthesis. We therefore decided to undertake a final attempt using a TBS protected alcohol **2.77** to avoid catalyst degradation due to the presence of the primary alcohol functionality. Allylation with TBS protected **2.76** provided the final RCM precursor **2.77**, but unfortunately no RCM product **2.78** could be obtained (**Scheme 2.32**).



Scheme 2.32: *Reagents and conditions*: i) DIBAL, CH_2Cl_2, –78 °C. ii) TBSCl, imidazole, CH_2Cl_2, 0 °C→rt. iii) $MgBr_2 \cdot OEt_2$, CH_2Cl_2, –78 °C→–25 °C. iv) Grubbs' 2 (**1.140**), CH_2Cl_2, reflux.

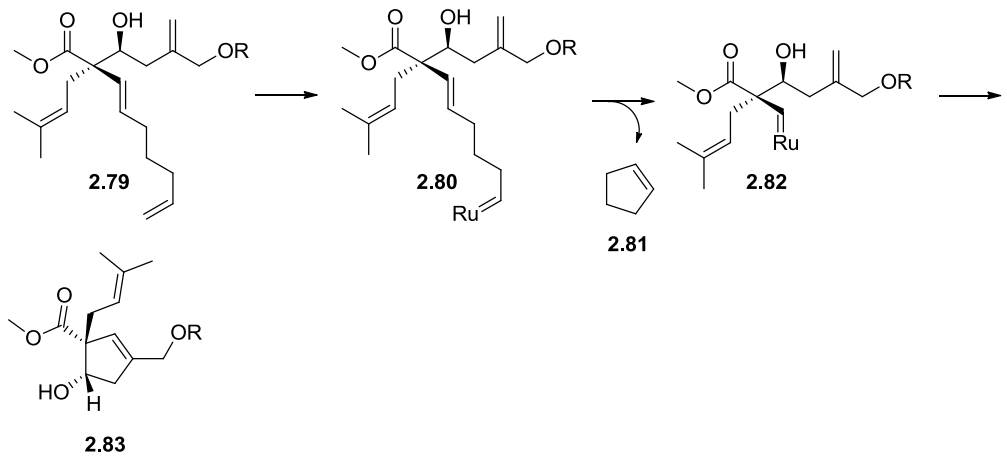
The increased reactivity of diol **2.74** can not only be justified by the reduced steric bulk about the disubstituted alkene, but also by the activating effect of allylic hydroxy groups. First described for RCM in 1999,[107] free allylic alcohols have been shown to increase reaction rates when compared to their ether derivatives by directing the Ru catalyst to the alkene activation site.

Despite the positive results achieved using RCM in the asymmetric approach, the yields were not satisfactory, leading us to investigate alternative metathesis approaches.

2.6 A RRCM approach towards vibralactone

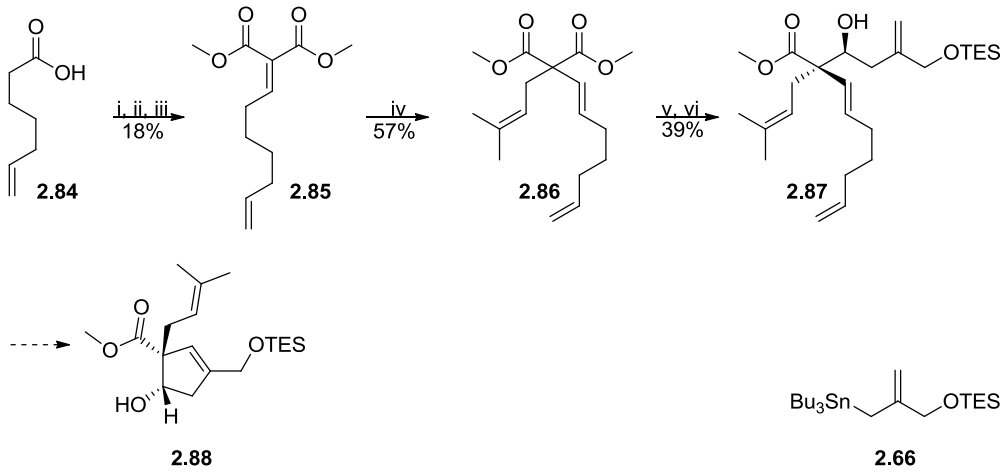
The low reactivity observed for the above trienes led us to consider application of an alkene tether, within a relay ring-closing metathesis (RRCM) precursor. The use of such tethers was first reported in 2004 by Hoye *et al.*[108] and since then has become a powerful tool in site-selective initiation, and also for the initiation of alkenes otherwise unreactive to metathesis reagents.[109,110]

Our aim was to synthesise the tethered alkene **2.79** (**Scheme 2.33**). Based on the previous reports, this should favour initiation of the Ru catalyst at the unhindered alkene (**2.80**), which will be subsequently directed to the vinylic alkene *via* RCM and elimination of cyclopentene (**2.81**). If successful, RCM should follow forming the required cyclopentene derivative **2.83**.



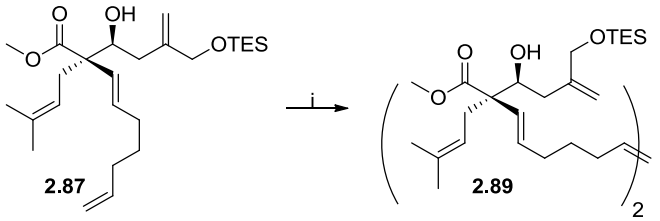
Scheme 2.33: RRCM approach to vibralactone (**1.01**).

We therefore set out to investigate this alternative cyclisation procedure by adaptation of the synthetic route described above. Monomethyl malonate (**2.05**) was subjected to Knoevenagel condensation with heptenal, derived from heptenoic acid (**2.84**) in poor yield over the three steps. No optimisation of this process was undertaken, although literature precedent suggests higher yields can be obtained.[111] Deconjugative alkylation with prenyl bromide (**2.02**) successfully provided the required relay arm in **2.86** in fair yield. Unlike the deconjugative approach with ethylidene malonate **2.01**, this intermediate (**2.86**) could be isolated from the reaction mixture. Reduction followed by diastereoselective allylation provided RRCM precursor **2.87** as a single diastereoisomer (by crude ^{1}H NMR) (**Scheme 2.34**). RRCM using Grubbs' 2 (**1.140**) was then attempted.



Scheme 2.34: *Reagents and conditions*: i) $LiAlH_4$, Et_2O, 0 °C. ii) Oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, −78 °C→rt. iii) Dimethyl malonate (**2.05**), piperidine, AcOH, CH_2Cl_2, 0 °C→rt. iv) LDA, prenyl bromide (**2.02**), THF, −78 °C→rt. v) DIBAL, CH_2Cl_2, −78 °C. vi) $MgBr_2 \cdot OEt_2$, allyltin reagent **2.66**, CH_2Cl_2, −78 °C→−30 °C.

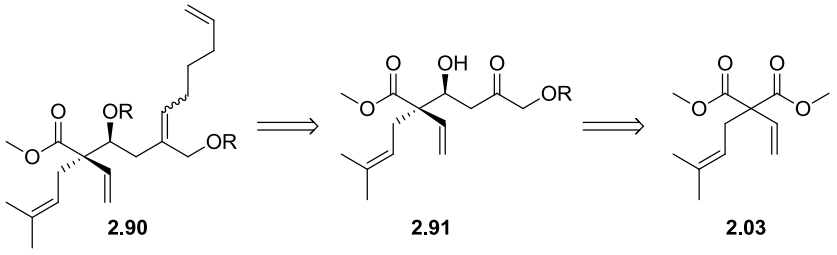
Initially, we undertook the RRCM in CH_2Cl_2 (concentration of **2.87** = 0.025 M) with 10% Grubbs' 2 (**1.140**) pre-catalyst. After 3 days, consumption of the starting material was achieved. Unfortunately, NMR and MS (ES^+ MS 895.4 $[M+Na]^+$) analysis of semi-purified material (analytical standard could not be obtained due to degradation on column) suggested cross metathesis (CM) had occurred, giving **2.89** (**Scheme 2.35**). This further supports the proposed low reactivity of the alkenyl group attached to the quaternary centre preventing initiation at this alkene.



Scheme 2.35: *Reagents and conditions*: i) Grubbs' 2 (**1.140**), CH_2Cl_2, reflux.

An attempt was made to suppress the CM by slow dropwise addition of the relay precursor **2.87** over 10 h to a refluxing solution of the pre-catalyst (maximum concentration of precursor **2.87** = 0.004 M). Unfortunately, crude data obtained from this reaction once again suggested CM, and so initiation at this position was avoided.

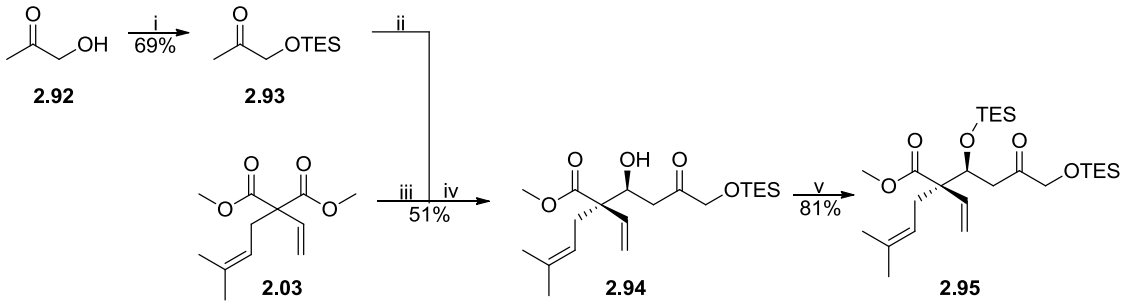
We next attempted to install a relay arm at the disubstituted alkene. Relay metathesis has proven very successful in the initiation of *gem*-disubstituted alkenes,[112,110] and was envisioned to be a suitable strategy for the initiation of malonate precursor **2.90**. It was thought that the relay arm could be installed by olefination of ketone **2.91**. Under the same control achieved during the allylation, we envisioned a Mukaiyama aldol could be implemented in the synthesis of this ketone (**2.91**). If successful, ketone olefination procedures could be undertaken to install the appropriate hydrocarbon functionality in **2.90** (**Scheme 2.36**).



Scheme 2.36: Retrosynthesis of RRCM precursor **2.90** from **2.03**.

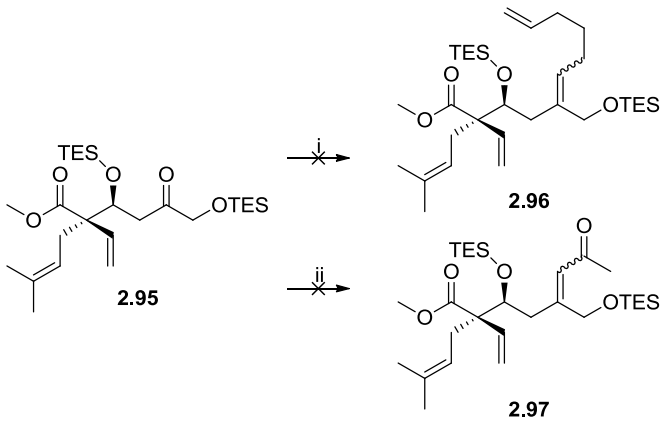
Hydroxyacetone (**2.92**) was TES protected, and then a silyl enol ether was installed regioselectively. A number of bases were considered (Et_3N, LDA, 2,6-lutidine), and 2,6-lutidine in toluene at −40→0 °C was found to give the optimum regioselectivity of ca. 1.8:1. The mixture of regioisomers were then reacted under chelation control with the

DIBAL reduction product of **2.03**, providing hydroxy ketone **2.94** in fair yield as a single diastereoisomer (by crude ^{1}H NMR). Alcohol protection with TESOTf was then achieved in good yield (**2.95**) (**Scheme 2.37**).



Scheme 2.37: *Reagents and conditions*: i) TESCl, DMAP, Et_3N, CH_2Cl_2, 0 °C→rt. ii) TMSOTf, 2,6-lutidine, toluene, −40 °C→0 °C. iii) DIBAL, CH_2Cl_2, −78 °C. iv) $MgBr_2 \cdot OEt_2$, CH_2Cl_2, −78 °C→−14 °C. v) TESOTf, Et_3N, CH_2Cl_2, 0 °C→rt.

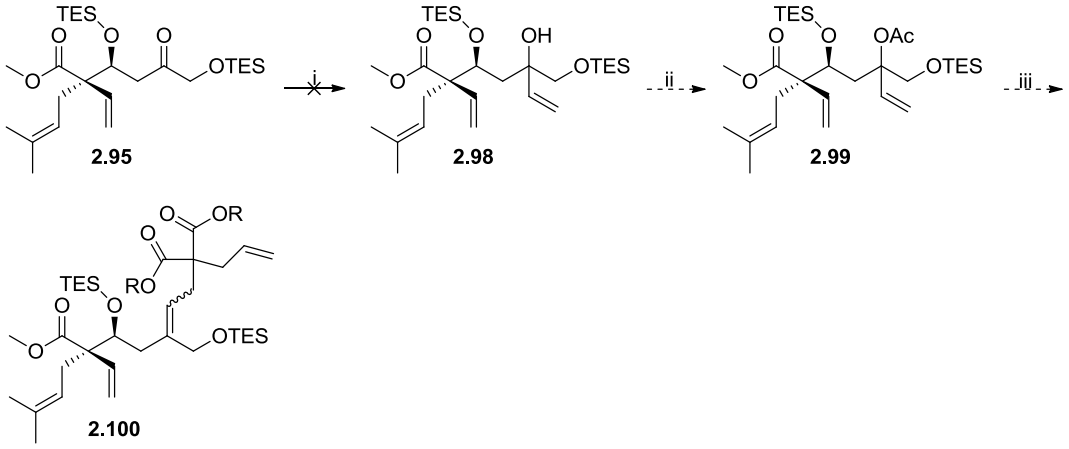
We next attempted to olefinate ketone **2.95**. Initially, an olefination using deprotonated dimethyl hex-5-en-1-ylphosphonate was explored to directly install the relay arm in **2.96** (**Scheme 2.38**).[113] Unfortunately this proved unsuccessful, providing a complex mixture of inseparable products. A Horner-Emmons olefination, using dimethyl (2-oxopropyl)phosphonate, was subsequently attempted towards conjugated ketone **2.97**. We rationalised that the less nucleophilic dimethyl (2-oxopropyl)phosphonate anion may minimise side reactions at electrophilic sites other than the ketone within **2.95** (**Scheme 2.38**). Unfortunately though, this once again provided a fairly complex mixture of products, with none of the formed products being identified.



Scheme 2.38: *Reagents and conditions*: i) dimethyl hex-5-en-1-ylphosphonate, *n*-BuLi, THF, −78 °C→rt. ii) dimethyl (2-oxopropyl)phosphonate, NaH, THF, 0 °C→45 °C.

We finally attempted a more laborious route, where vinylation of the ketone **2.95**, followed by alcohol acylation would provide a Tsuji Trost precursor **2.99**. This could then be reacted in the presence of Pd(0) with allyl malonate to provide a suitable relay

precursor **2.100**.[109] Attempting the vinylation of **2.95** with vinyl Grignard proved to be unsuccessful (**Scheme 2.39**). Crude analysis of the reaction showed loss of the ester function, which suggested attack at this electrophilic site in preference to the sterically hindered ketone. It is worthy of note that when the secondary alcohol was methylated rather than TES protected, vinylation of the ketone was successful, although the formed product could not be further functionalised. Attempts to install alternative alcohol protecting groups also failed.



Scheme 2.39: *Reagents and conditions*: i) Vinylmagnesium bromide, THF, 0 °C. ii) Acylation. iii) Tsuji-Trost, allyl malonate diester.

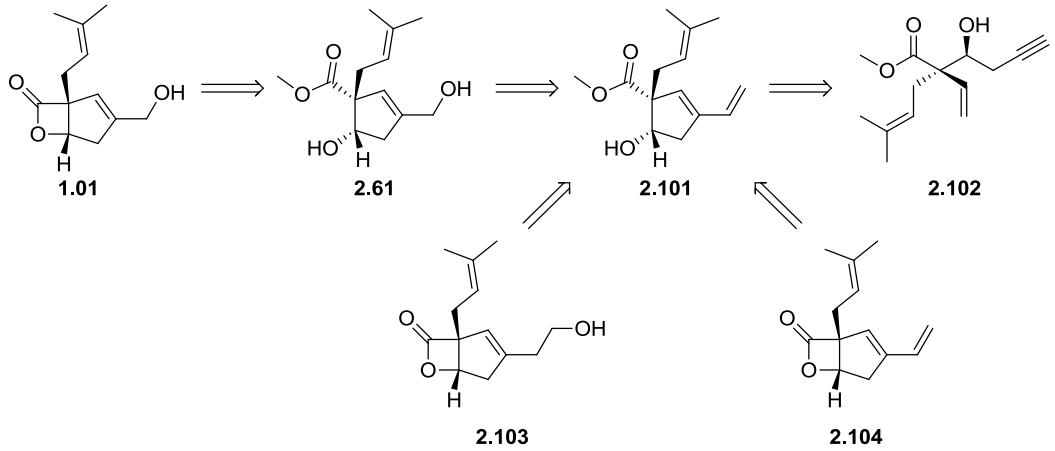
This inability to functionalise the ketone (**2.95**) led us to investigate one final metathesis route.

2.7 Racemic synthesis towards vibralactone by RCEM

Our final attempt to apply metathesis to form the cyclopentene ring focussed on ring closing enyne metathesis (RCEM). First described in 1994,[114] Grubbs' catalysts have proven successful in the synthesis of 1,3-dienes using this cycloisomerisation. Using such Ru-based pre-catalysts, initiation of this cycloisomerisation can occur either at the alkyne function (yne-then-ene pathway) or the alkene (ene-then-yne pathway). Elegant practical and theoretical papers have been published regarding mechanistic aspects of the reaction,[115-117] accumulating evidence that the ene-then-yne pathway predominates, although the yne-then-ene cannot be unequivocally ruled out.[118]

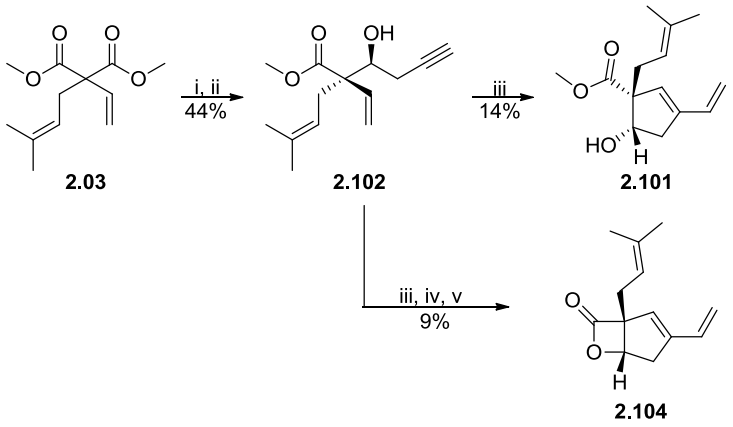
Intrigued by this fact, we decided to apply this metathesis technique to derivative **2.102**. As shown above, initiation at the vinylic alkene is highly disfavoured, and if metathesis is successful we could infer an yne-then-ene mechanism. A $MgBr_2$ directed diastereoselective propargylation of aldehyde **2.19** should provide the RCEM precursor **2.102**. Cycloisomerisation followed by oxidative cleavage of the resulting 1,3-diene

(**2.101**) could provide a route to vibralactone (**1.01**) (**Scheme 2.40**). Triene **2.101** would also provide a route to a vibralactone homologue (**2.103**) and derivative **2.104** by oxidation or direct lactonisation.



Scheme 2.40: Retrosynthesis of vibralactone (**1.01**) and derivatives using a RCEM.

Following DIBAL reduction of **2.03** the diastereoselective propargylation with allenyltributyltin proved successful, providing alkyne **2.102** in 44% yield as a single diastereoisomer (by crude ^{1}H NMR) (**Scheme 2.41**).



Scheme 2.41: *Reagents and conditions*: i) DIBAL, CH_2Cl_2, –78 °C. ii) $MgBr_2 \cdot OEt_2$, allenyltributyltin, CH_2Cl_2, –78 °C. iii) Grubbs' 1 (**1.139**), CH_2Cl_2, 30 °C. iv) $LiOH \cdot H_2O$, MeOH, H_2O, rt. iii) *p*-TsCl, pyridine, 0 °C→–5 °C.

A crystal structure of alkyne **2.102** was successfully obtained confirming the relative stereochemistry achieved during propargylation (**Figure 2.5**). The RCEM was subsequently investigated. Following a number of attempts, poor conversion was observed at rt (ca. 25% over 5 days). Increased temperatures, above 40 °C, led to substantial degradation. 30 °C was found to be an optimum temperature, although conversion was incomplete and purification complicated due to the formation of side

products. Conducting the reaction under an ethylene atmosphere was also investigated,[119,120] although no noticeable improvement was observed. Based on conversion, yields of ca. 40% of **2.101** were expected, although due to difficult purifications a 14% yield of analytically pure material was obtained (**Scheme 2.41**).

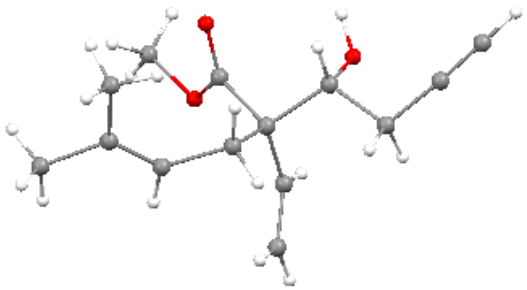


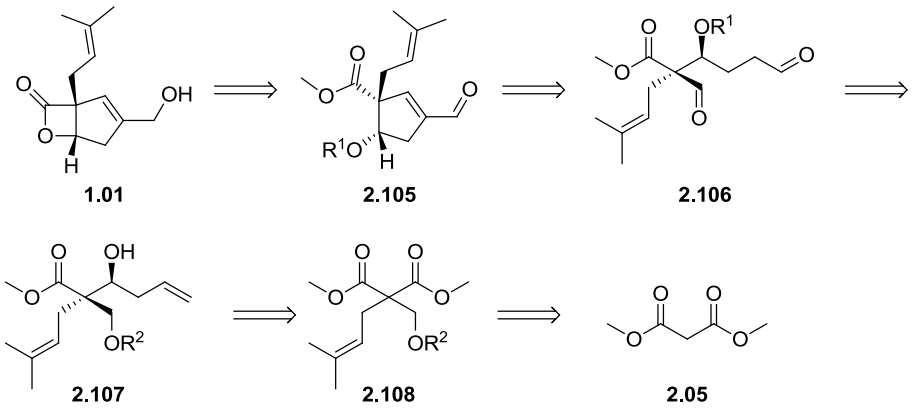
Figure 2.5: Crystal structure of alkyne **2.102**.

Despite providing a relatively low yield to finalise the total synthesis, the RCEM of **2.102** proved to be much more successful when compared to RCEM of similarly sterically hindered alkenes reported in the literature.[119,121] Optimisation by establishing an efficient purification method, or use of alternative protecting groups, is believed to be achievable. Intermediate **2.102** constitutes an interesting substrate to investigate the possibility of an yne-then-ene mechanistic pathway.

Although insufficient material was obtained to complete the synthesis of vibralactone, the triene **2.102** did provide access to a second vibralactone derivative **2.104**, *via* hydrolysis then lactonisation. Impure **2.101** was taken forward due to the difficulties during purification, providing **2.104** in 9% over 3 steps from **2.102** (**Scheme 2.41**).

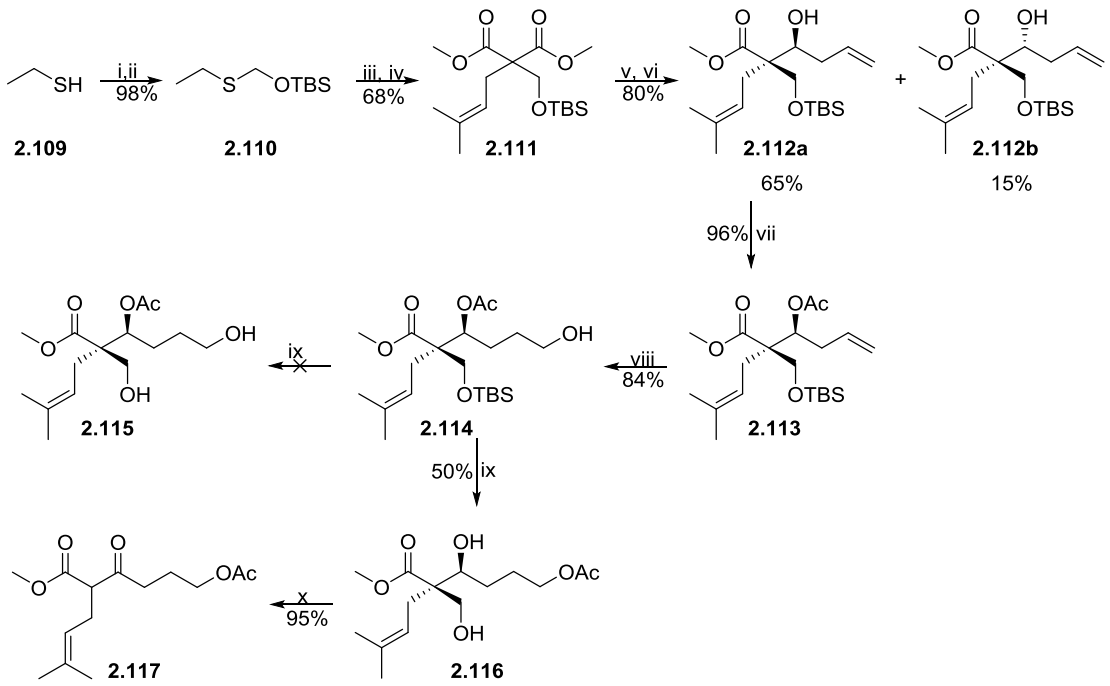
2.8 An aldol condensation approach to (±)-vibralactone

At this stage of the project, work on metathesis approaches to form the sterically congested vibralactone cyclopentene ring was halted. Snider and co-workers, in their total synthesis of vibralactone (**1.01**), had demonstrated that the aldol condensation was a suitable method for ring closure.[36,37] We therefore decided to implement an aldol condensation into our developed sequence (**Scheme 2.42**), maintaining the improved derivatisation potential of our route when compared to Sniders previous syntheses of vibralactone (**1.01**). The vibralactone cyclopentene precursor **2.105** could be obtained from dialdehyde **2.106**. Suitable oxidation procedures should provide access to **2.106** from allyl derivative **2.107**, wherein relative stereochemistry can be defined using the chelation-controlled allylation procedure described above (see section 2.2).



Scheme 2.42: Retrosynthesis of vibralactone (**1.01**) using an aldol condensation reaction.

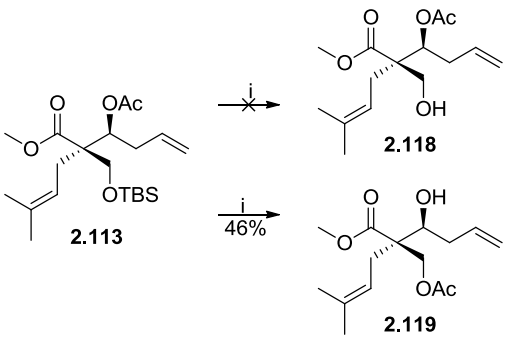
The route began with the synthesis of protected hydroxymethyl malonates **2.108**. TBS protection of the primary alcohol was chosen (**Scheme 2.43**) as related substrates had been investigated by Linclau and co-workers.[99] Prenyl malonate **2.06** was alkylated in fair yield with an unstable electrophile derived from **2.110**, synthesised from ethane thiol (**2.109**) and paraformaldehyde as previously described.[122] Following DIBAL reduction, diastereoselective allylation with allyltributyltin provided **2.112a** and **2.112b** as a separable mixture of diastereoisomers (3.8:1 respectively, 1H NMR) in 80% combined yield (65% and 15% after separation). In our allylation, we witnessed an increased diastereoselectivity when compared those reported in the Linclau paper,[99] caused by the increased size of the second α-substituent when compared to their example (prenyl *vs* methyl). There was a marked increase in stability of the allylated product **2.112** when compared to the vinyl-substituted derivatives prepared during our metathesis approach, underlining the ease of retro-aldol with the vinyl group in place. Protection of alcohol **2.112a** once again proved to be more challenging than expected, with poor conversion in attempted MOM protections and acetate protections with AcCl. Thankfully, use of Ac_2O, DMAP and DIPEA provided acetate **2.113** in quantitative yield. Hydroboration with 9-BBN (9-borabicyclo[3.3.1]nonane) was achieved in good yield, and so we next attempted to remove the TBS group to provide diol **2.115**. However, the acyl migration product **2.116** was obtained under TBAF deprotection conditions. This migration was initially overlooked, but became apparent when Dess–Martin oxidation led to an elimination product **2.117** in good yield.



Scheme 2.43: *Reagents and conditions*: i) Paraformaldehyde, NaOMe, 40 °C. ii) TBSCl, imidazole, CH_2Cl_2, rt. iii) SO_2Cl_2, CH_2Cl_2, 0 °C. iv) Prenyl malonate **2.06**, NaH, THF, 0 °C→rt. v) DIBAL, CH_2Cl_2, –78 °C. vi) $MgBr_2 \cdot OEt_2$, allyltributyltin, CH_2Cl_2, –78 °C. vii) Ac_2O, DMAP, DIPEA, CH_2Cl_2, 0 °C→rt. viii) 9-BBN, THF, 0 °C→rt, then NaOAc, H_2O_2, H_2O, 0 °C→rt. ix) TBAF, THF, 0 °C→rt. x) DMP, CH_2Cl_2, rt.

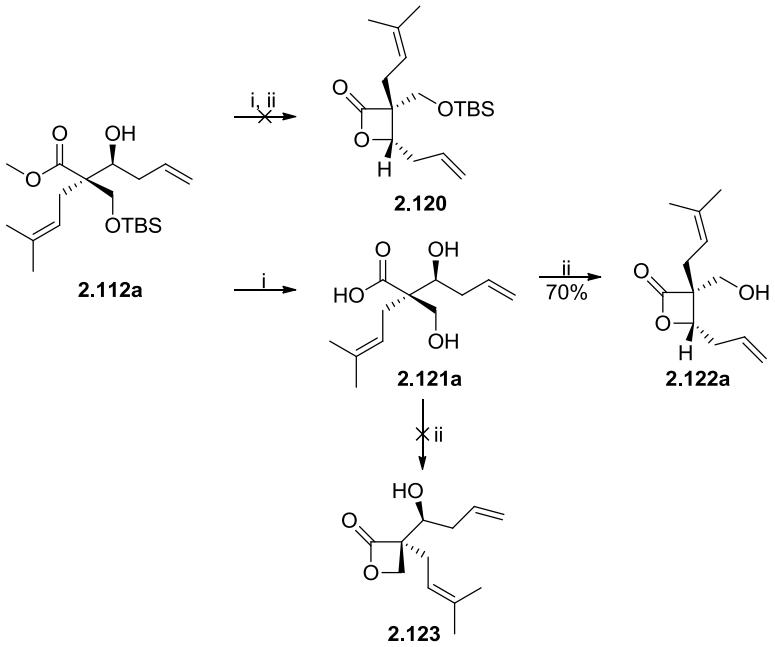
Transesterification has been previously reported to occur in the presence of TBAF.[123,124] As we were unsuccessful in substituting the acyl function for a different protecting group, we attempted alternative deprotection procedures in an attempt to circumvent this migration. Initially, deprotection using TFA was attempted, leading to a complex mixture of products. Following this, desilylation using HF·pyridine and HF in acetonitrile was attempted, unfortunately also resulting in the acyl migration product **2.116**.

We therefore tried to remove the opportunity for migration by postponing the hydroboration until after TBS deprotection (**Scheme 2.44**). Unfortunately, under all conditions applied, including use of a buffered TBAF solution,[125] migration to the hydroxymethyl primary alcohol occurred, providing migration product **2.119**.



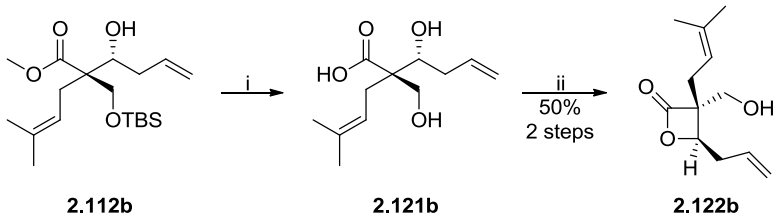
Scheme 2.44: *Reagents and conditions*: i) TBAF, pH 7 phosphate buffer, THF, 0 ˚C→rt.

As we could not solve the silyl migration problem, in place of the acyl protecting group, we considered an internal 'protection' strategy whereby the secondary alcohol was converted to the β-lactone ring of vibralactone (**1.01**). We hoped to be able to finalise the synthesis without compromising this fragile functionality. Initially, hydrolysis of the methyl ester **2.112a** followed by lactonisation was expected to provide the 'protected' alcohol **2.120** (**Scheme 2.45**). After undertaking this sequence, we were surprised to discover that alongside the desired lactonisation onto the secondary alcohol, the TBS protecting group had been lost. After repeating the sequence, it became evident that the TBS group was removed during the ester hydrolysis, leading to a regioselective lactonisation of **2.121a** to give **2.122a**. Analysis of the crude product mixture showed no evidence for the alternatively cyclised product **2.123**.



Scheme 2.45: *Reagents and conditions*: i) $LiOH \cdot H_2O$, MeOH, H_2O, 50 ˚C. ii) *p*-TsCl, pyridine, 0 ˚C→-5 ˚C.

We then undertook the same sequence of reactions using the minor diastereoisomer **2.112b** which also provided the same regioselectivity in 50% yield (some material was lost during purification). This result demonstrates the relative stereochemistry of **2.121** has no effect on regioselectivity of lactonisation.



Scheme 2.46: *Reagents and conditions*: i) $LiOH \cdot H_2O$, MeOH, H_2O, 50 °C. ii) *p*-TsCl, pyridine, 0 °C→-5 °C.

With both diastereoisomers **2.122a** and **2.122b** in hand, NOESY NMR data was obtained on each, providing confirmation of the indicated relative stereochemistry (**Figure 2.6**).[99]

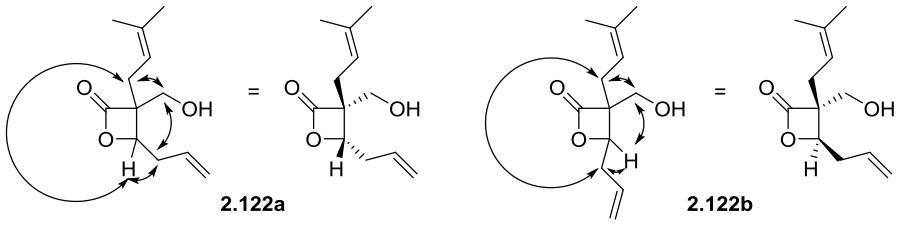
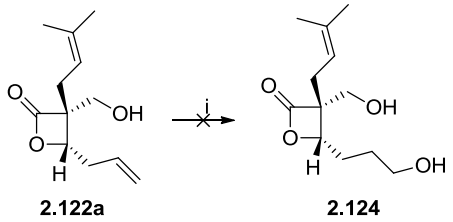


Figure 2.6: NOESY NMR data obtained from lactone diastereoisomers **2.122a** and **2.122b**.

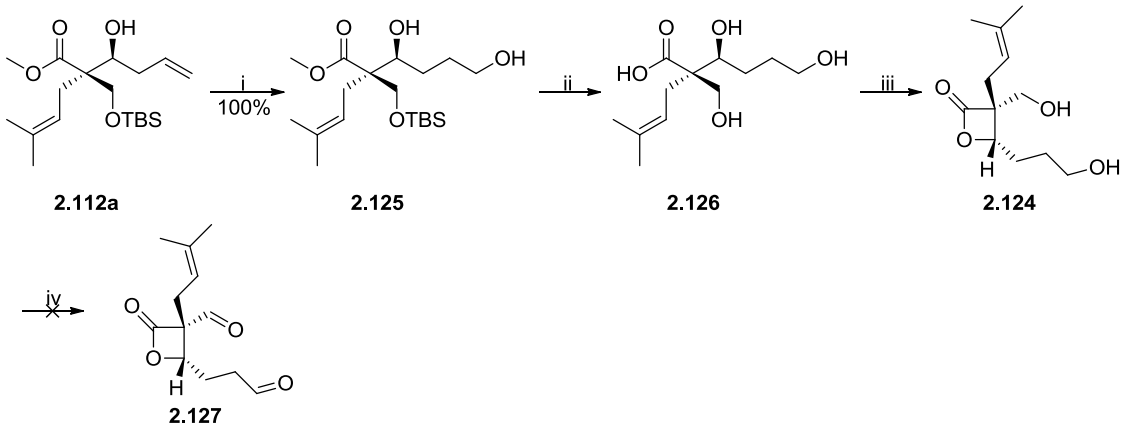
We then proceeded to hydroborate/oxidise lactone **2.122a** to form diol **2.124** (**Scheme 2.47**). Analysis of the crude product looked very promising with disappearance of the allylic alkene. Despite this, difficulties in separation from the hydroboration side products, combined with instability of the diol, prevented purification of **2.124**.



Scheme 2.47: *Reagents and conditions*: i) 9-BBN, THF, 0 °C→rt, then NaOAc, H_2O_2, H_2O, 0 °C→rt.

In an attempt to simplify the purification of diol **2.124**, we undertook an alternative approach. Allylated product **2.112a** was converted into the corresponding alcohol **2.125** by hydroboration/oxidation in quantitative yield. Removal of the ester and TBS

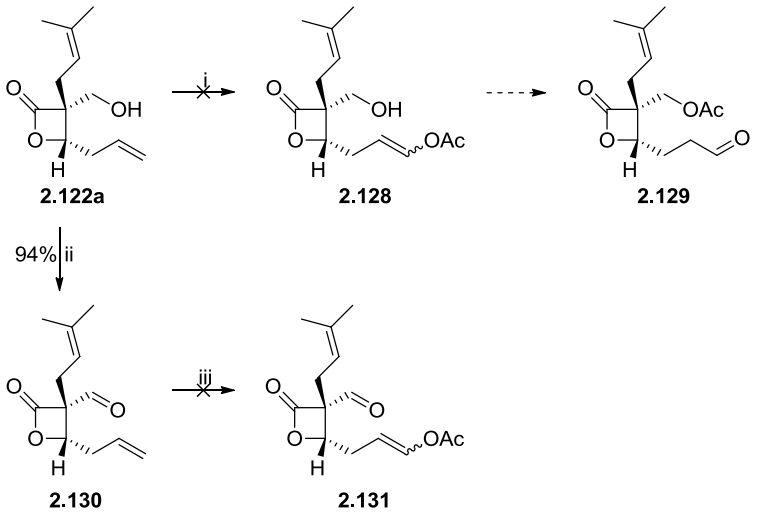
group was then undertaken, and confirmed by crude analysis to have formed trihydroxy acid **2.126**. Lactonisation was then repeated on this substrate, and once again the NMR data strongly suggested lactonisation at the disubstituted alcohol (characteristic lactone CHO at 80.5 ppm in the ^{13}C NMR spectrum) provided **2.124** (**Scheme 2.48**). Unfortunately, the instability of this diol (**2.124**) once again prevented purification. A single attempt was made to oxidise up to dial **2.127** using a Swern oxidation in order to avoid potential lactol/lactone formation,[126] but unfortunately a complex mixture of products resulted.



Scheme 2.48: *Reagents and conditions*: i) 9-BBN, THF, 0 °C→rt, then NaOAc, H_2O_2, H_2O, 0 °C→rt. ii) $LiOH \cdot H_2O$, MeOH, H_2O, 50 °C. iii) *p*-TsCl, pyridine, 0→-5 °C. iv) Oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, -78 °C→rt.

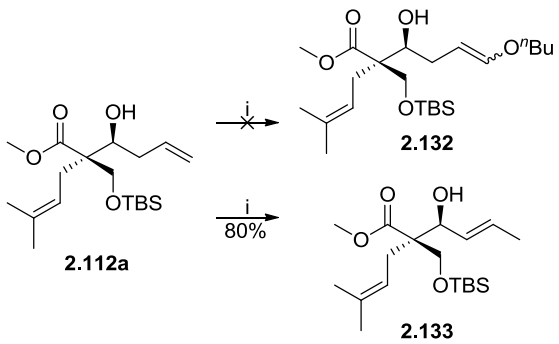
The final approach investigated towards vibralactone (**1.01**) was to install an enol ether as a 'masked' aldehyde using CM. As mono-alcohol **2.122a** had proven to be a robust intermediate, we presumed the propyl alcohol function of **2.124** was causing the instability of this intermediate. If we could directly install the aldehyde, avoiding alcohol formation (**2.124**), we hoped to circumvent the stability issues.

First attempted was the CM of hydroxyl lactone **2.122a** with vinyl acetate at rt, which proved unsuccessful (**Scheme 2.49**). We subsequently oxidised **2.122a** to aldehyde **2.130** in good yield, as to prevent acyl migration (**2.129**) of CM product **2.128**. A number of CM reactions were subsequently attempted (rt→45 °C, 5 eq. vinyl acetate, 18-48 h) on aldehyde **2.130**, but unfortunately no conversion to diene **2.131** was witnessed.



Scheme 2.49: *Reagents and conditions*: i) vinyl acetate, Grubbs' 2 (**1.140**), CH_2Cl_2, rt→reflux. ii) Oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, -78 °C→rt. iii) Vinyl acetate Grubbs' 2 (**1.140**), CH_2Cl_2, rt→reflux.

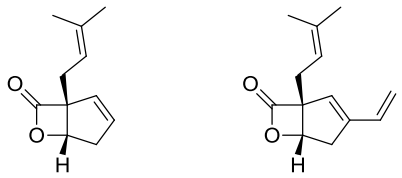
A last attempt was made with linear alkene **2.112a** and butyl vinyl ether. Unfortunately, although complete conversion was observed, only alkene isomerisation product **1.133** was obtained from the reaction mixture (**Scheme 2.50**). There are literature procedures to suppress alkene migration during metathesis reaction,[127] but due to time constraints, it was not possible to explore these modifications for CM of derivative **1.112a**.



Scheme 2.50: *Reagents and conditions*: i) *n*-Butyl vinyl ether, Grubbs' 2 (**1.140**), CH_2Cl_2, reflux.

2.9 Conclusions and Future Work

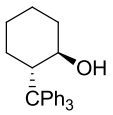
Two vibralactone derivatives **2.16** and **2.104** have been synthesised successfully, by application of RCM and RCEM methods (**Figure 2.7**). Following further synthetic optimisation, improved yields are expected to be attainable. A biological screen of these two derivatives would provide interesting insight into the biological applicability of each derivative.



2.16 **2.104**

Figure 2.7: Synthesised model compounds **2.16** and **2.104**.

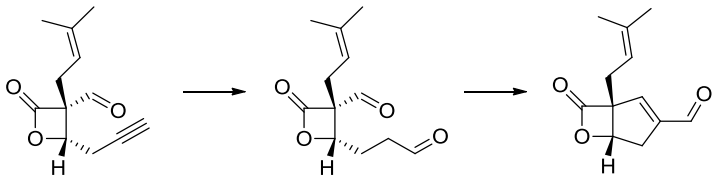
The application of a novel chiral auxiliary TTC (**1.130**) was investigated in the context of a formal enantioselective synthesis of model **2.16** (**Figure 2.8**). It has also provided improved yields for the synthesis of intermediates in our attempted total synthesis of vibralactone (**1.01**) when compared to the racemic derivatives. Further optimisation of the diastereoselective alkylation reaction conditions using the TTC auxiliary is expected to lead to improved stereocontrol.



1.130

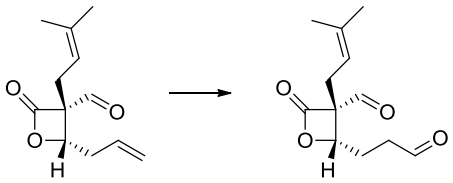
Figure 2.8: Structure of TTC (**1.130**), an auxiliary applied to the synthesis towards model compound **2.16**.

As RCM methodologies proved ineffective towards vibralactone (**1.01**), an aldol approach was explored, providing promising preliminary results. As already investigated in the RCEM approach, diastereoselective propargylation product **2.134** should be accessible. Following hydroboration, direct access to aldehyde **2.127** could prove successful (**Scheme 2.51**), providing the required aldol-condensation precursor towards cyclisation product **1.34**.



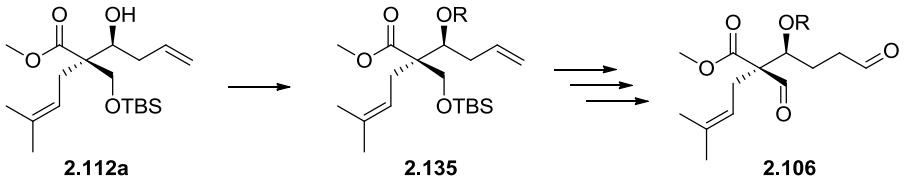
Scheme 2.51: Potential propargyl route to diketone **1.127**.

Direct oxidation procedures on alkene **2.130** should also provide an alternative route to cyclisation precursor **2.127** (**Scheme 2.52**). These procedures can also be applied to the linear derivatives, allowing numerous different potential routes to vibralactone *via* this aldol method.



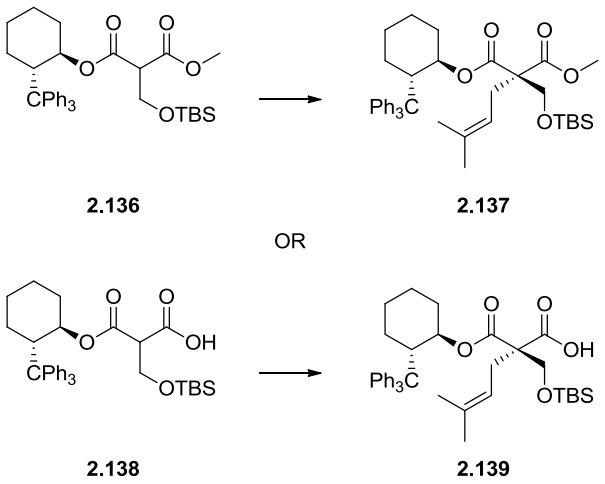
Scheme 2.52: Direct oxidation route to aldehyde **2.127**.

Although not surmounted during the investigations described above, alternative secondary alcohol protection could also provide means to an aldol precursor **2.106**. Attempts to install MOM and silyl protection proved unsuccessful, but if the acyl group could be substituted for a non-migrating group, linear aldol precursor **2.106** should be obtainable *via* the developed route.



Scheme 2.53: Alternative alcohol protection route to aldol precursor **2.106**.

This aldol route could also potentially allow increased auxiliary controlled diastereoselectivities. Selenoxide elimination prevented use of the mono-acid during alkylation reaction of **2.49**. As the selenoxide elimination reaction is no longer used in the aldol approach, an investigation into the optimum substrate for alkylation can be undertaken. For example, a malonic acid mono-ester such **2.138** may well deliver enhanced diastereoselectivity when compared to diester **2.136** (**Scheme 2.54**).

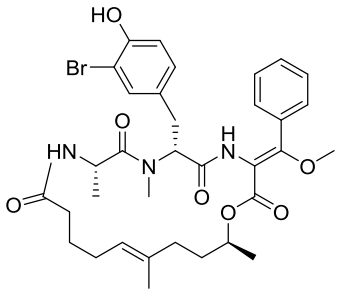


Scheme 2.54: Future optimisation toward the synthesis of (–)-vibralactone (**1.01**) by auxiliary control.

In summary, development of a synthetic route to the framework of vibralactone (**1.01**) has been successfully achieved, providing two novel vibralactone derivatives; **2.16** and **2.104**. These syntheses included implementation of metathesis methodologies in the synthesis of the cyclopentene fragment. Diastereocontrol was efficiently applied to both syntheses, *via* allylation, aldol and propargylation procedures. Auxiliary control has also been employed, achieving fair levels of diastereoselectivity and paving the way towards an enantioselective synthesis. The relative and absolute stereochemistry obtained during each synthesis has been confirmed by spectroscopic methods, and through X-ray structure determination. A number of metathesis approaches were applied to vibralactone (**1.01**), but unfortunately could not provide an efficient formation of the sterically congested trisubstituted olefin. An aldol ring-closure strategy, conserving much of the knowledge developed during the metathesis approach, was investigated, securing an advanced diol intermediate **2.124**. Further adaptation of this route holds great promise for the successful future synthesis of vibralactone (**1.01**).

3. Introduction

Miuraenamide A (**3.01**) is a macrocyclic depsipeptide which was isolated in 2006 from myxobacteria (**Figure 3.1**).[128] Following the discovery of its potential use as an antimicrobial, miuraenamide A (**3.01**) was shown to be an actin filament stabilizing reagent.[129] This section of the thesis is concerned with the IS:CE-Chem asymmetric approach to miuraenamide A (**3.01**), with the goal of allowing sufficient quantities to be obtained for further biological evaluation.



3.01

Figure 3.1: Structure of miuraenamide A (**3.01**).

Below, ecological concerns related to infection by the plant fungus *Phytophthora capsici* are presented. Following presentation of the miuraenamide family's isolation, structural elucidation and anti-fungal activity, synthetic methods applied to functionally similar anti-fungal natural products will be discussed.

The subsequent discovery of miuraenamide A (**3.01**) as an actin binder will be presented, with emphasis on its potential use as an anti-cancer agent. Key synthetic approaches to structurally related actin-binders will be overviewed. The only synthetic attempt towards miuraenamide A (**3.01**), to our knowledge, will then be described prior to presenting the IS:CE-Chem asymmetric approach to miuraenamide A (**3.01**).

3.1 *Phytophthora capsici* crop fungal infection

Fungal plant disease poses a global concern to the safety of vegetable and fruit production. *Phytophthora capsici* is one of the most important fungal strains relating to economic losses worldwide,[130] causing root, stem, leaves and fruit rot in a number of fruits and vegetables, including; cucurbits, tomatoes and beans.[131,132] *P. capsici* has been shown to cause crop losses of over 50% when infecting diverse ecosystems,[133,134] demonstrating the requirement for reliable methods to manage such infections. The use of fungicides remains an important component for treatment to ensure economically viable crop yields.[135] Despite the continued addition of available

fungicides for the treatment of *P. capsici*, there are still few fungicides available for soil treatment.[135] Also, problems arising from the development of fungicide resistant fungal strains and environmental factors of residual compounds[132] continue to drive research towards safe and reliable solutions to protect against infection. In 2006, miuraenamide A (**3.01**) was discovered to be a potent inhibitor of *P. capsici*, demonstrating its potential use as a lead for fungicidal treatment.

3.2 Fungicidal extracts from myxobacteria

Myxobacteria are Gram-negative strains of bacteria which are ubiquitously found in soil and plant debris.[136] These strains have been recognised as great sources of structurally and biologically novel secondary metabolites, including; antibiotics,[137] anti-tumour compounds,[138] and with relevance to this thesis, a diverse number of fungicides. Although many structural variants of anti-fungal metabolites have been extracted,[139-142] a common methoxyacrylate has been discovered in the families of myxothiazol (**3.02**),[143,144] cystothiazole (**3.03**),[145] melithiazole (**3.04**),[146] haliangicin (**3.05**)[147,148] and cyrmenin (**3.06**).[149] Each of these derivatives has been shown to be highly active against varying fungal strains (**Figure 3.2**).

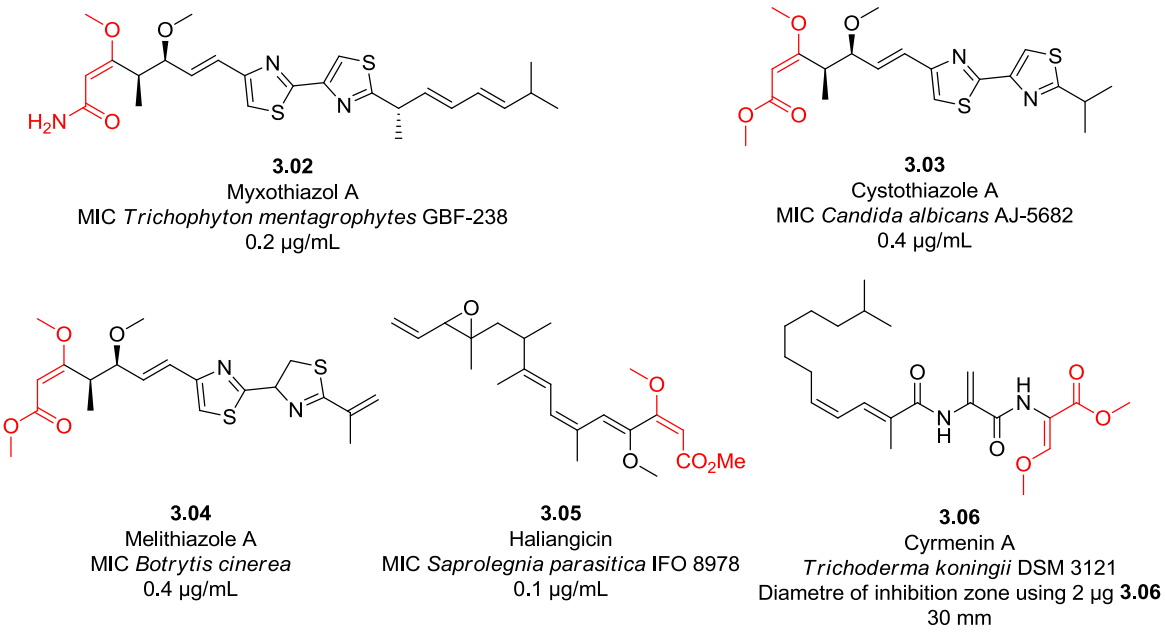
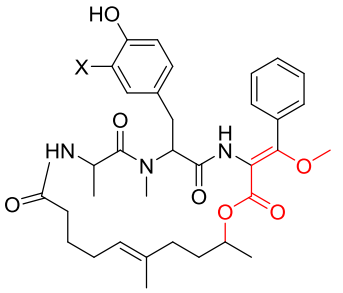


Figure 3.2: Structures of methoxyacrylate containing fungicides extracted from myxobacteria.

In 2006, Iizuka *et al*. isolated two macrocyclic methoxyacrylates, miuraenamide A (**3.01**) and B (**3.07**), from the new strain of myxobacteria, SMH-27-4 (named *Paraliomyxa miuraensis*) (**Figure 3.3**).[128] Miuraenamide A (**3.01**) was found to have a

minimum inhibitory concentration (MIC) of 0.4 μg/mL against *P. capsici*, although it proved completely inactive against the bacterial strains *Escherichia coli* NIHJ, *Staphylococcus aureus* AJ 12510 and *Bacillus subtilis* ATCC 6051.

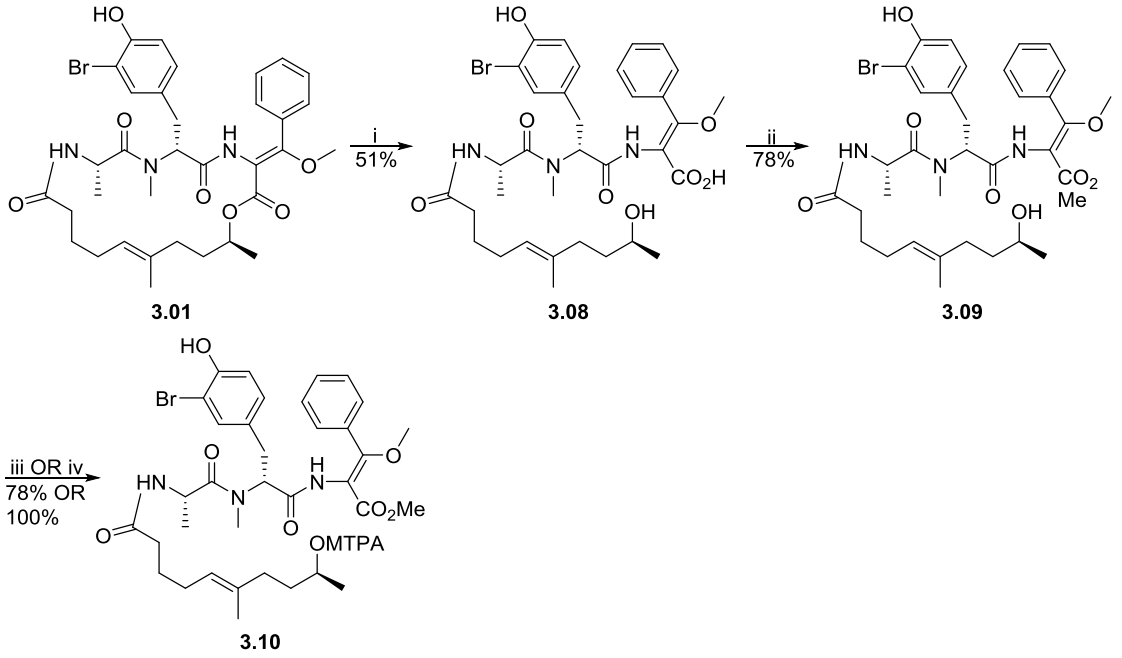


Miuraenamide A, X = Br **3.01**
Miuraenamide B, X = I **3.07**

Figure 3.3: Structure of miuraenamide A (**3.01**) and B (**3.07**).

3.3 Structural elucidation and fungicidal activity of the miuraenamide family

Although the structures of miuraenamide A (**3.01**) and B (**3.07**) were presented in 2006, the absolute stereochemistries were not reported until 2008,[150] where another 4 members of the family were also described (miuraenamide C–F, **3.11** to **3.14**) (**Figure 3.4**). The formula of miuraenamide A (**3.01**) was primarily deduced using HRMS. Subsequently, IR and NMR (^{1}H, ^{13}C, COSY, HMQC, and HMBC) were used to assign the connectivity within the macrocyclic structure. The geometry of each double bond was established using NOESY experimentation. Crystallisation of miuraenamide A (**3.01**) was attempted as to elucidate the absolute stereochemistry, but unfortunately proved unsuccessful. The absolute stereochemistry at the ester functionality was therefore achieved using the modified Mosher's method.[43] Formation of seco-acid **3.08** by ester hydrolysis preceded treatment with $TMSCHN_2$, to provide hydroxyester **3.09**. Following coupling with (*R*) and (*S*)-MTPA chloride, the change in adjacent chemical shifts obtained from COSY NMR data of **3.10** permitted the (*S*)-stereochemistry about the secondary alcohol to be deduced (**Scheme 3.1**).



Scheme 3.1: *Reagents and conditions*: i) NaOH, EtOH, rt. ii) $TMSCHN_2$, Et_2O, C_6H_6, MeOH, rt. iii) (*S*)-MTPACl, pyridine. iv) (R)-MTPACl, pyridine.

The absolute stereochemistries of each of the amino acids were deduced by heating miuraenamide A (**3.01**) in 12 N HCl, with subsequent treatment of the hydrolysate with 1-fluoro-2,4-dinitrophenyl-5-L-leucinamide or the corresponding 5-D-leucinamide (L or D-FDLA).[151] HPLC trace comparison with authentic samples of these diastereoisomers confirmed the alanine and tyrosine functionalities to have the L and D-configurations respectively.

Miuraenamide B (**3.07**) and C (**3.11**) were inferred as congeners of miuraenamide A (**3.01**). Based on HRMS data, and similarities in NMR spectra, it was deduced that these derivatives vary only at the halogen substituent on the phenolic ring. Miuraenamide D (**3.12**) has the same formula as miuraenamide A (**3.01**), although differences in ^{1}H NMR shifts about the methoxyacrylate suggested the *E/Z* isomer, which was confirmed by NOESY experiments. The structure of miuraenamide E (**3.13**) was assigned as the hydrolysed derivative of miuraenamide A (**3.01**) based on MS and 2D NMR data. It is worthy of note that it was suggested miuraenamide D (**3.12**) and E (**3.13**) could be artefacts formed during the extraction procedure. The structure of miuraenamide F (**3.14**) was once again established using HRMS and 2D NMR data, suggesting it to be a hydroxylated derivative of miuraenamide A (**3.01**). The absolute stereochemistry at this centre was deduced using the MTPA ester method as detailed above. This report deduced the structures of the entire family to be as shown in **Figure 3.4**.

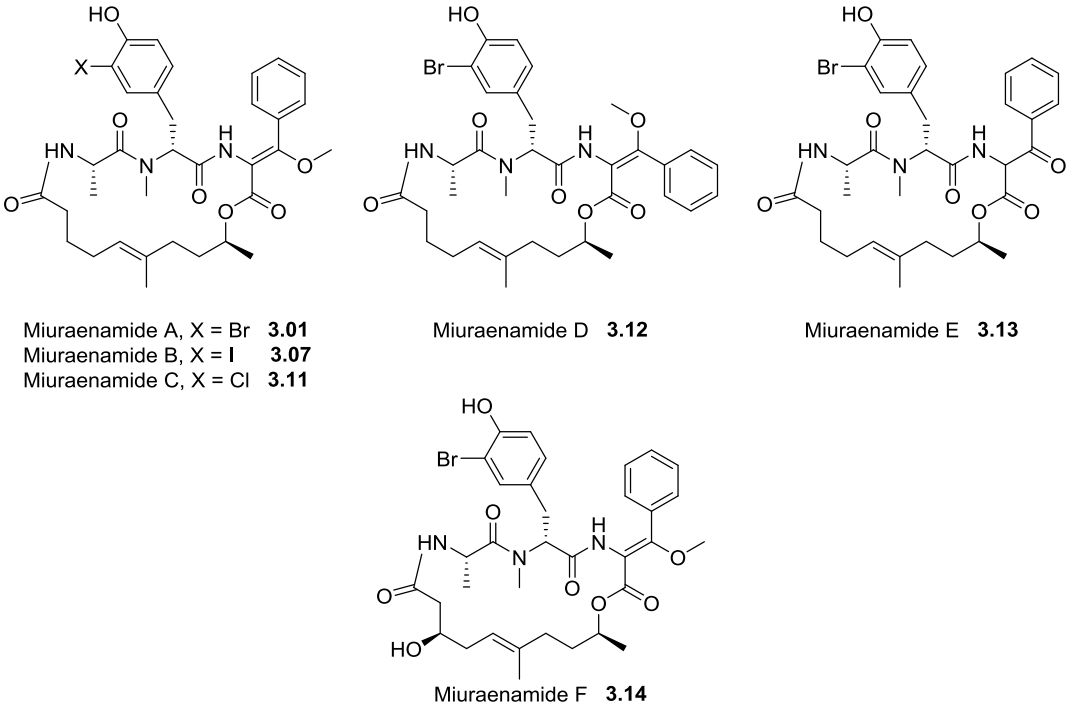


Figure 3.4: The structures of the miuraenamide family.

A biological comparison of the derivatives for activity against *Phytophthora capsici* was undertaken, which showed the halogen functionalities had no effect on inhibitory activity. The stereochemistry about the acrylate proved important, with a large drop in activity going from miuraenamide A (**3.01**) to miuraenamide D (**3.12**). This was underlined by the substantial drop in activity observed for miuraenamide E (**3.13**). Finally, the lipophilicity of the polyketide fragment is thought to be important due to the decreased activity of miuraenamide F (**3.14**) compared to miuraenamide A (**3.01**) (**Table 3.1**).

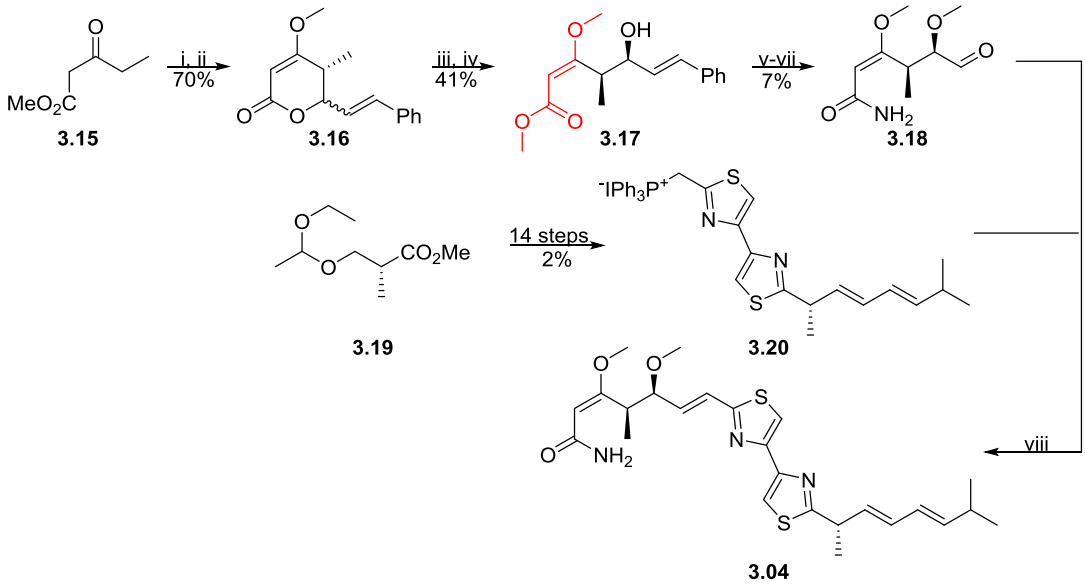
Table 3.1: Minimum doses of the miuraenamide family to affect anti-*Phytophthora* activity.

Miuraenamide	A (**3.01**)	B (**3.07**)	C (**3.11**)	D (**3.12**)	E (**3.13**)	F (**3.14**)
Dose (μg/disk)	0.025	0.025	0.025	1	10	0.13

In the previous reports of methoxyacrylate containing fungicides, the anti-fungal activity has been attributed to NADH oxidase inhibition.[147,146,145,149] Due to the structural similarity, miuraenamide A's (**3.01**) ability to inhibit NADH was tested using *Candida*-derived Mitoplast, and showed an IC_{50} of 50 μg/mL. These results suggest, in common with other methacrylate derived anti-fungicides, the miuraenamide family's cellular target is the electron transfer system of the mitochondrial respiratory chain.[128]

3.4 Synthetic strategies to the methoxyacrylate functionality of myxobacterial anti-fungal extracts

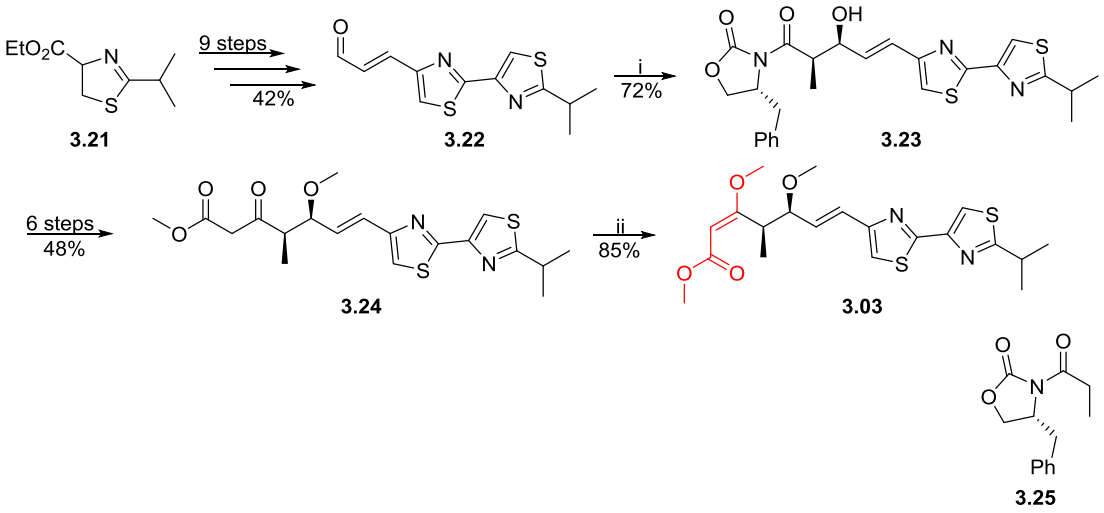
Although no total synthesis of the miuraenamide family has been achieved, the fungicidal activity has previously led to numerous total syntheses of related myxobacterial extracts. Despite the number of synthetic methods, only 4 techniques have been applied to the synthesis of the methoxyacrylate functionality. The first approach was applied by Pattenden *et al.* in the first synthesis of (±)-myxothiazol A (**3.04**), using pyranone derivative **3.16**.[152] Condensation between the dianion of **3.15** and cinnamaldehyde followed by methylation provided pyranone **3.16**. Subsequent hydrolysis and methylation provided the (*E*)-methoxyacrylate **3.17**. Further functionalisation, and coupling with Wittig salt **3.20** gave (±)-myxothiazole A (**3.04**) (yield and selectivity not provided) (**Scheme 3.2**).



Scheme 3.2: *Reagents and conditions*: i) NaH, *n*-BuLi, THF, 0 °C, then PhCH=CHCHO. ii) Me_2SO_4 K_2CO_3, Me_2CO, reflux. iii) KOH, H_2O. iv) CH_2N_2. v) MeI, Ag_2O, Et_2O. vi) Me_2AlNH_2, CH_2Cl_2, reflux. vii) OsO_4, NMMO, Me_2CO/H_2O then $NaIO_4$, THF/H_2O. viii) LiHMDS, THF, 0 °C.

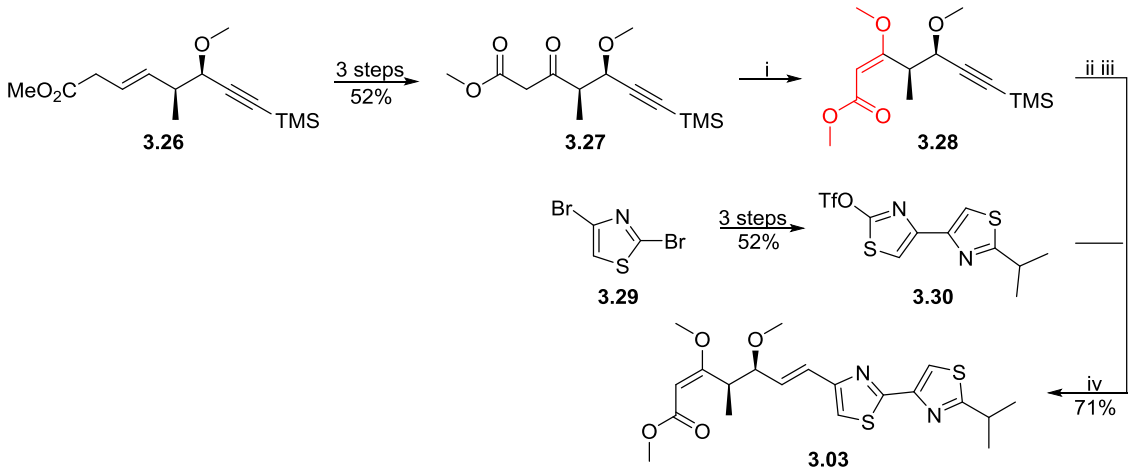
The second approach was adopted by Williams *et al.* in the first asymmetric synthesis of cystothiazole A (**3.03**), utilizing an *O*-methylation of a β-ketoester **3.24**.[153] The absolute stereochemistry was controlled using an Evans aldol of aldehyde **3.22** with **3.25** (*E*-alkene geometry controlled using Horner-Emmons coupling). Methanolysis followed by methylation and chain extension of **3.23** provided methoxyacetate precursor **3.24**. Deprotonation with NaH in HMPA and treatment with Me_2SO_4 successfully provided (*E*)-methoxyacrylate functionality, and cystothiazole A (**3.03**)

(**Scheme 3.3**). This approach was also applied to subsequent syntheses by the Akita,[154,155] Charette,[156] Pattenden [157] and Dallavalle groups.[158,159]



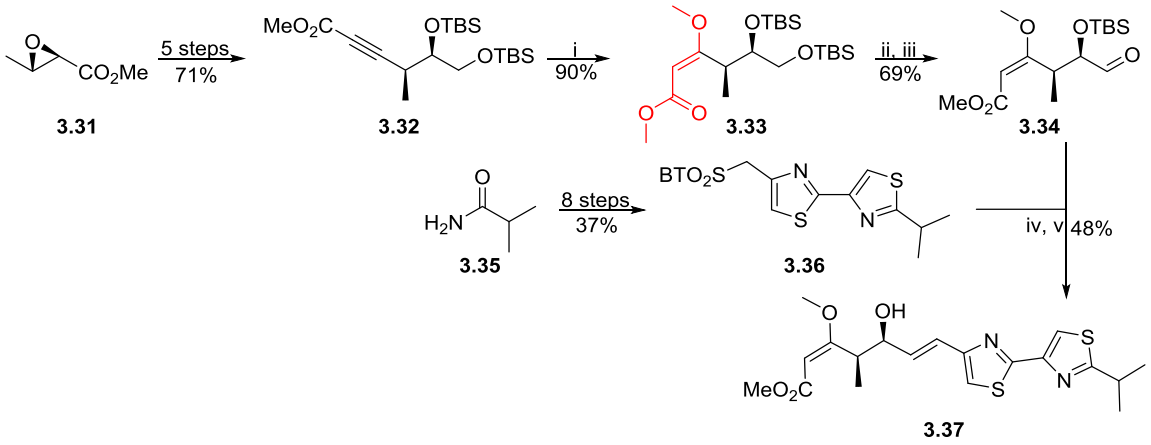
Scheme 3.3: *Reagents and conditions*: i) **3.25**, *n*-Bu_2BOTf, Et_3N, 0 ˚C, then **3.22**, –78 ˚C. ii) NaH, HMPA, Me_2SO_4.

In 2004, Panek *et al.* reported an alternative approach during their concise synthesis of cystothiazole A (**3.03**).[160] Oxidative cleavage, aldol addition and oxidation of **3.26** provided methoxyacrylate precursor **3.27**. Enol ether formation by treatment with catalytic H_2SO_4 in MeOH in the presence of trimethyl orthoformate as a dehydrating agent provided the required acrylate product **3.28**. Functionalisation and coupling with triflate **3.30** provided cystothiazole A (**3.03**) (**Scheme 3.4**). The Cossy group later applied this approach in their synthesis of melithiazole, myxothiazole and cystothiazole derivatives.[161,162]



Scheme 3.4: *Reagents and conditions*: i) $CH(OMe)_3$, H_2SO_4, MeOH, rt. ii) K_2CO_3, MeOH, rt, iii) $SnBu_3H$, $PdCl_2(PPh_3)_2$, CH_2Cl_2, 0 ˚C→rt. iv) $Pd(PPh_3)_4$, LiCl, dioxane, 100 ˚C.

The final approach employing a conjugate addition has been achieved by Akita *et al*.[163] Epoxide opening, protecting group manipulation and acetylation of **3.31** gave ester **3.32**. Conjugate addition with methanol in the presence of PBu_3 provided the methoxyacrylate system **3.33**.[164] Modified Julia olefination of aldehyde **3.34** subsequently provided access to cystothiazole C (**3.37**) (**Scheme 3.5**). Akita *et al*. also applied this method to the synthesis of cystothiazole, melithiazole and myxothiazole derivatives.[165,166]



Scheme 3.5: *Reagents and conditions*: i) $Bu_3P/MeOH/CH_2Cl_2$. ii) HF·pyridine, THF. iii) Dess-Martin periodinane, CH_2Cl_2. iv) LiHMDS, THF. v) TBAF, THF.

The number of syntheses of these natural extracts demonstrates the continued curiosity in the development of new fungicidal treatments, and supports our synthetic interest towards miuraenamide. This interest was enhanced when in 2011 it was demonstrated miuraenamide A (**3.01**) could possibly be used as an anti-cancer lead candidate.

3.5 Miuraenamide A as an actin binder

In 2011, Uesugi and co-workers presented an examination of the morphological effects of 400 known natural products on several lines of mammalian cells.[129] During this study, 9 compounds were found to induce nucleus protrusion of mammalian cells (most drastic alterations were witnessed in HeLa cells), one of which was miuraenamide A (**3.01**). Uesugi *et al*. proceeded to shown that miuraenamide A's (**3.01**) biological action as an actin filament stabilizer was responsible for this morphological effect. These actin binding properties can potentially extend miuraenamide A's (**3.01**) pharmaceutical uses from a fungicide to the use as an anti-cancer lead compound.

3.6 Actin protein, a potential anti-cancer target

Actin is one of the most abundant and conserved proteins in eukaryotic cells, with two structural forms, of which globular actin (G-actin) is the monomer. Under physiological conditions, these monomers can self-assemble, forming a double stranded polymer, named filament actin (F-actin).[167] This polymerization occurs in an ordered manner, where elongation occurs faster from one end (named the barbed end), and depolymerisation occurs primarily at the opposite end (named the pointed end), providing directional lengthening/shortening. Polymer length is maintained by an internal G-actin concentration, which if exceeded promotes polymerization into F-actin. This lowering of the intracellular G-actin concentration subsequently leads to depolymerisation. This phenomena is called 'treadmilling', and is sustained unless the dynamics are modified by actin binding proteins.[168] Such proteins can shorten or extend actin filaments by capping either the barbed or pointed end respectively, or shorten by actively severing F-actin. This facilitated directional polymerization/depolymerisation provides the basic infrastructure for such cellular functions as motility, adhesion, division and mechanical strength/structure.[169]

The integral function of these proteins in such fundamental processes has made them important receptor targets as to gain insights into cellular mechanisms. Many small molecular probes from natural sources have therefore found use by mimicking the actions of actin-binding proteins.[169] These actin binders can be divided into two categories, those which destabilise F-actin causing depolymerisation, and those which stabilise F-actin leading to polymerisation.[170] Although many structural types of actin destabilisers have been extracted from natural sources, the actin stabilisers are generally much less variable. A common macrocyclic depsipeptide, structurally similar to the miuraenamides, has been found to be prevalent throughout many families of these natural compounds (**Figure 3.5**). Following the extraction of these natural products, it has been discovered that these actin filament stabilisers are cytotoxic against many cancer cells, and could serve as anti-cancer therapeutic lead candidates.

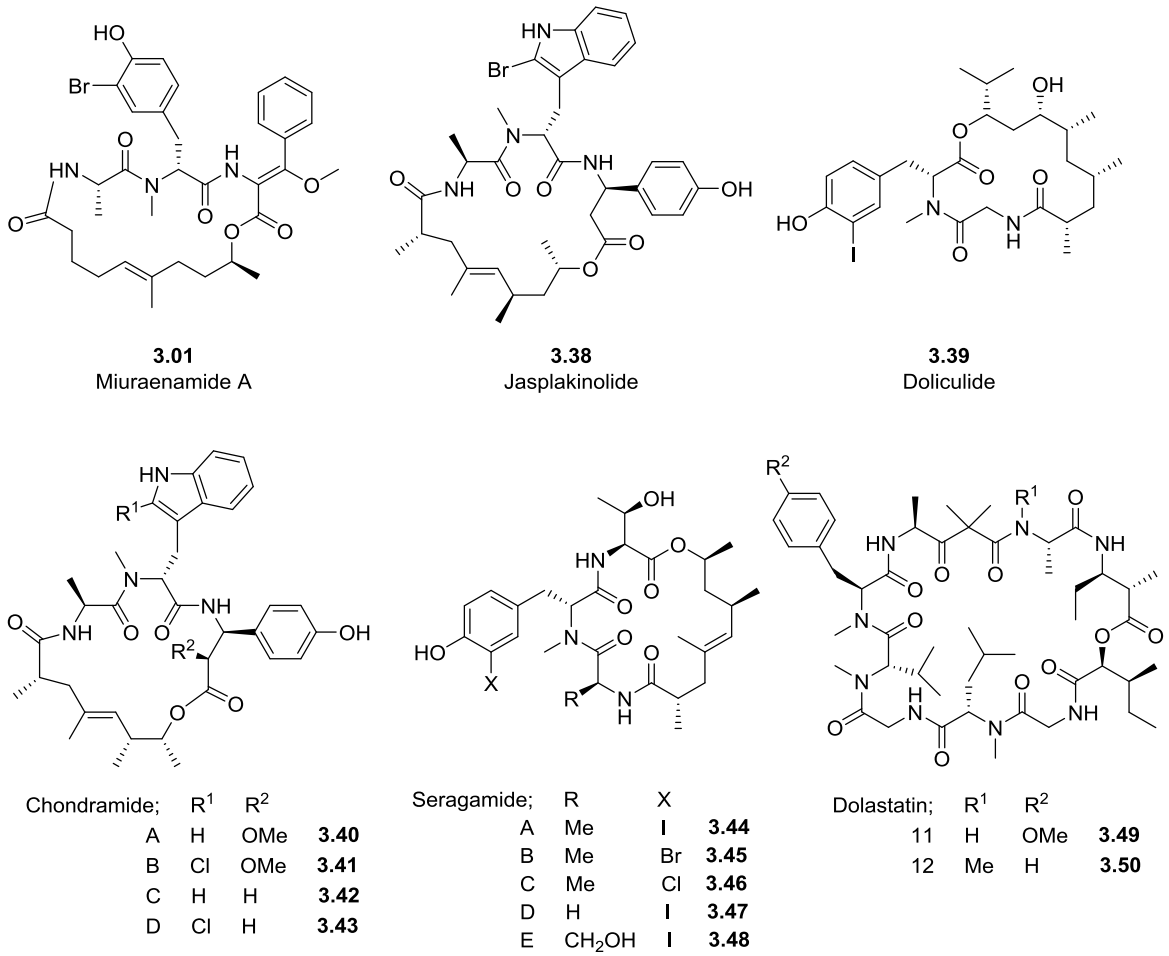


Figure 3.5: Structures of macrocyclic depsipeptide actin stabilisers.

Since the first report of the dolastatin 11 (**3.49**) inhibiting the growth of PS leukaemia with an ED_{50} of 2.7 ng/mL,[171] the effect of the structurally related actin stabilisers on varying cancer cells has been thoroughly investigated. The extracts presented in **Figure 3.5** alone have been shown to be effective in the inhibition of many cancer cell lines, including HeLa,[172] prostate [173] and lung.[174] Although these results are very promising, the actin binding functions of these natural products also prove cytotoxic against healthy mammalian cells[175] due to the conserved nature of the proteins. Although these natural products can be developed towards selective cytotoxic treatments, their ability to affect motility is also being investigated as a cancer treatment without being cytotoxic towards cancer or mammalian cells.

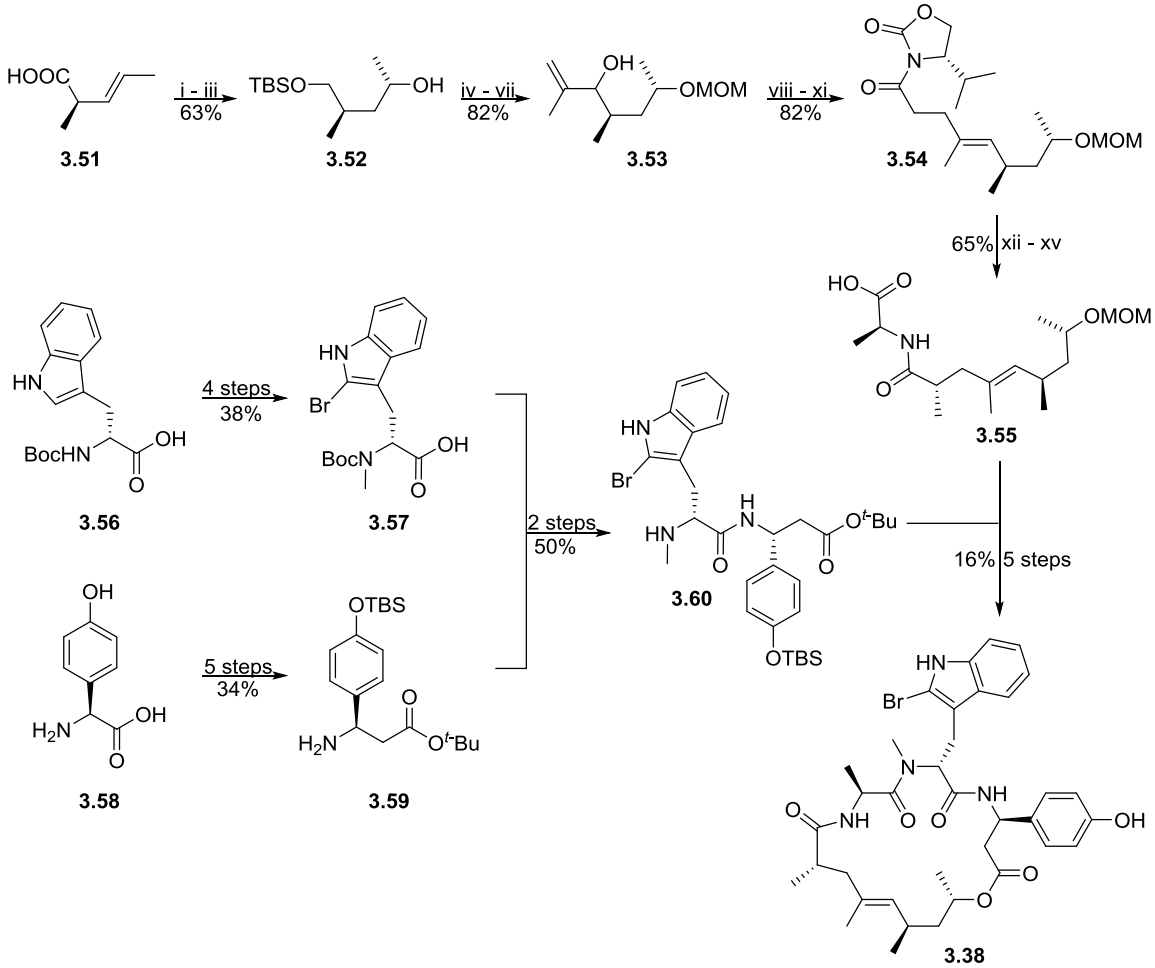
As cancer metastases are accountable for more than 90% of cancer mortalities,[176] minimizing the migration of tumour cells from the primary tumour provides a mechanism to reduce cancer related mortalities. The actin cytoskeleton plays a crucial role in the migration of tumour cells through tissues,[177] providing means for actin-binders to find use as metastases inhibitors. Supporting evidence for the use of actin binders for this purpose was presented in a study undertaken in 2004, which showed

modification to the locomotion of cancer cells could be achieved using doses of actin binders which were not cytotoxic to the cancer cells.[178]

Although no anti-cancer pharmaceutical actin binders are currently available, the potential uses for such drugs are evident. In the interest of developing selective treatments, many groups have undertaken total syntheses of the described natural products. This thesis will focus on the asymmetric synthesis of the hydrocarbon fragments of jasplakinolide (**3.38**) and the chondramide series (**3.40** to **3.43**) (no completed syntheses of seregamides **3.44** to **3.48** were found). Although many elegant approaches have been established in the syntheses of the other natural products discussed above (**Figure 3.5**), structural homogeneity between miuraenamide A (**3.01**) and these two families of natural products makes an interesting synthetic comparison with the IS:CE-Chem approach to miuraenamide A (**3.01**). As syntheses of the peptide fractions of these products have generally utilized standard peptide coupling/functionalising methods, they will not be discussed in detail here.

3.7 Claisen rearrangement approach to (+)-jasplakinolide

Although subsequently common throughout the syntheses of the natural products described above (**Figure 3.5**), the Claisen rearrangement was first applied in 1988 by Grieco *et al.* in the synthesis of (+)-jasplakinolide (**3.38**).[179] Unsaturated acid **3.51** [180] was diastereoselectively iodolactonised, reduced and mono-protected to give alcohol **3.52**. Alcohol protection then deprotection was followed by oxidation under Swern conditions, and vinylation with isopropenylmagnesium bromide, provided Claisen precursor **3.53**. The Claisen rearrangement was achieved using triethylorthoformate, before preparing oxazolidine **3.54** by acid activation and coupling with lithio-(*S*)-4-isopropyl-2-oxazolidinone. Diastereoselective methylation under auxiliary control provided the polyketide chain, which was hydrolysed, activated with $(PyS)_2$ in the presence of PPh_3, and then coupled with (*N*)-TMS-Ala-OTMS providing the finalised fragment **3.55**. Tryptophan derivative **3.57** was synthesised using standard protection and methylation (MeI, NaH) procedures from (*N*)-Boc-D-tryptophan (**3.56**). β-Tyrosine derivative **3.59** was synthesised from L-4-hydroxyphenylglycine (**3.58**) by homologation using the Wolff rearrangement. Suitable deprotection and coupling reactions (DCC with HOBT or DMAP·TFA) subsequently provided (+)-jasplakinolide (**3.38**) in 20 linear steps (**Scheme 3.6**).



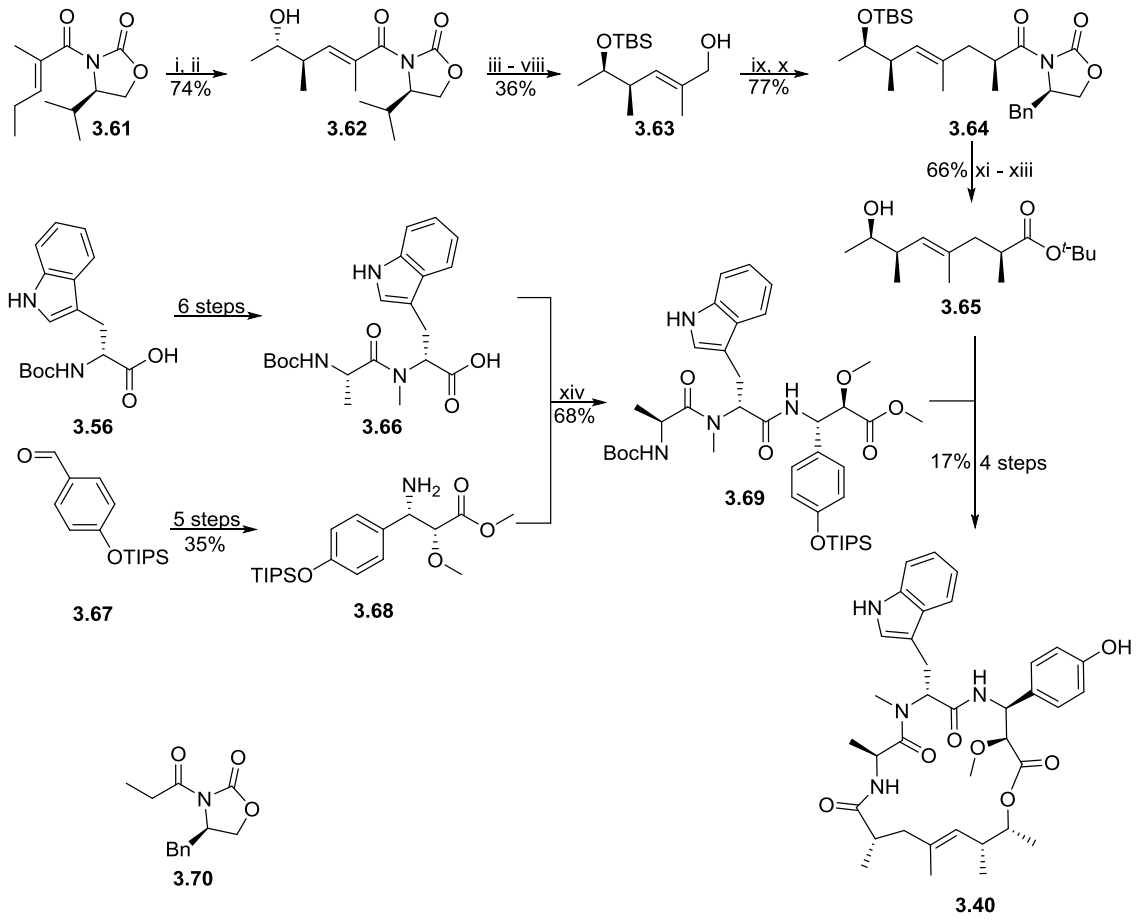
Scheme 3.6: *Reagents and conditions*: i) $NaHCO_3$, I_2, H_2O, MeOH. ii) $LiAlH_4$, Et_2O, 0 ˚C. iii) TBSCl, DMAP, Et_3N, CH_2Cl_2. iv) MOMCl, DIPEA, CH_2Cl_2 0 ˚C→rt. v) TBAF, THF. vi) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ˚C. vii) isopropenylmagnesium bromide, THF, -78 ˚C. viii) $CH_3C(OEt)_3$, propionic acid, 120 ˚C. ix) KOH, MeOH, H_2O. x) *t*-BuCOCl, Et_3N, Et_2O. xi) lithio-(*S*)-4-isopropyl-2-oxazolidinone, THF, -78 ˚C. xii) NaHMDS, MeI, THF, -78 ˚C. xiii) KOH, MeOH, H_2O. xiv) $(PyS)_2$, PPh_3, CH_2Cl_2. xv) *N*-TMS-Ala-OTMS, THF.

Similar approaches to jasplakinolide have been applied by Schmidt,[181] Konopelski,[182] Rao[183,184] and Ghosh.[185]

3.8 Vinylogous aldol approach to chondramide A

Between 2008 and 2010, Maire and co-workers presented their approach to chondramide A (**3.40**), using a Kobayashi vinylogous aldol approach.[186,187] The TBS enol ether formation of aldehyde **3.61**, followed by vinylogous aldol with acetaldehyde in the presence of $TiCl_4$ gave *anti*-alcohol **3.62**. Mitsunobu inversion with benzoic acid and reduction of the auxiliary was followed by protecting group manipulation, providing alcohol **3.63**. Iodination, followed by auxiliary controlled substitution

provided imide **3.64**. Hydrolysis, esterification and TBS deprotection provided the *t*-Bu-ester polyketide function **3.65**. The tryptophan derivative **3.66** was synthesised in 6 steps by following a known procedure. The β-tyrosine function **3.68** was synthesised from benzaldehyde derivative **3.67**. Horner-Emmons olefination, asymmetric dihydroxylation with $(DHQD)_2PHAL$ followed by Mitsunobu-type reaction with HN_3 provided the basic framework, which was protected and reduced forming β-tyrosine derivative **3.68**. Standard peptide-coupling techniques were once again applied, leading to chondramide A (**3.40**) in 17 linear steps (**Scheme 3.7**).

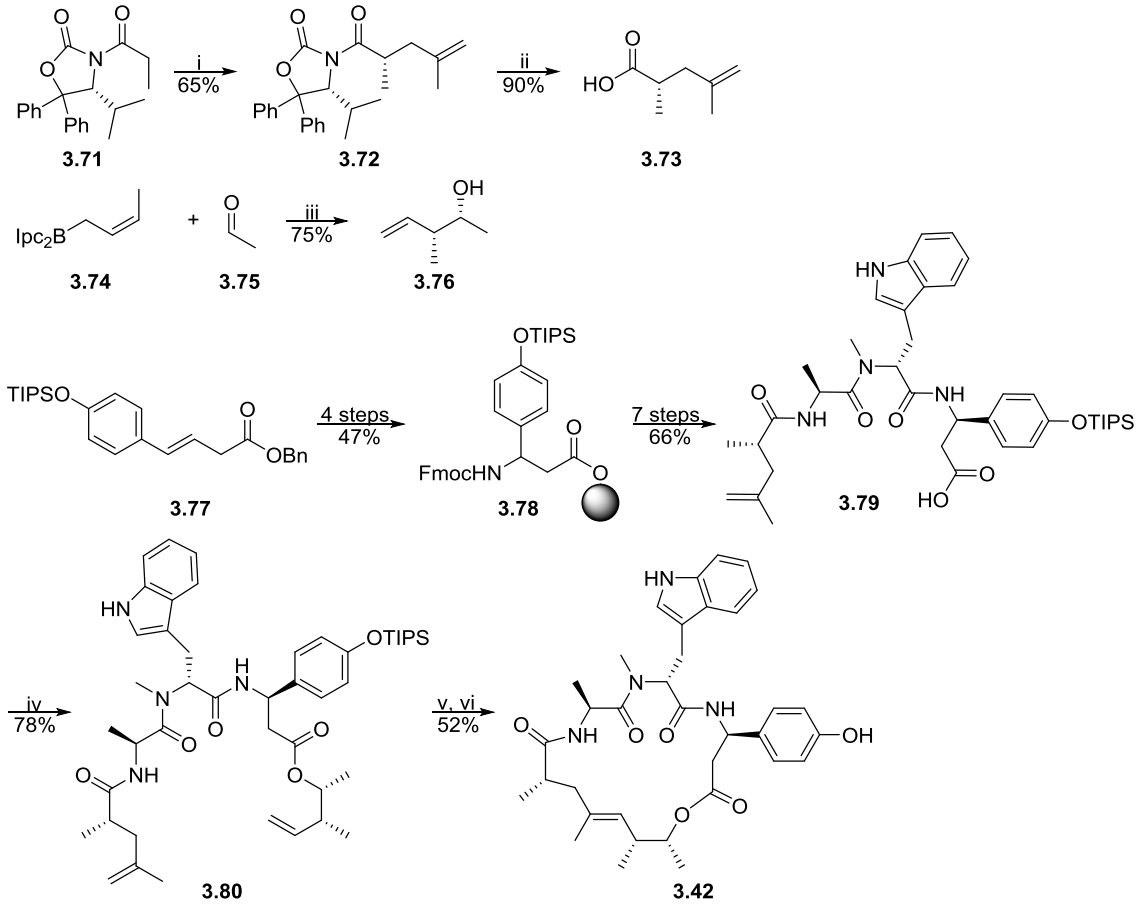


Scheme 3.7: *Reagents and conditions*: i) NaHMDS, TBSCl, THF, -80 °C. ii) $TiCl_4$, acetaldehyde, CH_2Cl_2, -80 °C. iii) $PhCO_2H$, PPh_3, DEAD, toluene 0 °C. iv) $NaBH_4$, THF, 0 °C. v) NaOH, MeOH, rt. vi) PivCl, pyridine, CH_2Cl_2. vii) TBDPSCl, imidazole, CH_2Cl_2, 0 °C. viii) DIBAL, CH_2Cl_2, -80 °C. ix) $(PhO)_3P^+MeI^-$, DMF, 0 °C. x) **3.70**, NaHMDS, THF, -80 °C. xi) H_2O_2, LiOH, THF, H_2O. xii) $Cl_3C_6H_2COCl$, *t*-BuOH, DMAP, toluene. xiii) TBAF, THF, 50 °C. xiv) HOBt, TBTU, DMF, 0 °C.

A similar approach has also been applied by Kelesse *et al.*[188] in their synthesis of chondramide C (**3.42**), although a *syn*-selective crotylation was used to install the alkene functionality in place of the vinylogous aldol.

3.9 A ring closing metathesis approach to chondramide C

The final approach was demonstrated by Waldmann *et al*. in their 2008 synthesis of chondramide C (**3.42**).[189] In this approach, alkenes **3.73** and **3.76** were synthesised by diastereoselective alkylation using Seebach's oxazolidinone,[190] and Brown crotylation respectively.[191] The peptide backbone was synthesised on solid phase, providing peptide **3.79** in good yield once removed from the support. Coupling with alcohol **3.76** provided the protected linear structure **3.79** of chondramide C (**3.42**). Ring closing metathesis catalysed by Grubbs' second generation catalyst caused macrocyclisation, which following deprotection gave chondramide C (**3.42**) in 14 linear steps (**Scheme 3.8**).

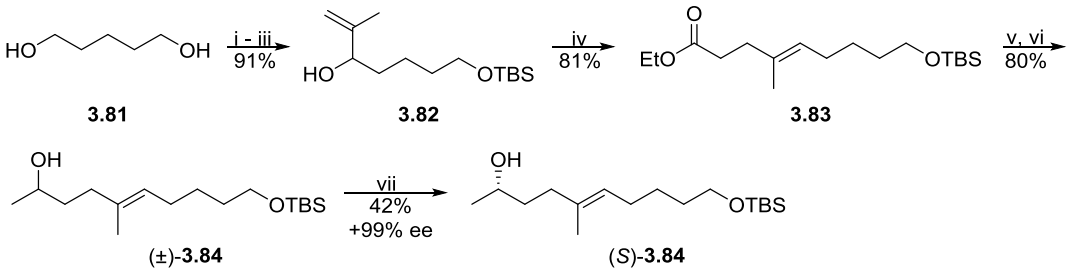


Scheme 3.8: *Reagents and conditions*: i) LDA, $ZnBr_2$, methallyl bromide, -78 °C→rt. i) NaOH, H_2O, rt. iii) -78 °C then NaOH, H_2O_2. iv) **3.76**, EDC, DMAP, DIPEA, CH_2Cl_2/DMF (20:1). v) Grubbs' 2, (25-30 mol %), toluene, 110 °C. vi) TBAF, THF, 0 °C.

The same group later applied this solid phase/ring closing metathesis approach to the total synthesis of jasplakinolide (**3.38**).[192]

3.10 Schultz and Kazmaier's synthetic approach to miuraenamide E

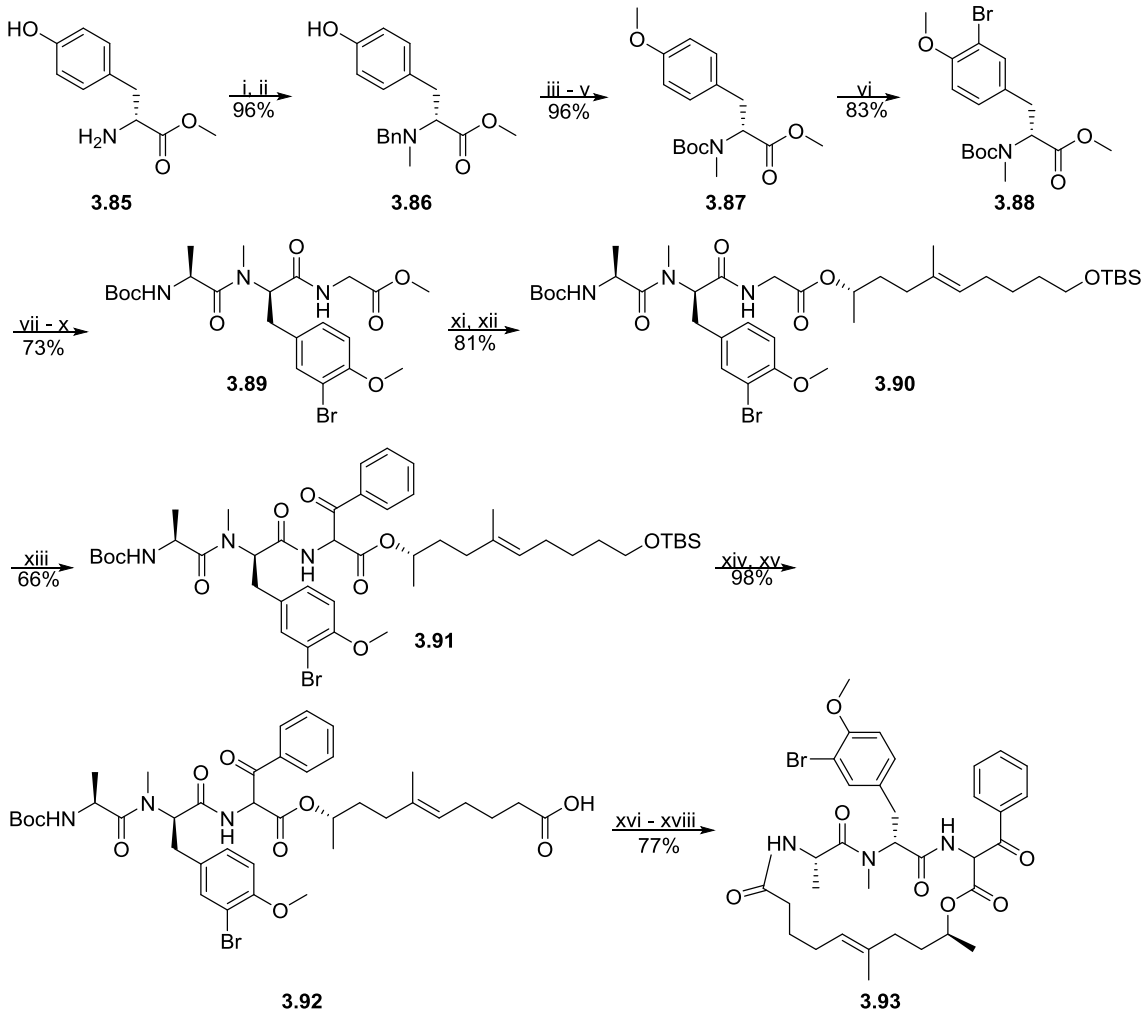
In 2010, Schultz and Kazmaier presented a PhD thesis describing their route towards miuraenamide E (**3.13**), successfully achieving a constitutional isomer of miuraenamide A/D (**3.10**/**3.12**).[193] Their synthetic route to the polyketide functionality used a Claisen rearrangement to install the *E*-double bond, and an alcohol resolution to achieve the correct *S*-stereochemistry about the secondary alcohol. Diol **3.81** was mono-protected and subsequently oxidised and vinylated with isopropenylmagnesium bromide, providing Claisen precursor **3.82** in good yield. This was subjected to triethyl orthoformate in the presence of propionic acid, providing ethyl ester **3.83**, which was reduced by DIBAL and methylated with MeLi, providing alcohol (±)-**3.84**. This alcohol ((±)-**3.83**) was resolved by enzymatic kinetic resolution using the lipase enzyme Novozym® 435 in vinyl acetate, achieving (*S*)-**3.84** in 42% with +99% ee (**Scheme 3.9**).



Scheme 3.9: *Reagents and conditions*: i) TBSCl, $NaHCO_3$, ii) DMSO, $(COCl)_2$, Et_3N. iii) isopropenylmagnesium bromide, Et_2O. iv) Triethyl orthoformate, propionic acid, reflux. v) DIBAL, –78 °C. vi) MeLi, –78 °C. vii) Vinyl acetate, Novozyme® 435.

After achieving the synthesis of the hydrocarbon fragment (*S*)-**3.84**, they synthesised peptide fragment **3.89** using standard methods. Reductive amination of D-tyrosine (**3.85**) with benzaldehyde followed by formaldehyde provided methylated tyrosine **3.86**. Benzyl hydrogenation, *N*-Boc protection followed by phenol methylation provided the tri-protected tyrosine derivative **3.87**. Subsequent bromination gave the appropriately functionalised tyrosine derivative **3.88** in good yield. Following deprotection procedures, this derivative was *O*-coupled with glycine, and *N*-coupled with L-alanine. Peptide fragment **3.89** was then hydrolysed and coupled with the resolved alcohol (*S*)-**3.84** prepared above to provide the linear fragment **3.90**. Benzoylation of the glycine fragment was then undertaken. Schultz and Kazmaier achieved this using a benzoylation procedure developed within their group.[194] Linear fragment **3.90** was subjected to 4.1 eq. of LiHMDS, 1.2 eq. of $ZnCl_2$ and 1.1 eq. benzoyl chloride to afford the miuraenamide linear structure **3.91** in moderate yield. TBS deprotection, and subsequent alcohol oxidation led to acid **3.92**. Acid activation with pentafluorophenol,

deprotection and macrocyclisation in the presence of $NaHCO_3$ gave macrocycle **3.93** in good yield. Unfortunately, partial racemisation of one of the centres occurred during the cyclisation, providing a mixture of diastereoisomers in a 2:1 ratio (benzoylic centre ratio ca. 1:1) (**Scheme 3.10**). In this report, attempts were made to remove the phenol methyl ether to provide miuraenamide E (**3.13**), but unfortunately this led to extensive degradation.

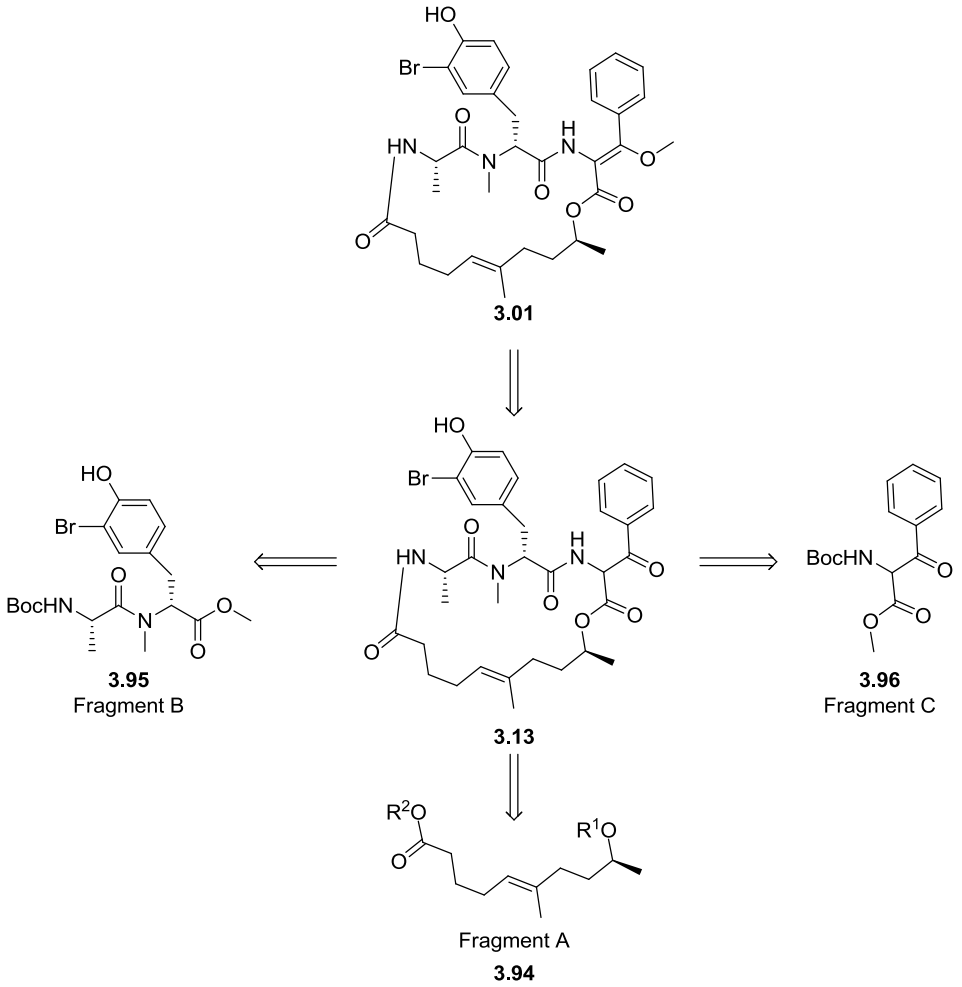


Scheme 3.10: *Reagents and conditions*: i) PhCHO, $NaBH_3CN$, MeOH, H^+. ii) paraformaldehyde, $NaBH_3CN$. iii) H_2, Pd/C, MeOH. iv) Boc_2O. v) MeI, NaH. vi) Br_2, $Hg(OAc)_2$, HOAc. vii) LiOH, viii) Gly-OMe, TBTU, DIPEA. ix) HCl, dioxane. x) Boc-(L)-Ala-OH, TBTU, DIPEA. xi) LiOH, THF, MeOH, H_2O. xii) **3.84**, DCC, DAMP, 0 °C. xiii) BzCl, LiHMDS, $ZnCl_2$, THF, -78 °C. xiv) HF, CH_3CN, 0 °C. xv) H_2SO_4, CrO_3, acetone, 0 °C. xvi) pentafluorophenol, EDC, CH_2Cl_2. xvii) THF, CH_2Cl_2. xviii) $NaHCO_3$, $CHCl_3$, CH_2Cl_2.

3.11 The IS:CE-Chem approach to miuraenamide A

The bioactivity of the miuraenamide family, and potential as pharmaceutical lead candidates has been demonstrated above, but unfortunately the isolation of these natural products in substantial amounts has thus far not proved possible.[150] The bacterial strain *Paraliomyxa miuraensis* is very slow growing, requiring 18 days of cultivation for production of the secondary metabolites. 20 L of culture broth was subsequently extracted and purified providing 19.6 mg of miuraenamide A (**3.01**), 0.4 mg of miuraenamide B (**3.07**) and 1.9 mg of miuraenamide E (**3.13**). Fractions from previous cultures, equalling a total 33 L, then provided 0.1 mg of miuraenamide C (**3.11**), 0.4 mg of miuraenamide D (**3.12**) and 0.5 mg of miuraenamide F (**3.14**). This low yield of material provided us with further interest in establishing an efficient synthesis of miuraenamide A (**3.01**), amendable to the other miuraenamide derivatives, in order to obtain access to larger quantities, making further biological evaluation possible.

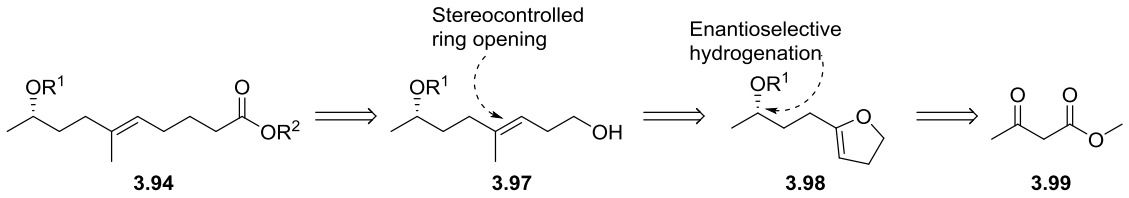
Our initial target would be towards the synthesis of miuraenamide E (**3.13**). Having established a route to the ketoester **3.13** enol ether strategies, such as those described previously, could be applied to the synthesis of miuraenamide A (**3.01**). We envisioned a convergent approach with the macrocycle of miuraenamide E (**3.13**) being derived from three fragments, fragment A (**3.94**), fragment B (**3.95**) and fragment C (**3.96**). Deprotection and coupling/macrocyclisation methods would then be applied in appropriate combination to establish the macrocycle of miuraenamide E (**3.13**) (**Scheme 3.11**).



Scheme 3.11: The IS:CE-Chem approach to miuraenamide A (**3.01**), *via* miuraenamide E (**3.13**).

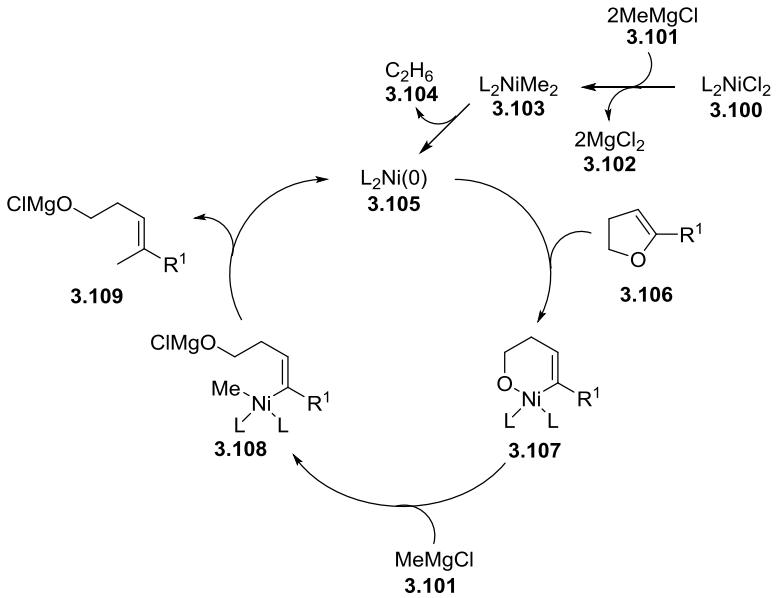
3.11.1 Retrosynthesis of fragment A

Our initial retrosynthesis of the hydrocarbon fragment **3.94** relied on a furan ring opening reaction to install the appropriate *E*-alkene. It was envisioned ester **3.94** could be synthesised by dihomologation of homoallylic alcohol **3.97**. We deduced it would be feasible to ring open/methylate furan derivative **3.98** to obtain the required *E*-homoallylic alcohol **3.97** selectively. Using appropriate reduction, protecting and coupling techniques, furan **3.98** should be accessible from methyl acetoacetate (**3.99**) (**Scheme 3.12**). The benefit of this approach is, unlike the approach by Schultz and Kazmaire,[193] a catalytic asymmetric reduction could be used to install the secondary alcohol, preventing the +50% losses inherent within a resolution approach.



Scheme 3.12: Retrosynthesis of fragment A (**3.94**).

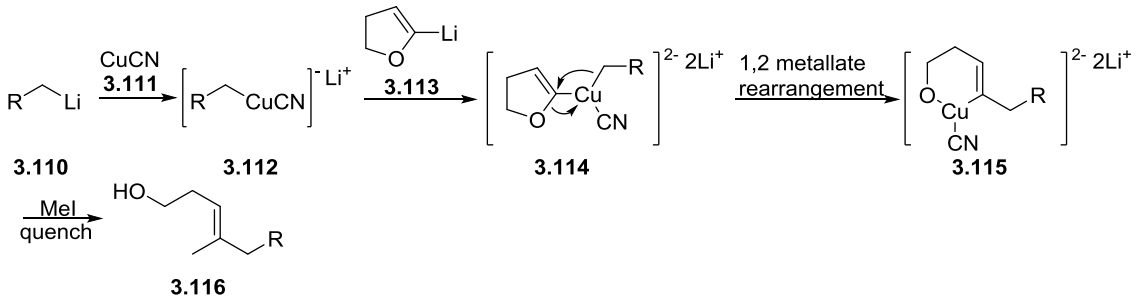
Two potential methods were envisioned for the successful installation of the trisubstituted alkene **3.97**. The first makes use of Ni(0) catalysis (**3.105**) for the stereoselective synthesis of trisubstituted alkenes from substituted 2,3-dihydrofuran and dihydropyran derivatives. First described by Wenkert *et al.*[195] this method was later developed by Kocienski and co-workers.[196] *In situ* formation of the Ni(0) catalyst **3.105** in the presence of Grignard reagents can be achieved from commercially available $NiCl_2(PPh)_3$ (**3.100**). Transmetalation of the Ni(II) species **3.100** with a Grignard reagent, in this case MeMgCl (**3.101**), provides dimethyl nickel intermediate **3.103**, which reductively eliminates providing the Ni(0) catalyst **3.105**. Insertion into the C-O bond of dihydrofuran **3.106** provides intermediate **3.107**, which by transmetalation with methyl Grignard (**3.101**), and subsequent reductive elimination, provides the *E*-alkene **3.109** (**Scheme 3.13**). The insertion into the C-O bond determines the alkene stereochemistry, where reductive elimination occurs in the same position as insertion, maintaining the initial geometry of the alkene.



Scheme 3.13: Proposed mechanism of Ni(0) catalysed 2,3-dihydrofuran opening

The second method was later reported in 1989 by Kocienski *et al.* using CuCN (**3.111**).[197] Although the stereochemistry of the alkene is once again controlled by the dihydrofuran O-C geometry, the C-M bond forms with inversion by a 1,2-metallate

rearrangement.[198] This procedure allows the trisubstituted alkene to be synthesised from 2,3-dihydrofuran in one pot. Alkyllithium **3.110** is believed to react with CuCN (**3.111**) providing lower order cuprate **3.112**, which when treated with lithiated 2,3-dihydrofuran **3.113**, provides the higher order cuprate **3.114**. The 1,2-metallate rearrangement subsequently occurs on warming, leading to oxycuprate **3.115** with inversion of the C-M bond, which when quenched with excess R-X (in this case MeI) provides the trisubstituted alkene **3.116** (**Scheme 3.14**).

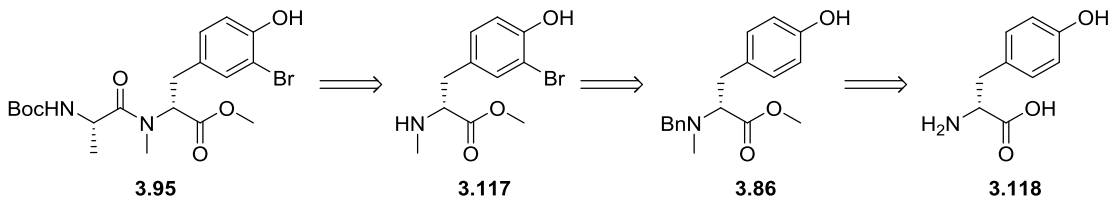


Scheme 3.14: Cu approach to 2,3-dihydrofuran ring opening.

Each of these methods provides a potential route to the formation of a trisubtituted *E*-alkene, and thus we were keen to investigate both for the synthesis of fragment A (**3.94**).

3.11.2 Retrosynthesis of fragment B

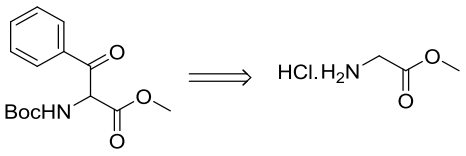
Although the peptide fragment B (**3.95**) is a literature compound,[199] we envisioned a more concise approach related to that undertaken by Schultz and Kazmaire.[193] We initially intended to take dipeptide **3.95** through the synthesis without protection of the phenol, to avoid the final phenolic deprotection problems witnessed in the Schultz approach,[193] whilst minimising the number of steps. Coupling of brominated *N*-methyl tyrosine **3.117** with Boc-L-Ala-OH would provide the required dipeptide **3.95**. Bromo tyrosine **3.117** should be accessible from hydrogenolysis of benzyl amine **3.86**, which itself can be accessed from commercially available D-tyrosine (**3.118**) (**Scheme 3.15**).



Scheme 3.15: Retrosynthesis of fragment B (**3.95**).

3.11.3 Retrosynthesis of fragment C

Many approaches are available for the formation of known intermediate **3.96**, and thus we envisioned its synthesis to be achieved from Gly-OMe (**3.119**) using established procedures (**Scheme 3.16**).



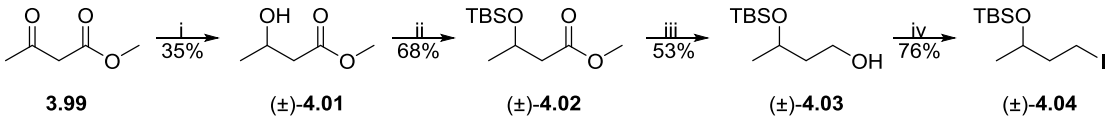
3.96 **3.119**

Scheme 3.16: Retrosynthesis of fragment C (**3.96**).

4. Results and discussion.

4.1 Dihydrofuran ring opening approach to the trisubstituted (*E*)-alkene

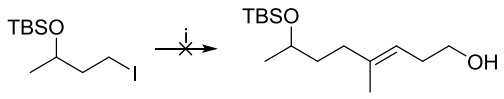
Our primary focus was towards the synthesis of fragment A (**3.94**). As we were yet to establish a feasible furan ring opening procedure, this was initially undertaken using more accessible racemic material. Methyl acetoacetate (**3.99**) was reduced using $NaBH_4$, providing the hydroxyester (±)-**4.01** in 35% yield. Despite the low yield, the reaction was undertaken on sufficient scale for material to be taken forward. Although we postponed optimisation for the asymmetric approach, we believed the low yield was caused by losses during aq. extraction. The alcohol was TBS protected before ester reduction using DIBAL, and iodinating with PPh_3 and I_2, providing a suitable precursor ((±)-**4.04**) to investigate the furan opening reactions (**Scheme 4.1**).



3.99 (±)-**4.01** (±)-**4.02** (±)-**4.03** (±)-**4.04**

Scheme 4.1: *Reagents and conditions*: i) $NaBH_4$, MeOH, 0 ˚C. ii) TBSCl, imidazole, DMAP, DMF, 0 ˚C→rt. iii) DIBAL, CH_2Cl_2, 0 ˚C→rt. iv) I_2, PPh_3, imidazole, CH_2Cl_2, rt.

We first attempted the CuCN (**3.111**) promoted furan opening established by Kocienski *et al*.[197] Unfortunately, all attempts to achieve this reaction proved unsuccessful (**Scheme 4.2**). Although the crude data suggested partial formation of unsaturated alcohol (±)-**4.05**, poor mass recovery alongside formation of side products made this reaction unviable. Although this reaction can be achieved in one step, it is practically demanding requiring many temperature changes and flask transitions. Also, the requirement for 3 eq. of *t*-BuLi makes this reaction unsuitable for large-scale application.

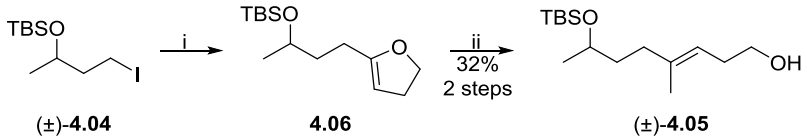


(±)-**4.04** (±)-**4.05**

Scheme 4.2: *Reagents and conditions*: i) 2,3-Dihydrofuran, *t*-BuLi, CuCN (**3.111**), Et_2O, THF, MeI, -78 ˚C→-20 ˚C.

We next attempted the Ni-catalysed approach to alcohol (±)-**4.05**.[195] Dihydrofuran **4.06** was first synthesised using *t*-BuLi and 2,3-dihydrofuran in sufficient purity for use

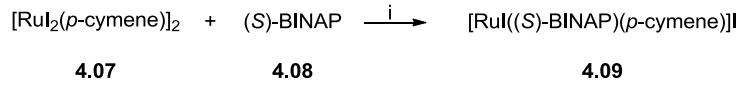
directly in the next step. Furan **4.06** was then heated to reflux in benzene, in the presence of the *in situ* formed nickel catalyst **3.105**, successfully providing homoallylic alcohol (±)-**4.05** in 32% yield over 2 steps (**Scheme 4.3**). Although this yield was less than optimal, the TLC and crude NMR data suggested the reaction proceeded very cleanly, and that product was most likely lost during extraction/purification. At this stage we did not possess enough material to undertake any optimisation. Due to the observed purity of the crude reaction mixture, we believed optimisation could be easily achieved, and therefore elected to progress with the asymmetric synthesis.



Scheme 4.3: *Reagents and conditions*: i) 2,3-dihydrofuran, *t*-BuLi, HMPA, THF, 0 °C→ −45 °C. ii) $NiCl_2(PPh_3)_2$ (**3.100**), MeMgCl (**3.101**), C_6H_6, reflux.

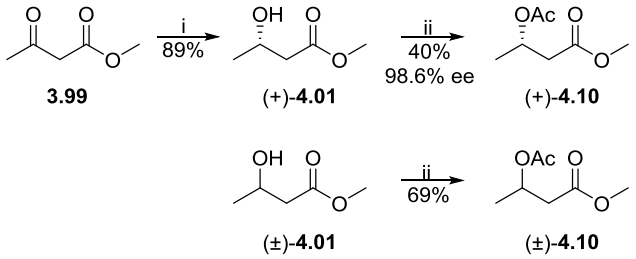
4.2 Asymmetric synthesis of fragment A

For the asymmetric synthesis towards fragment A (**3.94**), we first required methyl (*S*)-3-hydroxybutanoate ((+)-**4.01**). Although (+)-**4.01** can be purchased in 98% ee, the expense (£78.40/g, SigmaAldrich) was considered too high as a starting material for the proposed synthesis. We therefore explored a literature method to access (+)-**4.01**, applying a Noyori asymmetric hydrogenation.[200] Takaya and co-workers have presented an investigation into the optimum catalyst for the asymmetric synthesis of methyl (*S*)-3-hydroxybutanoate ((+)-**4.01**).[201] They found the catalyst [RuI((*S*)-BINAP)(*p*-cymene)]I (**4.09**) to be highly effective for the asymmetric reduction of methyl acetoacetate (**3.99**). Although the yield and enantioselectivity achieved for the asymmetric hydrogenation proved to be only as effective as those described by Noyori, Takaya's procedure has the benefit of using an easily synthesisable catalyst, starting from the cheap commercially available reagents $[RuI_2(p\text{-cymene})]_2$ (**4.07**) and (*S*)-BINAP (**4.08**). We therefore synthesised catalyst **4.09** (**Scheme 4.4**). Although the analysis for the reaction product showed formation of **4.09** was successful using the procedure described by Takaya,[201] the catalyst could not be isolated in analytically pure form. Despite this, catalyst **4.09** proved highly effective in the hydrogenation described below.



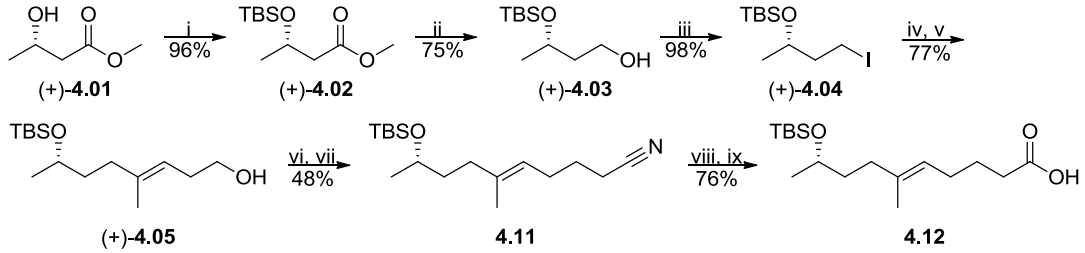
Scheme 4.4: *Reagents and conditions*: i) EtOH, CH_2Cl_2, 50 °C.

Following Takaya's procedure,[200] methyl acetoacetate (**3.99**) was hydrogenated at 100 bar H_2 using 0.08 mol% of catalyst **4.09** (on a 10 g scale the reaction took 6 days when compared to Takaya's 1.61 g scale which took 35 h) providing alcohol (+)-**4.01** in 89% yield. Although the product was distilled to remove the catalyst for chiral analysis, the crude reaction was very clean with full conversion of starting ketone. Removal of the purification step should allow quantitative yield to be achieved for the hydrogenation. We next investigated the enantiopurity of the hydroxyester. Using chiral GC, we attempted to separate the enantiomers of racemic alcohol (±)-**4.01**, which unfortunately proved unsuccessful. Acylation of each alcohol (±)-**4.01** and (+)-**4.01** was therefore undertaken providing (±)-**4.10** and (+)-**4.10** which could be separated by GC (adapting a procedure described by Andrade *et al.*),[202] showing (+)-**4.01** to have a 98.6% ee (**Scheme 4.5**). In the interest of time, the acylation of (+)-**4.01** was stopped after 2 h despite incomplete conversion, accounting for the drop in yield.



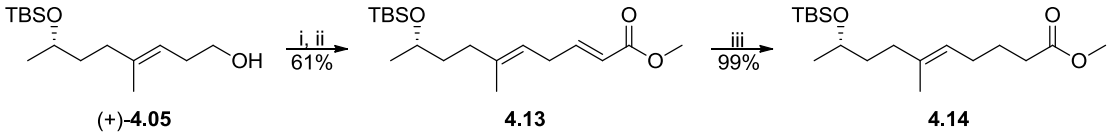
Scheme 4.5: *Reagents and conditions*: i) Ru[I(*S*-BINAP)-*p*-cymene]I (**4.09**), H_2 (100 bar), MeOH, rt. ii) AcCl, DMAP, CH_2Cl_2, 0 °C→rt.

Chiral alcohol (+)-**4.01** was then converted to the homo-allylic alcohol (+)-**4.05** using the methods previously established for the synthesis of (±)-**4.05**. Additional care during extraction and purification procedures resulted in increased yields. Subsequent protection, reduction and iodination were realised, providing (+)-**4.04** in 71% over 3 steps. Dihydrofuran coupling, and ring opening provided homoallylic alcohol (+)-**4.05** in 77% over two steps. Again, NMR data for the crude product suggested very clean conversion had been achieved, so optimisation of the purification process should improve the isolated yield of (+)-**4.05** further. We next required a two-carbon homologation of alcohol (+)-**4.05** to complete the hydrocarbon fragment. Although this could have been avoided in principle by using larger ring systems in place of 2,3-dihydrofuran, the use of such alkenes has previously been shown to require longer reaction times and afford lower yields,[203] and thus was avoided. Therefore, bromination of alcohol (+)-**4.05**, and then substitution with lithiated acetonitrile, provided nitrile **4.11** in 48% yield. This was then reduced using DIBAL, and subjected to Pinnick oxidation providing the required carboxylic acid **4.12** (**Scheme 4.6**).



Scheme 4.6: *Reagents and conditions*: i) TBSCl, imidazole, DMF. ii) DIBAL, CH_2Cl_2, 0 °C→rt. iii) I_2, PPh_3, imidazole, DMF, rt. iv) 2,3-dihydrofuran, *t*-BuLi, HMPA, THF, 0 °C→–45 °C. v) $NiCl_2(PPh_3)_2$ (**3.100**), MeMgCl (**3.101**), C_6H_6, 90 °C. vi) NBS, PPh_3, CH_2Cl_2, 0 °C→rt. vii) LDA, CH_3CN, THF, –78 °C→rt. viii) DIBAL, CH_2Cl_2, –78 °C. ix) $NaClO_2$, $NaHPO_3$, 2-methyl-2-butene, *t*-BuOH, THF, 0 °C.

Despite providing a successful route to acid **4.12**, all attempts to increase the yield for the substitution reaction with acetonitrile were unsuccessful. This was potentially caused by deprotonation of the product (**4.11**) by the acetonitrile anion due to similarities in pKa.[204] Unsatisfied with this yield, we sought an alternative approach. This was achieved by primarily oxidising alcohol (+)-**4.05** to the aldehyde, before undertaking a Horner Emmons reaction with trimethyl phosphonoacetate, providing diene **4.13** in 61% yield over the two steps. A regioselective 1,4-reduction was then required to form ester **4.14**, which was successfully achieved using $NaBH_4/NiCl_2 \cdot 6H_2O$ in quantitative yield (**Scheme 4.7**). Hydrolysis of the ester **4.14** proceeded without the need for purification of the resulting carboxylic acid. This alternative route approximately doubled the overall yield when compared to the acetonitrile process described above.

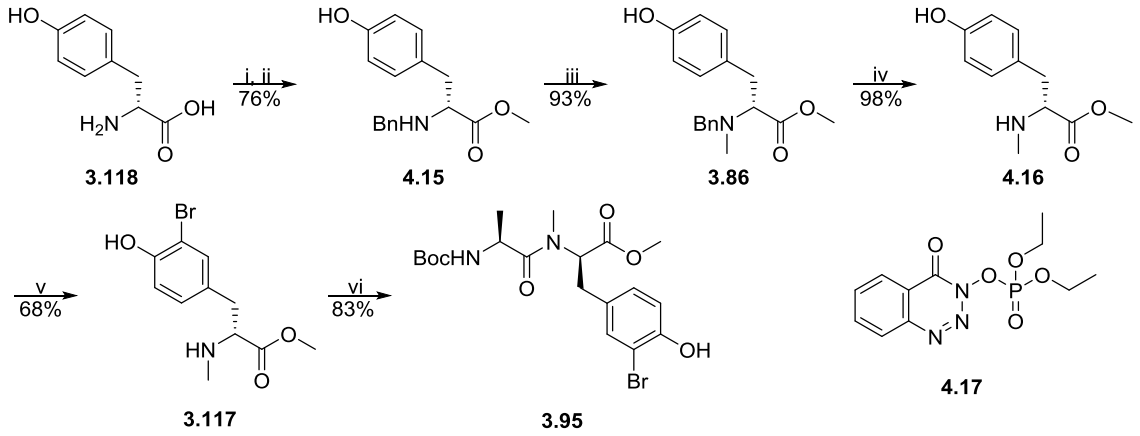


Scheme 4.7: *Reagents and conditions*: i) DMP, CH_2Cl_2, rt. ii) trimethyl phosphonoacetate, NaH, THF, 0 °C→rt. iii) $NaBH_4$, $NiCl_2 \cdot 6H_2O$, THF, 0 °C.

The crude analysis of conjugated ester **4.13** showed conversion over the two steps from (+)-**4.05** was clean and complete. It is therefore believed optimisation of these two steps, improving the yield beyond 61%, can be achieved if investigated further. Despite this fact, the di-protected hydrocarbon fragment **4.14** was successfully synthesised in 29% yield and >98% ee over 9 steps from methyl acetoacetate (**3.99**).

4.3 Synthesis of fragment B

As mentioned above, fragment B (**3.95**) has been described in the literature,[199] where it was synthesised from D-tyrosine (**3.118**) in 8 steps. In our approach, we aimed to reduce this synthetic sequence to 6 steps using a methylation approach described by Konopelski *et al.*[205] D-Tyrosine (**3.118**) was esterified and then benzylated by reductive amination, providing **4.15** in 76% yield. Subsequent reductive amination with formaldehyde provided *N*-methyl derivative **3.86** in 93% yield, which was then hydrogenolysed, proving *N*-Me-D-tyr-OMe (**4.16**) in quantitative yield. Bromination using Ye's approach[199] gave the appropriately functionalised tyrosine derivative **3.117** in 47% overall yield from D-tyrosine (**3.118**), compared to a 31% yield achieved previously. **3.117** was then coupled with Boc-L-ala-OH using a procedure described by Ye (DEPBT (**4.17**),[206] NMM), successfully completing the synthesis of fragment B (**3.95**) in 83% yield (**Scheme 4.8**).



Scheme 4.8: *Reagents and conditions*: i) $SOCl_2$, MeOH, 0 °C→65 °C. ii) Benzaldehyde, $NaBH(OAc)_3$, AcOH, THF, rt. iii) Formaldehyde, $NaBH(OAc)_3$, AcOH, THF, rt. iv) H_2, Pd/C, MeOH, rt. v) PTSA, NBS, CH_3CN, rt. vi) Boc-L-ala-OH, **4.17**, NMM, THF, 0 °C→rt.

It is noteworthy that coupling **3.117** with Boc-L-ala-OH using different coupling reagents (TBTU (**4.18**), HATU (**4.19**), PyBOP (**4.20**), EDCI.HCl (**4.21**)) (**Figure 4.1**) and bases (Et_3N, DIPEA) led to mixtures of products.

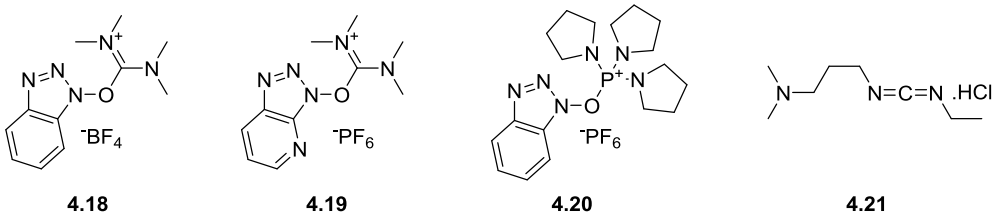
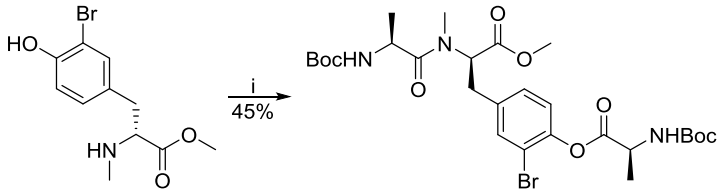


Figure 4.1: Structure of coupling reagents TBTU (**4.18**), HATU (**4.19**), PyBOP (**4.20**), EDCI.HCl (**4.21**).

The observed side reactions were most likely caused by deprotonation of the phenol leading to *O*-coupling, which was supported by the formation of the *O*-acylated by-product **4.22** using PyBOP (**4.20**)/DIPEA (**Scheme 4.9**). Although the presence of a stronger base is the most likely cause of the side reactions, no further investigation into the use of NMM with the alternative coupling reagents was investigated. The successful coupling allowed us to complete the synthesis of fragment B (**3.95**) in 39% yield over 6 steps.

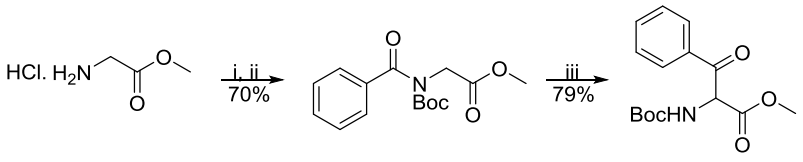


3.117 **4.22**

Scheme 4.9: *Reagents and conditions*: i) Boc-L-ala-OH, PyBOP (**4.20**), DIPEA, CH_2Cl_2, 0 °C→rt.

4.4 Synthesis of fragment C

The synthesis of fragment C (**3.96**) was achieved using an acyl migration procedure developed by Somfai *et al.*[207] HCl·Gly-OMe (**3.119**) was benzoylated with BzCl in the presence $NaHCO_3$ before Boc-protection in the presence of DMAP to give **4.23**. When treated with LDA in the presence of DMPU, deprotonation of the α-carbon subsequently led to the acyl migration, providing fragment C (**3.96**) in 55% yield over 3 steps (**Scheme 4.10**).



3.119 **4.23** **3.96**

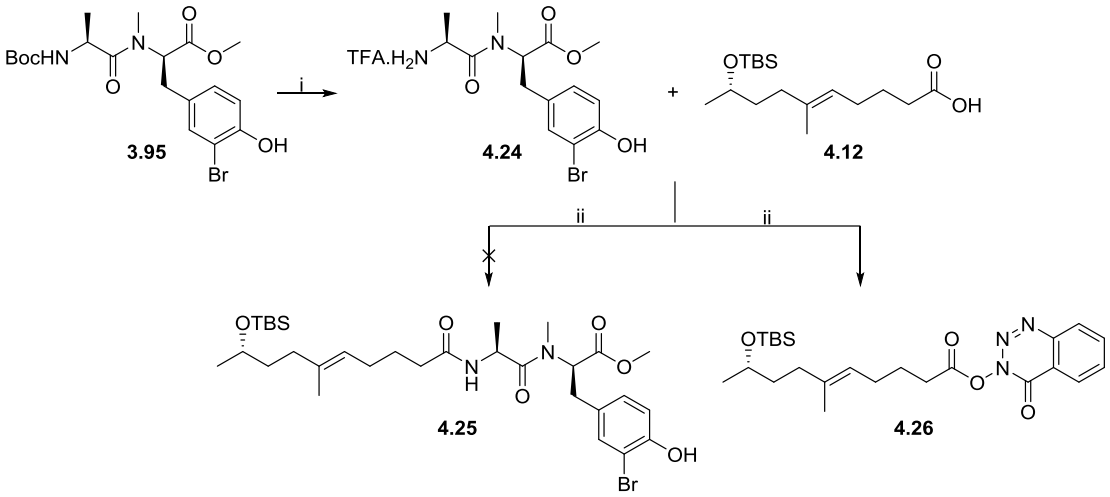
Scheme 4.10: *Reagents and conditions*: i) BzCl, K_2CO_3, Et_2O, 0 °C. ii) Boc_2O, DMAP, CH_3CN, rt. iii) LDA, DMPU, THF, -78 °C.

4.5 Coupling of fragments A, B and C

With each fragment in hand, we directed our attention towards coupling each fragment to form the macrocyclisation precursor of miuraenamide E (**3.13**). Because of the racemic nature of fragment C (**3.96**), we initially envisaged this would be the final

fragment to be conjoined in order to simplify characterisation by avoiding taking diastereoisomeric intermediates through the synthesis.

We had shown previously that NMM was effective in avoiding *O*-coupling, and therefore this base was the first choice for further couplings to avoid phenolic protection. A brief survey of different coupling reagents was therefore undertaken. Initially, the coupling of deprotected amine **4.24** with acid **4.12** was attempted using the same conditions applied during the synthesis of fragment B (**3.95**) (NMM/DEPBT (**4.17**)). Unfortunately, no evidence of the coupled product **4.25** was obtained. Instead, to our surprise, after purification it was evident that the activated acid **4.26** was the major product from the reaction (**Scheme 4.11**).



Scheme 4.11: *Reagents and conditions*: i) TFA, CH_2Cl_2, 0 °C→rt. ii) DEPBT (**4.17**), CH_2Cl_2, base (NMM, Et_3N, DIPEA).

Full analytical data was unfortunately not obtained on the activated ester intermediate **4.26**, although MS data ((ESI$^+$) *m/z* 482 [M+Na]$^+$) and NMR data supported its assignment (**Figure 4.2**). In an attempt to induce coupling between **4.26** and **4.24**, we applied excess (2–8 eq.) of stronger bases (Et_3N, DIPEA) to ensure formation of the free amine **4.24**, but each attempt unfortunately provided similar results to those achieved using NMM.

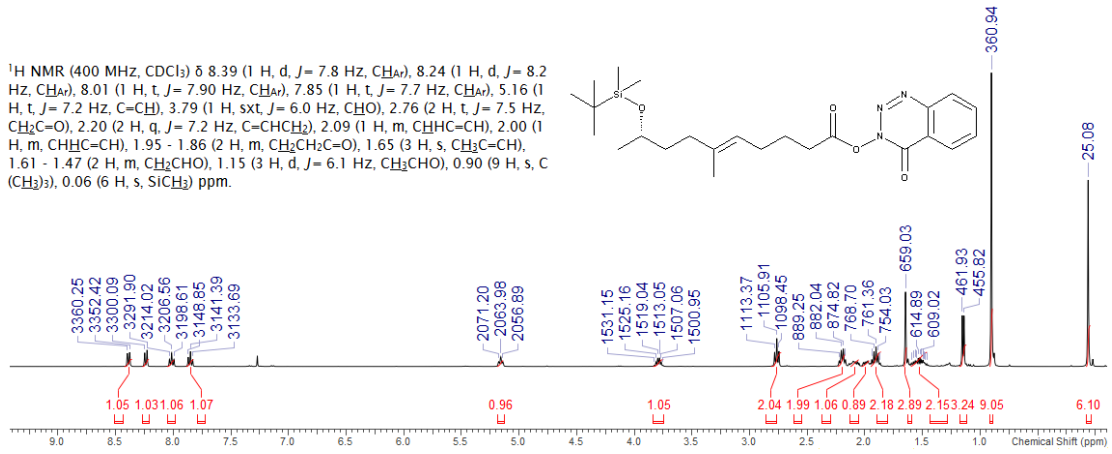
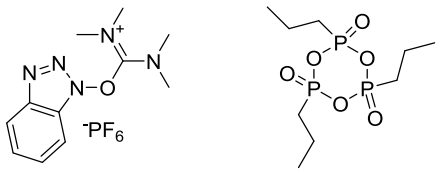


Figure 4.2: ^{1}H NMR data for the tentatively assigned activated ester product **4.26**.

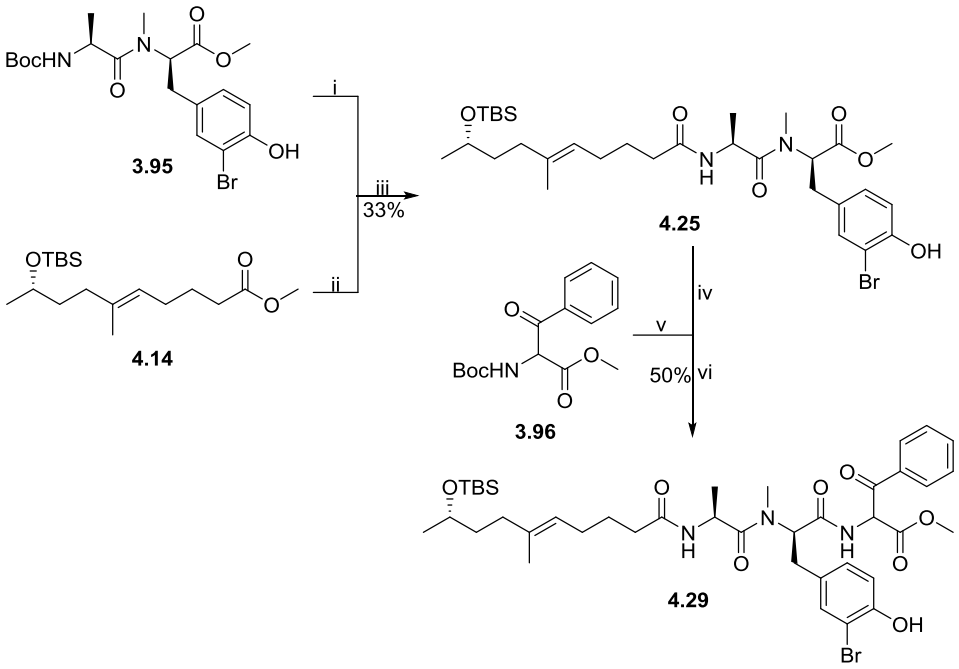
We therefore investigated alternative coupling reagents. Use of HBTU (**4.27**)/NMM over 24 h provided very poor conversion. Finally, the anhydride T3P (**4.28**) was applied in combination with NMM (**Figure 4.3**), and to our delight we obtained a 51% yield of fragment AB (**4.25**).



4.27 **4.28**

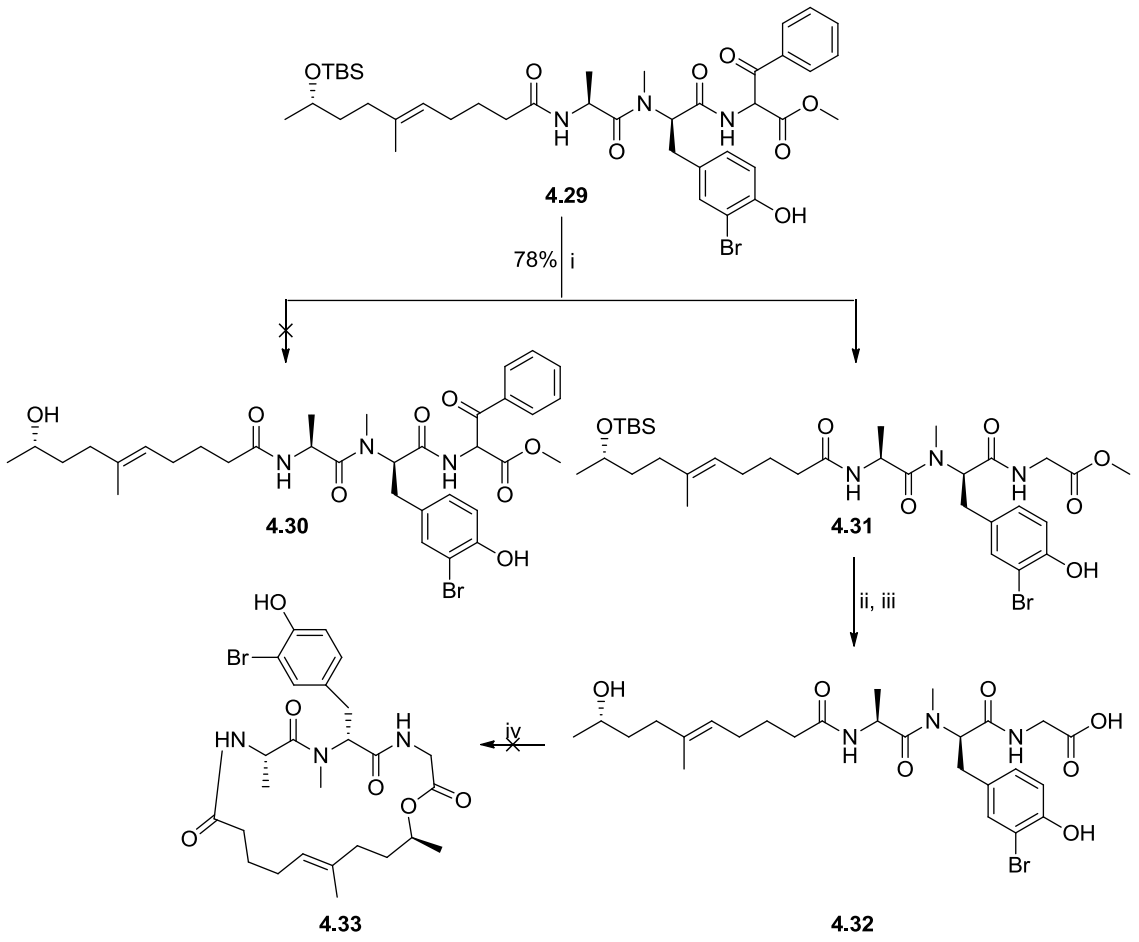
Figure 4.3: Structures of HBTU (**4.27**) and T3P (**4.28**).

Despite a great improvement on previous attempts, the coupling reaction was undertaken on a 0.06 mmol scale (20 mg of acid **4.12**). When conducted on a larger scale (1.74 mmol of acid **4.12**) the result could not be reproduced, and a lower optimised yield of 33% from ester **4.14** was obtained (**Scheme 4.12**). Although further optimisation of this reaction is evidently required, sufficient material was obtained from the reaction to proceed. Following suitable deprotection methods, fragment C (**3.96**) was coupled with fragment AB (**4.25**) using the same conditions (T3P/NMM). A modest 50% yield was realised, providing the di-protected linear miuraenamide E structure **4.29** in 17% yield from ester **4.14** (**Scheme 4.12**). None the less, we had now established a route to the complete backbone of the natural product that could undoubtedly be further optimised.



Scheme 4.12: *Reagents and conditions*: i) TFA, CH_2Cl_2, 0 °C→rt. ii) LiOH, H_2O, MeOH, rt. iii) T3P (**4.28**), NMM, CH_2Cl_2, 0 °C→rt. iv) LiOH, H_2O, MeOH, THF, rt. v) TFA, CH_2Cl_2, 0 °C→rt. vi) T3P (**4.28**), NMM, CH_2Cl_2, 0 °C→rt.

Deprotection of the alcohol was next required to provide a suitable derivative for macrocyclisation. Cleavage of the TBS protecting group was attempted using TBAF, leading to complete conversion. Unfortunately, alcohol **4.30** was not obtained from the deprotection, and instead, debenzoylation had occurred providing compound **4.31** in good yield (**Scheme 4.13**). Surprisingly, despite using 1.5 eq. TBAF, the TBS group remained intact. This debenzoylation is presumed to have occurred by retro-Claisen condensation, caused by the hydrolytic nature of the TBAF solution.



Scheme 4.13: *Reagents and conditions*: i) TBAF, THF, 0 ˚C→rt. ii) TFA, CH_2Cl_2, 0 ˚C→rt. iii) LiOH, H_2O, MeOH, THF, rt. iv) MNBA (**4.34**), NMM, DMAP (**4.35**), CH_2Cl_2 (1 mM).

Although intermediate **4.31** would not lead to miuraenamide E (**3.13**), we were keen to establish deprotection and macrocyclisation procedures using this derivative. We were first interested in whether an alternative procedure would prove effective for TBS removal, to avoid debenzoylation. Subjecting **4.31** to TFA successfully led to TBS deprotection, and the crude product was then hydrolysed using standard methods providing seco-acid **4.32** (**Scheme 4.13**). No purification of **4.32** was attempted as the crude material was considered to be sufficiently clean for progression. Next, macrocyclisation to the miuraenamide model **4.33** was attempted. For the macrocyclisation of **4.32**, we chose the MNBA activating agent **4.34**/**4.35**.[208] Although many macrocyclisation methods, such as the Yamaguchi (**4.36**/**4.35**),[209] the Keck (**4.37**/**4.38**)[210] and the Corey-Nicolaou (**4.39**/**4.40**) (**Figure 4.4**),[211] have been established, the MNBA (**4.34**) method has proven highly effective at rt. As we were keen to avoid heating and to keep the macrocyclisation conditions as mild as possible, the MNBA cyclisation method was selected for initial studies.

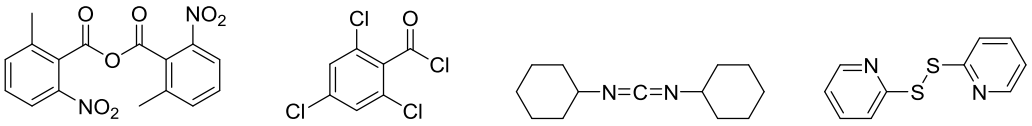
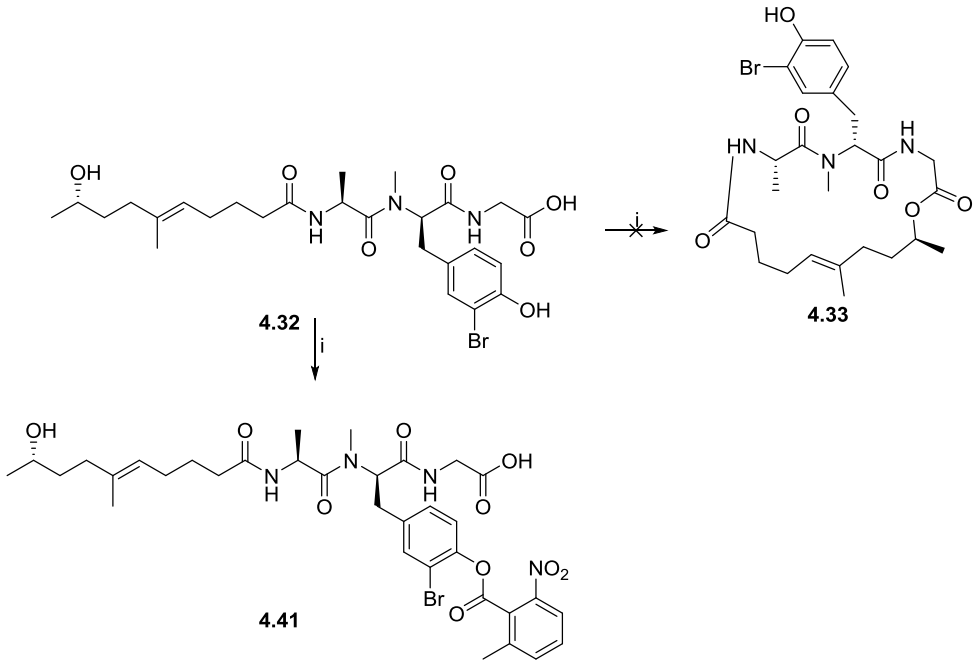


Figure 4.4: Reagents for the MNBA (**4.34**/**4.35**), Yamaguchi (**4.36**/**4.35**), Keck (**4.37**/**4.38**) and Corey-Nicolaou (**4.39**/**4.40**) macrocyclisation approaches.

Due to limited quantities of macrocyclisation material available, the cyclisation was attempted only once, and without success. The MS data retrieved for the crude product mixture showed ions with *m/z* of 747 and 749. The bromine isotope pattern, and molecular ions supported coupling of MNBA with seco-acid **4.32**, but no macrocyclisation. Inspection of the NMR data showed downfield shifts of the aromatic phenol peaks, again suggesting esterification of the phenol. We therefore propose that the initial acylation occurred at the phenol in place of the acid, providing phenolic ester **4.41** (**Scheme 4.14**).



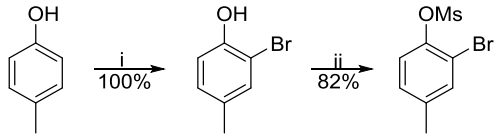
Scheme 4.14: *Reagents and conditions*: i) MNBA (**4.34**), NMM, DMAP (**4.35**), CH_2Cl_2 (1 mM).

The unwanted phenolic acylation was presumably caused by the excess DMAP (**4.35**) present within the reaction deprotonating the phenol, increasing its nucleophilicity beyond that of the carboxylate. Two possible methods were envisioned to circumvent this unwanted activation. The first approach would use 2 equivalents (compared to 1.1 previously employed) of MNBA (**4.34**) could be used. Initial acylation at the phenol

could be used as an *in situ* 'protection', allowing the second equivalent of MNBA (**4.34**) to be used as the acid activator. The second approach would be to have the phenol protected prior to attempting cyclisation. Although each approach is feasible, the selected route has to be applicable to hydrolysis of the phenolic functionality without hydrolysing the newly formed macrocyclic ester. At this stage of the project we were forced to return to the coupling of the three fragments (**3.95**, **3.96** and **4.14**) due to consumption of all of the advanced material in the initial macrocyclisation attempt. This provided an opportunity to introduce a phenol protecting group, and investigate the two possible macrocyclisation strategies.

4.6 A protecting group approach to the coupling of fragments A, B and C

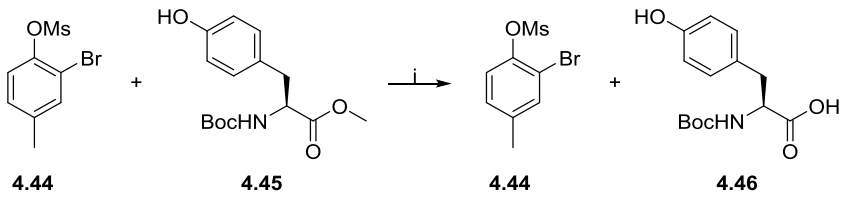
Previous studies into coupling the three fragments **3.95**, **3.96** and **4.14** suffered from low yields, at least in part due to the free phenol. Despite our best attempts to circumvent this, we decided the most appropriate method would be to use a phenolic protecting group. The first protecting group investigated was methanesulfonyl. Although mesylation should reduce the nucleophilicity of the phenol, we were unaware of how robust the aryl mesylate would be to the reaction conditions encountered during our synthesis. We therefore synthesised model derivative **4.44** to investigate reactivity under hydrolytic conditions. *p*-Cresol (**4.42**) was brominated and mesylated using standard procedures, providing model aryl mesylate **4.44** in good yield (**Scheme 4.15**). The ease of mesylation of **4.43** suggested installation of this protecting into fragment B (**3.95**) should be achieved without problem.



4.42 **4.43** **4.44**

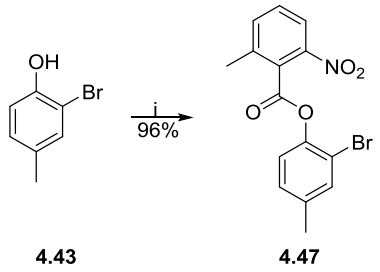
Scheme 4.15: *Reagents and conditions*: i) Br_2, CH_2Cl_2, 0 °C→rt. ii) MsCl, DIPEA, CH_2Cl_2, 0 °C.

Due to the requirement for ester hydrolysis prior to coupling fragment B (**3.95**) with fragment C (**3.96**), we investigated whether the mesylate function could withstand these conditions. Therefore, we placed Boc-D-Tyr-OMe (**4.45**) and model mesylate **4.44** under the hydrolytic reaction conditions previously applied (1 eq. tyr **4.45** and mesylate **4.44**, and 2.6 eq. LiOH) (**Scheme 4.16**). Thankfully, NMR data of the reaction mixture showed the ester had been selectively cleaved without compromising the phenolic mesylate.



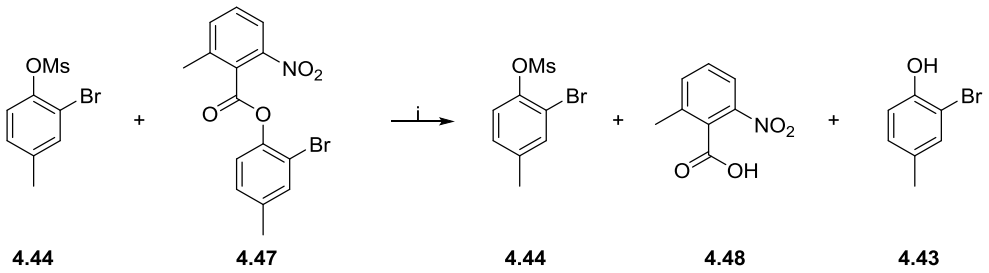
Scheme 4.16; *Reagents and conditions*: i) LiOH, H_2O, MeOH, THF, 0 °C→rt.

We next had to decide at what stage we would remove the mesylate group. As described above, this function could be maintained until after macrocyclisation, or the MNBA group could be used to 'protect' the phenol *in situ*. Phenolic ester **4.47** was therefore synthesised in good yield (**Scheme 4.17**).



Scheme 4.17: *Reagents and conditions*: i) MNBA (**4.34**), DMAP (**4.35**), CH_2Cl_2, rt.

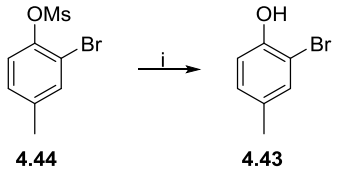
As the macrocyclic structure would have to be maintained when removing the phenolic function, the most labile 'protecting' group would seemingly be the most suitable to be present during macrocyclisation. This was investigated by submitting a mixture of each model protected phenol **4.44** and **4.47** to hydrolytic conditions (1 eq. LiOH). Following the reaction by TLC showed loss of the phenolic ester without compromising the mesylate function (**Scheme 4.18**). This led us to conclude that removal of the mesylate group would be required prior to macrocyclisation.



Scheme 4.18: *Reagents and conditions*: i) LiOH, H_2O, MeOH, THF, rt.

As the mesylate group had persisted under all hydrolytic conditions studied, we next investigated whether the protecting group could be removed under conditions compatible with the synthesis. When **4.44** was subjected to 2.6 eq. of LiOH for 2 h,

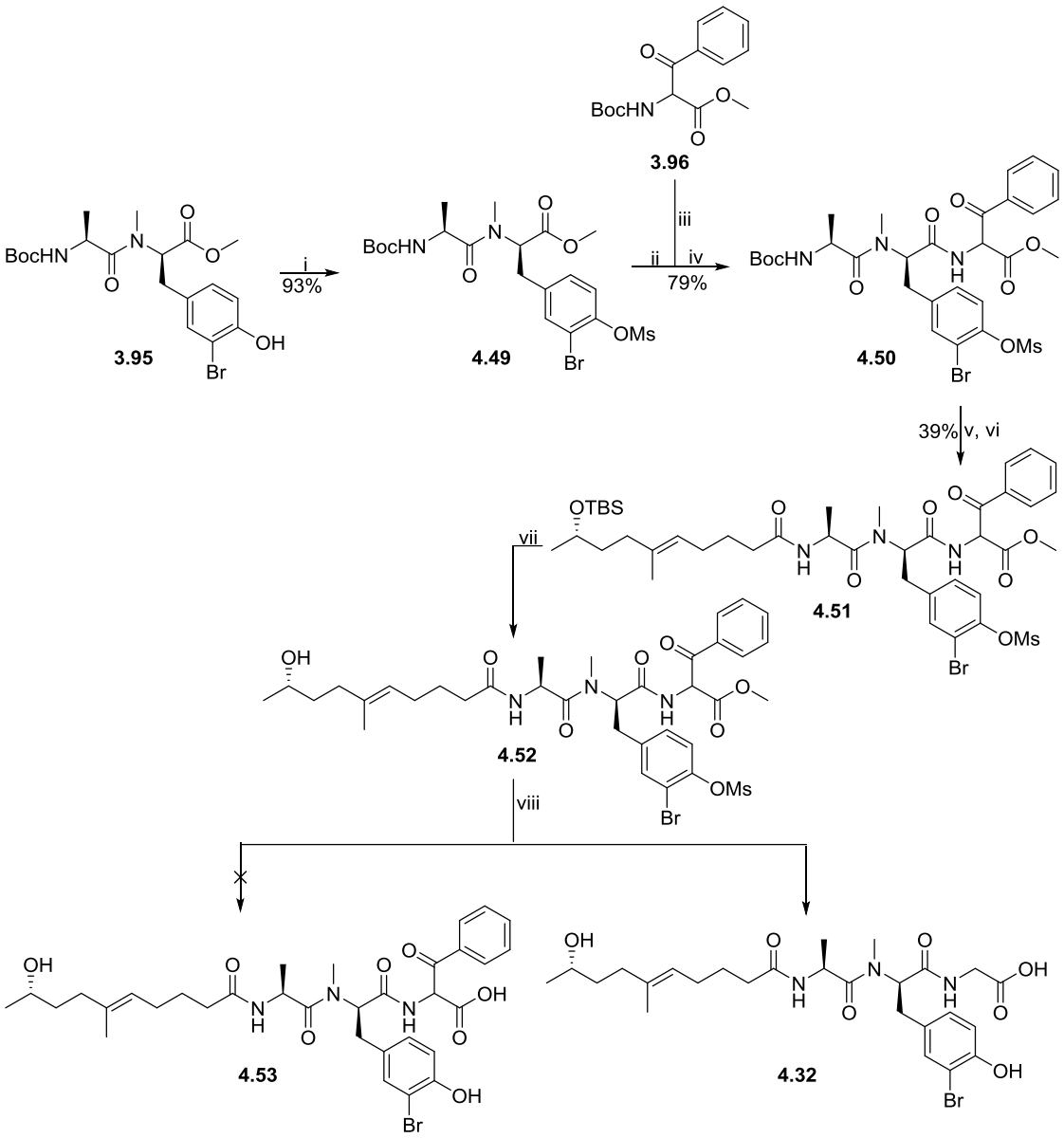
approximately 30% conversion was realised. If the amount of LiOH was increased to 20 eq., complete conversion to **4.43** was achieved within 16 h (**Scheme 4.19**).



Scheme 4.19: *Reagents and conditions*: i) LiOH, H_2O, MeOH, THF, rt.

Satisfied with the stability of the mesylate group, we undertook a "protected phenol" approach towards miuraenamide E (**3.13**). When attempting this alternative route, we modified the order of coupling. In our first attempt, we first coupled fragments A (**4.14**) and B (**3.95**) in order to simplify analysis of the intermediates. Although this route reduces the number of intermediates containing diastereomeric mixtures, the linear synthetic length is maximised due to fragment A (**4.14**) being one of the first installed intermediates. Fragment B (**3.95**) and fragment C (**3.96**) were therefore coupled first during the "protected phenol" approach to minimise the linear steps, and potentially optimize the overall yield towards miuraenamide A (**3.01**).

Mesylation of fragment B (**3.95**) was achieved without event. Selective ester hydrolysis was then accomplished, and the resulting acid was coupled with deprotected fragment C (**3.96**) (**Scheme 4.20**). To our delight, using the protected phenol we achieved an improved 79% yield of **4.50** over the two steps. Next, amine deprotection and coupling with acid **4.12** was required. Using the established methods, **4.51** was obtained in 39% yield. Acid **4.12** was not freshly prepared for the reaction, and thus it is believed that some degradation may have occurred during storage, leading to the observed reduction in yield. TBS deprotection was successfully realised using TFA, providing alcohol **4.52** without affecting the integrity of the benzoyl function. We next attempted to hydrolyse both the ester and mesylate functions in one pot. Unfortunately, but unsurprisingly, **4.53** was not retrieved as the major product of the reaction. Although NMR proved inconclusive, MS data (ESI^+ *m/z* 584 $[MBr^{79}+H]^+$, 586 $[MBr^{81}+H]^+$) confirmed that although mesylate and ester hydrolysis had occurred, debenzoylation had once again occurred leading to **4.32** (**Scheme 4.20**).



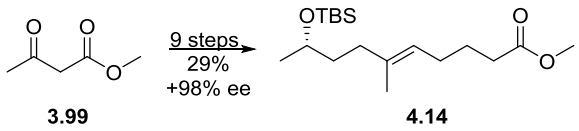
Scheme 4.20: *Reagents and conditions*: i) MsCl, DIPEA, CH_2Cl_2, 0 °C→rt. ii) LiOH, H_2O, MeOH, THF, 0 °C→rt. iii) TFA, CH_2Cl_2, 0 °C→rt. iv) T3P (**4.28**), DIPEA, THF, 0 °C→rt. v) TFA, CH_2Cl_2, 0 °C→rt. vi) acid **4.12**, T3P (**4.28**), DIPEA, THF, 0 °C→rt. vii) TFA, CH_2Cl_2, 0 °C→rt. viii) LiOH, H_2O, MeOH, THF, 0 °C→rt.

Although the retro-Claisen was considered as a potential side reaction prior to attempting hydrolysis of **4.52**, the route was explored as the intermediates were in hand and we lacked time to prepare alternative, more robust intermediates. If ester hydrolysis in **4.52** had proceeded at a faster rate than debenzoylation, the reduced stability of the anion α to the carboxylate was predicted to prevent debenzoylation. Unfortunately, this was not the case. As a mixture of benzoic acid and acid **4.32** were formed during the reaction, no further reactions were undertaken in this scheme. Time

constraints thereafter prevented any further synthetic efforts towards miuraenamide A (**3.01**).

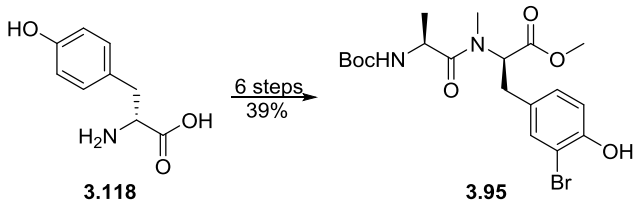
4.7 Conclusions and future work

The polyketide function **4.14** has been successfully synthesised in enantiomerically enriched form using a novel approach to the described macrocyclic actin binders. Although optimisation of intermediate steps is believed to be possible, fragment **4.14** was achieved in a respectable 29% yield and >98% ee over 9 steps from methyl acetoacetate (**3.99**) (**Scheme 4.21**).



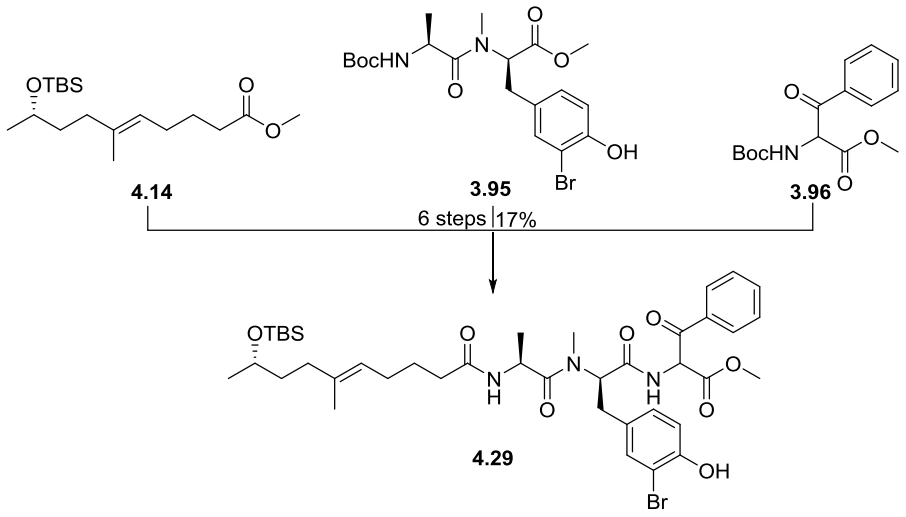
Scheme 4.21: Synthesis of fragment A (**4.14**).

The dipeptide fragment **3.95** has been synthesised using an alternative approach to that described in the literature, reducing the number of steps and with improved overall yield (**Scheme 4.22**).



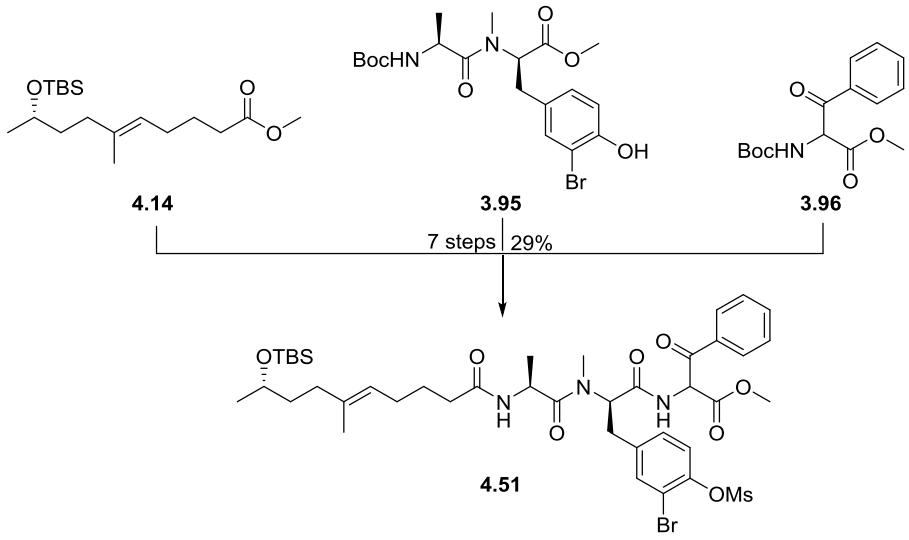
Scheme 4.22: Synthesis of fragment B (**3.95**).

Synthesis of the protected linear derivative **4.29** was successfully achieved using two routes. The first, without protection of the phenolic functionality, was accomplished in 17% yield over 4 linear steps from fragments A (**4.14**), B (**3.95**) and C (**3.96**) (**Scheme 4.23**).



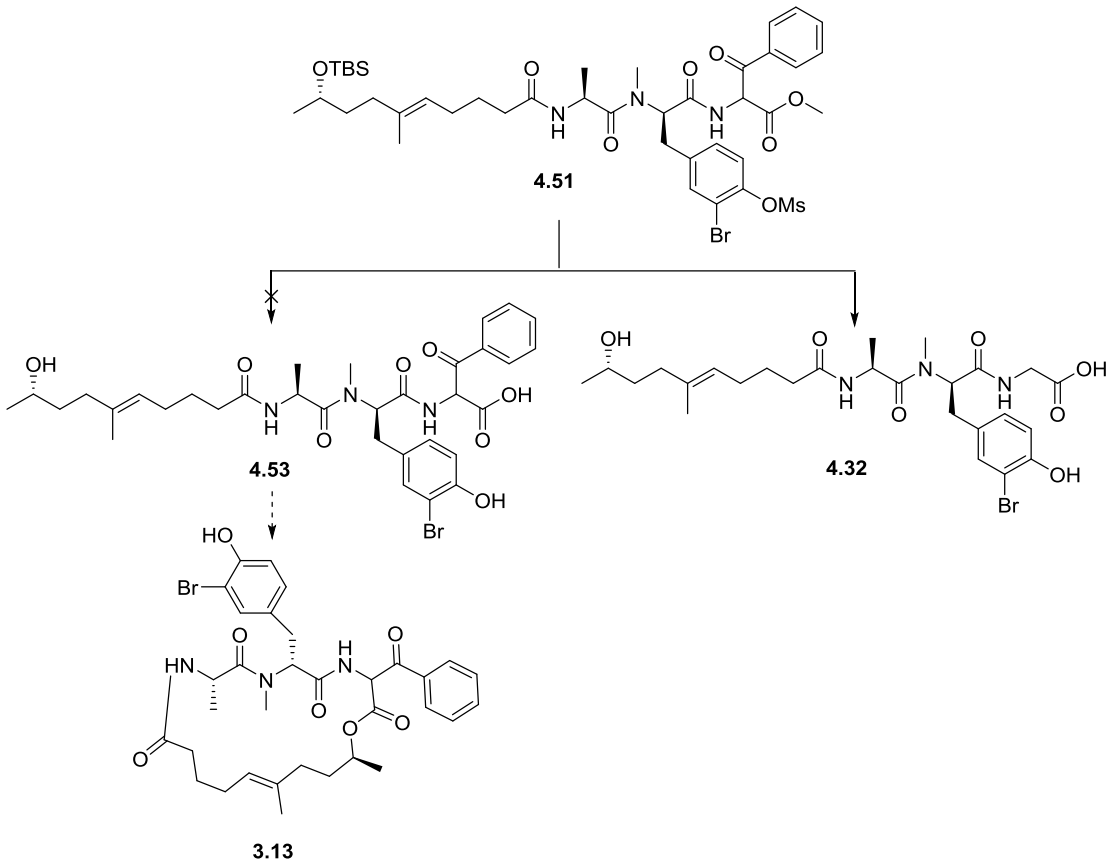
Scheme 4.23: First approach to linear derivative **4.29**.

Following an investigation into phenolic protection, the yield was increased to 29% over 5 linear steps (**Scheme 4.24**). Although the obtained increase is modest, an optimisation of the final coupling is expected to lead to further improvements.



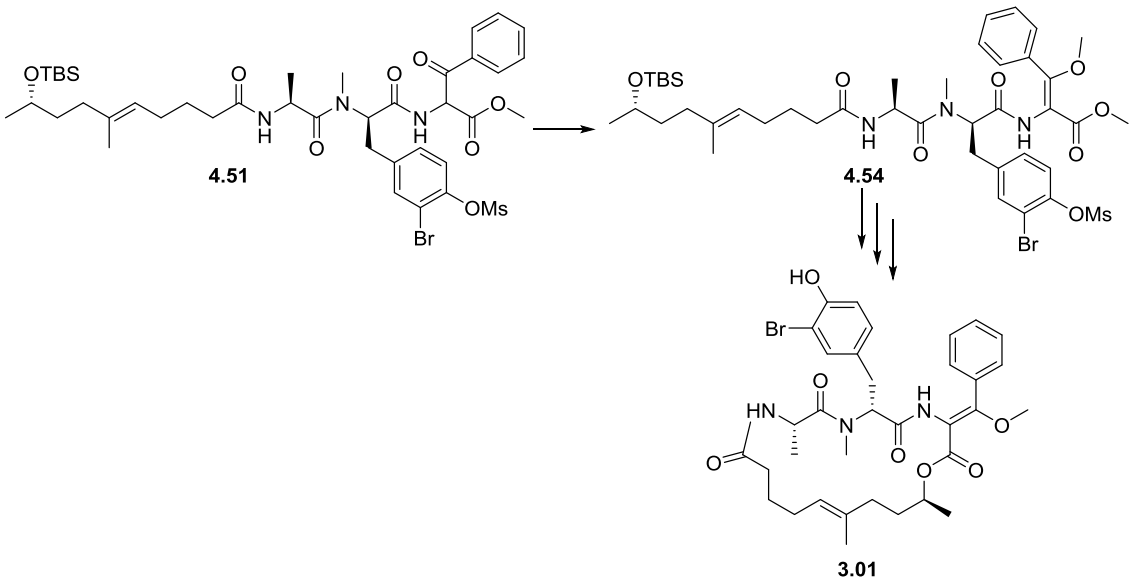
Scheme 4.24: "Phenolic protection" approach to linear derivative **4.51**.

Despite the efficient production of the protected linear depsipeptide precursor, attempted ester hydrolysis to provide macrocyclisation precursor **4.53** was unsuccessful (**Scheme 4.25**). Therefore, an alternative approach is required to avoid the observed debenzoylation (**4.32**).



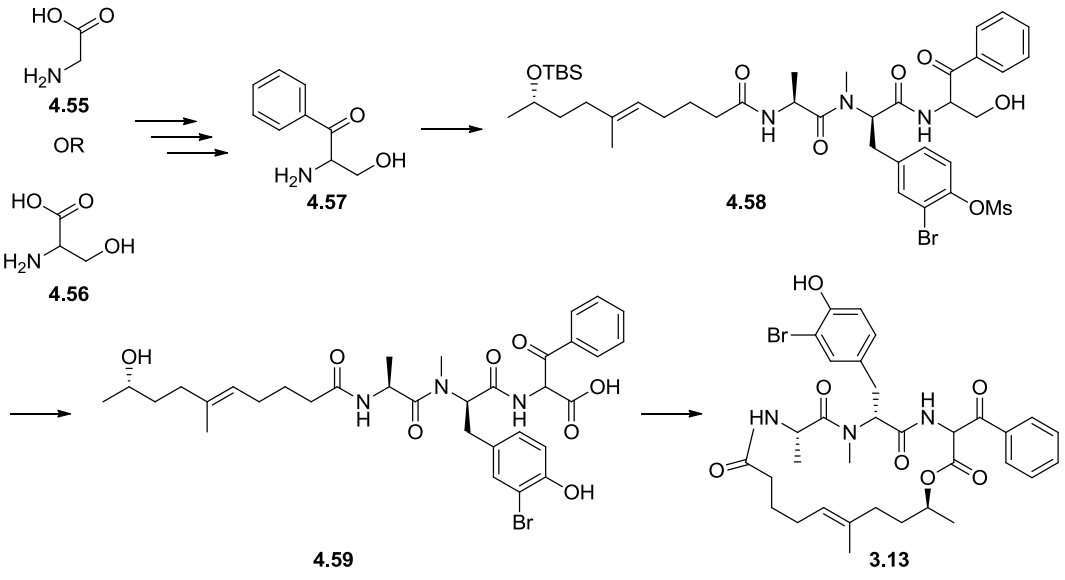
Scheme 4.25: Debenzoylation side reaction leading to hydroxyacid **4.32.**

Given more material and time, an initial approach to avoid debenzoylation could investigate formation of the enol ether prior to hydrolysis of the ester. Formation of derivative **4.54** could be achieved by using methodology presented within the introduction, allowing the stereoselective enol ether formation. The "protection" of the ketone as the base-stable enol ether should prevent debenzoylation under the conditions of ester hydrolysis. Support for this proposal is seen in the reported hydrolytic ring-opening of miuraenamide A (**3.01**).[146] Furthermore, the modified route would directly lead to miuraenamide A (**3.01**) after cyclisation (**Scheme 4.26**).



Scheme 4.26: Alternative approach to miuraenamide A (**3.01**) installing the enol ether prior to macrocyclisation.

An alternative method, avoiding the requirement for late stage hydrolytic conditions, would employ serine derivative **4.57**, synthesised from glycine (**4.55**) or serine (**4.56**). The intermediate linear alcohol **4.58** could first be hydrolysed to remove the phenol protecting group, and then oxidised to the acid **4.59** under mild conditions, circumventing potential retro-Claisen reactions (**Scheme 4.27**).



Scheme 4.27: Alternative approach to miuraenamide E (**3.13**) using an alcohol oxidation approach.

In summary, the three fragments (**3.95**, **3.96** and **4.14**) of miuraenamide E (**3.13**) have been successfully synthesised. Using a novel approach to actin binding macrocyclic

depsipeptides, the polyketide fragment **4.14** has been synthesised in good yield and high ee. The peptide fragment **3.95** has also been synthesised in a reduced number of steps and improved yields in comparison to the literature method. Although the synthesis of a macrocyclisation precursor **4.53** was thwarted at a late stage by an undesired retro-Claisen reaction, minor adaptation of the overall route should ultimately allow synthesis of miuraenamide E (3**.13**), and subsequently miuraenamide A (**3.01**).

5. Experimental

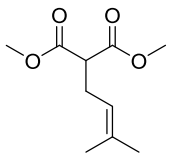
5.1 General Experimental Details

Chemicals were purchased from Sigma-Aldrich, Fisher Scientific, Alfa Aesar, Fluorochem or Apollo Scientific. NaH was used as a 60% dispersion in oil, H_2O_2 was used as a 30% aq. solution, prenyl bromide was used as a 90% oil, allyltributyltin was used as a 95% oil, KOH was used as a >85% solid, $NaClO_2$ was used as an 80% solid, $NaBH(OAc)_3$ was used as a 95% solid, and T3P was used as a >50% solution in EtOAc. All air/ moisture sensitive reactions were carried out under an inert atmosphere, in oven-dried or flame-dried glassware. The solvents THF and Et_2O (from Na/benzophenone), CH_3CN and CH_2Cl_2 (from CaH_2) and MeOH (from $Mg(OMe)_2$) were distilled before use, and where appropriate, other reagents and solvents were purified by standard techniques.[212] TLC was performed on aluminium-precoated plates coated with silica gel 60 with an F_{254} indicator; visualised under UV light (254 nm) and/or by staining with anisaldehyde, ceric ammonium molybdate, iodine, phosphomolybdic acid, potassium permanganate or vanillin. Flash column chromatography was performed using; high purity silica gel, pore size 60 Å, 230-400 mesh particle size, purchased from Sigma-Aldrich. Optical rotations were collected on an Optical Activity PolAAr 2001 machine. $CHCl_3$ was used as the solvent to measure optical activity unless otherwise stated in the experimental. Melting points were obtained using a Gallenkamp Electrothermal apparatus and are uncorrected. Fourier-transform infrared (FT-IR) spectra are reported in wavenumbers (cm^{-1}) and were collected as solids or neat liquids on a Nicolet 380 fitted with a Smart Orbit Goldengate attachment using OMNIC software package. The abbreviations s (strong), m (medium), w (weak) and br (broad) are used when reporting the spectra. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 solutions (purchased from Cambridge Isotope Laboratories, Inc. and Sigma-Aldrich) at 298 K using Bruker AC300, AV300 (300 and 75 MHz respectively) or Bruker DPX400 (400 and 101 MHz respectively) spectrometers. Chemical shifts are reported on the δ scale in ppm and were referenced to residual solvent ($CDCl_3$: 7.27 ppm for ^{1}H NMR spectra and 77.0 ppm for ^{13}C NMR spectra. DMSO-d_6: 2.50 ppm for ^{1}H NMR spectra and 39.5 ppm for ^{13}C NMR spectra). All spectra were reprocessed using ACD/Labs software version: 12.1 or ACD/Spectrus. Coupling constants (*J*) were recorded in Hz. The following abbreviations for the multiplicity of the peaks are s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sxt (sextet), br (broad), and m (multiplet). ^{13}C signals have been s, d, t, q, depending on the number of directly attached protons (0, 1, 2, 3 respectively). Electrospray (ES) low resolution mass spectra were recorded on a Waters ZMD or Waters TQD quadrupole spectrometer. Electron impact (EI) and chemical ionisation (CI) low resolution mass spectra were recorded on a

Experimental

Trace 2000 Series GC-MS. High resolution mass spectra were recorded on a Bruker APEX III FT-ICR mass spectrometer. HPLC was performed on an Agilent 1220 Infinity LC System utilising the Agilent EZChrom software package eluting from Daicel Chiralcel® OD-H column eluting with IPA/*n*-hexane mixtures (details in the experimental). GC was performed on a Shimadzu GC-2014 system, utilising the Shimadzu Solutions Lite software package eluting from Varian WCOT fused silica (50 m x 0.25 mm x 0.25 μm) column coated with CP-cyclodextrin B, eluting with He (details in the experimental).

2.06 - Dimethyl 2-(3-methylbut-2-en-1-yl)malonate



$C_{10}H_{16}O_4$
M.W. = 200.23 g/mol

Following a procedure by Padwa *et al.*,[213] To a stirred suspension of NaH (670 mg, 16.7 mmol) in THF (24 mL) under Ar at 0 °C, was added dimethyl malonate (**2.05**) (1.73 mL, 15.1 mmol) dropwise over 10 min. After 30 min, prenyl bromide (**2.02**) (1.75 mL, 15.2 mmol) was added dropwise over 5 min. The mixture was warmed to room temperature and stirred for 2 h. The solution was washed with H_2O (30 mL), and the aq. phase was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:petrol, 1:10) give the title compound (**2.06**) (2.18 g, 10.9 mmol, 72%) as a clear oil. The analytical data acquired was in accordance with previously reported values.[213]

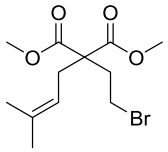
FT-IR (neat) ν_{max} 2955 (w, C-H), 1733 (s, C=O), 1148 (s, O-C) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.05 (1H, finely coupled t, *J* = 7.5 Hz, C=C<u>H</u>), 3.74 (6H, s, OC<u>H</u>$_3$), 3.37 (1H, t, *J* = 7.5 Hz, C<u>H</u>C=O), 2.60 (2H, apparent t, *J* = 7.5 Hz, C<u>H</u>$_2$), 1.69 (3H, s, CC<u>H</u>$_3$), 1.63 (3H, s, CC<u>H</u>$_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.6 (s, C=O), 135.1 (s, CH=<u>C</u>), 119.5 (d, <u>C</u>H=C), 52.4 (q, O<u>C</u>H$_3$), 51.9 (d, C=O<u>C</u>H), 27.6 (t, <u>C</u>H$_2$), 25.7 (q, C<u>C</u>H$_3$), 17.7 (q, C<u>C</u>H$_3$) ppm.

LRMS (EI) *m/z* 200 (11%) $[M]^{+\cdot}$, 69 (100%) $[M-C_5H_7O_4]^{+\cdot}$.

2.07 - Dimethyl 2-(2-bromoethyl)-2-(3-methylbut-2-en-1-yl)malonate



$C_{12}H_{19}BrO_4$
M.W. = 307.18 g/mol

By adaptation of the procedure by Brunce *et al.*,[76] *t*o a stirred suspension of NaH (0.14 g, 3.50 mmol) in THF (3 mL) under Ar at rt was added dropwise prenylmalonate **2.06** (500 mg, 2.50 mmol) in THF (2 mL). After 1 h, dibromoethane (0.21 mL, 2.44 mmol) was added dropwise, and the solution was warmed to 40 °C and stirred overnight. NH_4Cl (5 mL) was added and extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography twice (EtOAc:petrol, 1:5) gave the title compound (**2.07**) (157 mg, 0.51 mmol, 20%) as a clear oil. The analytical data acquired was in accordance with previously reported values.[85]

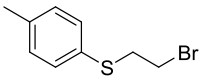
FT-IR (neat) ν_{max} 2953 (w, C-H), 1731 (s, C=O), 1162 (m, O-C) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.93 (1H, finely coupled t, *J* = 7.7 Hz, C=C<u>H</u>), 3.74 (6H, s, OC<u>H</u>$_3$), 3.34 (2H, t, *J* = 8.4 Hz, BrC<u>H</u>$_2$), 2.63 (2H, d, *J* = 7.7 Hz, CC<u>H</u>$_2$CH), 2.44 (2H, t, *J* = 8.4 Hz, CC<u>H</u>$_2$CH$_2$), 1.71 (3H, s, CC<u>H</u>$_3$), 1.63 (3H, s, CC<u>H</u>$_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0 (s, C=O), 136.5 (s, CH=<u>C</u>), 116.9 (d, <u>C</u>H=C), 57.8 (s, <u>C</u>CO), 52.6 (q, O<u>C</u>H$_3$), 36.2 (t, BrCH$_2$<u>C</u>H$_2$), 32.1 (t, CH<u>C</u>H$_2$), 27.3 (t, Br<u>C</u>H$_2$), 26.0 (q, C<u>C</u>H$_3$), 17.9 (q, C<u>C</u>H$_3$) ppm.

LRMS (CI) *m/z* 309 $[M^{Br81}+H]^+$, 307 $[M^{Br79}+H]^+$, 227 $[M-Br]^+$.

2.09 - (2-Bromoethyl)(*p*-tolyl)sulfane



$C_9H_{11}BrS$
M.W. = 231.15 g/mol

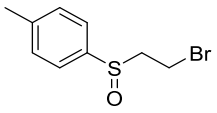
Following a procedure by Kinoshita *et al.*,[214] to a stirred solution of *t*-BuOK (1.07 g, 9.54 mmol) in *t*-BuOH (10 mL) was added 4-methylbenzenethiol (**2.08**) (1.60 g, 12.9 mmol) at rt. The solution was then added to a solution of dibromoethane (8.90 mL, 130 mmol) in *t*-BuOH (7.5 mL). The resultant solution was heated to reflux and stirred for 4 h before pouring over brine (50 mL). The aq. phase was extracted with EtOAc (3 x 50 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography twice (petrol) gave the title compound (**2.09**) (880 mg, 3.81 mmol, 40%) as pale yellow oil. The analytical data acquired was in accordance with previously reported values.[215]

FT-IR (neat) ν_{max} 3019 (w, aromatic C-H), 2919 (w, C-H), 612 (m, C-Br) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (2H, d, *J* = 8.1 Hz, C$\underline{H}_{Ar}$), 7.03 (2H, d, *J* = 8.1 Hz, C$\underline{H}_{Ar}$), 3.42 – 3.31 (2H, m, BrC$\underline{H}_2$), 3.22 – 3.08 (2H, m, SC$\underline{H}_2$), 2.24 (3H, s, C$\underline{H}_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 137.5 (s, $\underline{C}_{Ar}$), 131.5 (d, $\underline{C}H_{Ar}$), 130.0 (s, $\underline{C}_{Ar}$), 128.5 (d, $\underline{C}H_{Ar}$), 36.8 (t, S$\underline{C}H_2$), 30.0 (t, Br$\underline{C}H_2$), 21.1 (q, $\underline{C}H_3$) ppm.

2.10 – (±)-1-((2-Bromoethyl)sulfinyl)-4-methylbenzene



$C_9H_{11}BrOS$
M.W. = 247.15 g/mol

To a stirred solution of *t*-BuOK (6.20 g, 55.3 mmol) in *t*-BuOH (102 mL) was added 4-methylbenzenethiol (**2.08**) (8.80 g, 70.9 mmol) at rt. The solution was then added slowly to a solution of dibromoethane (91.8 mL, 1.07 mol) in *t*-BuOH (77 mL). The resultant solution was heated to reflux and stirred for 4 h before cooling to rt, and pouring over brine (130 mL). The aqueous phase was extracted with EtOAc (4 x 100

mL) and the combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was taken into CH_2Cl_2 (250 mL). *m*-CPBA (12.2 g, 70.7 mmol) was slowly added at rt before stirring for 70 min. $NaHCO_3$ (100 mL) was added and extracted with CH_2Cl_2 (4 x 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography twice (EtOAc:petrol, 1:5→EtOAc) gave the title compound (**2.10**) (10.0 g, 40.5 mmol, 73%) as a white solid.

Mp 41–43 °C (*solvent*: EtOAc/*n*-hexane).

FT-IR (neat) ν_{max} 1030 (s, S=O), 612 (s, C-Br) cm^{-1}.

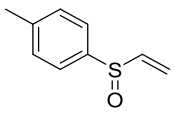
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (2H, d, *J* = 8.1 Hz, C<u>H</u>$_{Ar}$), 7.35 (2H, d, *J* = 8.1 Hz, C<u>H</u>$_{Ar}$), 3.80 – 3.67 (1H, m, SC<u>H</u>H), 3.48 – 3.37 (1H, m, SCH<u>H</u>), 3.29 – 3.20 (2H, m, BrC<u>H</u>$_2$), 2.42 (3H, s, C<u>H</u>$_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 142.0 (s, <u>C</u>$_{Ar}$) 139.2 (s, <u>C</u>$_{Ar}$) 130.2 (d, <u>C</u>H$_{Ar}$) 124.0 (d, <u>C</u>H$_{Ar}$) 59.1 (t, S<u>C</u>H$_2$) 23.2 (t, Br<u>C</u>H$_2$) 21.4 (q, <u>C</u>H$_3$) ppm.

LRMS (ES$^+$) *m/z* 249 $[M^{Br81}+H]^+$, 247 $[M^{Br79}+H]^+$.

HRMS (ES$^+$) For $C_9H_{12}Br^{81}OS$ calculated 248.9772, found 248.9770 Da.

2.11 - (±)-1-Methyl-4-(vinylsulfinyl)benzene



$C_9H_{10}OS$
M.W. = 166.24 g/mol

A solution of bromosulfoxide **2.10** (8.88 g, 35.9 mmol) in NaOH (2 N, 88 mL, 44.0 mmol) was stirred overnight at rt. NH_4Cl (40 mL) was added and extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give the title compound (**2.11**) (5.95 g, 35.8 mmol, 100%) as

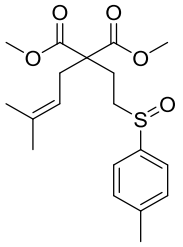
a clear oil. The analytical data acquired was in accordance with previously reported values.[216]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (2H, d, *J* = 8.1 Hz, C$\underline{H}_{Ar}$) 7.32 (2H, d, *J* = 8.1 Hz, C$\underline{H}_{Ar}$) 6.58 (1H, dd, *J* = 16.5, 9.5 Hz, SC$\underline{H}$) 6.19 (1H, d, *J* = 16.5 Hz, SCHC$\underline{H}H_{trans}$) 5.89 (1H, d, *J* = 9.5 Hz, SCHCH$\underline{H}_{cis}$) 2.41 (3H, s, C$\underline{H}_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 143.1 (d, SC$\underline{C}$H), 141.9 (s, $\underline{C}_{Ar}$), 140.1 (s, $\underline{C}_{Ar}$), 130.1 (d, $\underline{C}H_{Ar}$), 124.9 (d, CH_{Ar}), 120.3 (t, $\underline{C}H_2$), 21.4 (q, $\underline{C}H_3$) ppm.

LRMS (CI) *m/z* 167 $[M+H]^+$.

2.12 - Dimethyl 2-(3-methylbut-2-en-1-yl)-2-(2-(*p*-tolylsulfinyl)ethyl)malonate



$C_{19}H_{26}O_5S$
M.W. = 366.47 g/mol

To a stirred solution of NaH (57.6 mg, 1.44 mmol) in THF (30 mL) under Ar at 0 ˚C, was added prenylmalonate **2.06** (240 mg, 1.20 mmol) in THF (6 mL) dropwise. After 30 min, vinylsulfoxide **2.11** (200 mg, 1.20 mmol) in THF (3 mL) was added dropwise before warming to rt and stirring overnight. NH_4Cl (10 mL) was added and extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:petrol, 1:1) gave the title compound (**2.12**) (176 mg, 0.48 mmol, 40%) as a clear oil.

FT-IR (neat) ν_{max} 2953 (w, C-H), 1730 (s, C=O), 1167 (m, O-C), 1042 (s, S=O) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (2H, d, *J* = 8.4 Hz, C$\underline{H}_{Ar}$) 7.33 (2H, d, *J* = 8.4 Hz, C$\underline{H}_{Ar}$) 4.80 (1H, finely coupled t, *J* = 7.7 Hz, $CH_2C\underline{H}$) 3.68 (3H, s, OC$\underline{H}_3$) 3.67 (3H, s, OC$\underline{H}_3$) 2.83 – 2.78 (2H, m, SC$\underline{H}_2$) 2.56 (2H, d, *J* = 7.7 Hz, CC$\underline{H}_2$C)

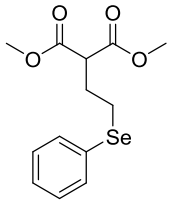
2.42 (3H, s, C$\underline{H}_3C_{Ar}$) 2.20 – 2.09 (2H, m, CC$\underline{H}_2CH_2$) 1.63 (3H, s, CC$\underline{H}_3$) 1.56 (s, 3 H, CC$\underline{H}_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1 (s, CO) 141.5 (s, $\underline{C}_{Ar}$) 140.1 (s, $\underline{C}_{Ar}$) 136.4 (s, CH=$\underline{C}$) 129.9 (d, $\underline{C}H_{Ar}$) 124.2 (d, $\underline{C}H_{Ar}$) 116.7 (d, $\underline{C}$H=C) 56.9 (s, $\underline{C}$CO) 52.5 (q, O$\underline{C}H_3$) 52.1 (t, S$\underline{C}H_2$) 32.0 (t, $\underline{C}H_2$CH) 25.9 (q, C$\underline{C}H_3$) 25.0 (t, C$\underline{C}H_2CH_2$) 21.4 (q, $\underline{C}H_3C_{Ar}$) 17.9 (q, C$\underline{C}H_3$) ppm.

LRMS (ES$^+$) *m/z* 367 $[M+H]^+$.

HRMS (ES$^+$) For $C_{19}H_{26}NaO_5S$ calculated 389.1393, found 389.1386 Da.

2.14 - Dimethyl 2-(2-(phenylselanyl)ethyl)malonate



$C_{13}H_{16}O_4Se$
M.W. = 315.22 g/mol

By adaptation of the procedure by Kocienski *et al.*,[89] to a stirred solution of PhSeSePh (10.1 g, 32.4 mmol) in MeOH (150 mL) under Ar at rt, was added $NaBH_4$ (2.90 g, 76.7 mmol) portionwise. The solution was stirred for 10 min until clear. Cyclopropylmalonate **2.13** (10.0 g, 63.2 mmol) in MeOH (60 mL) was added over 20 min before stirring for 2 days. HCl (1 N, 60 mL) was added and diluted with H_2O (60 mL). The solvent was removed under reduced pressure and the aq. phase was extracted with EtOAc (3 x 90 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:petrol, 1:10) gave the title compound (**2.14**) (15.5 g, 49.3 mmol, 78%) as a pale yellow oil.

FT-IR (neat) ν_{max} 2952 (w, C-H), 1731 (s, C=O), 1155 (s, C-OMe) cm^{-1}.

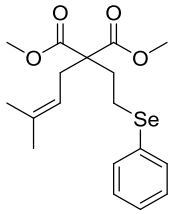
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 – 7.48 (2H, m, C$\underline{H}_{Ar}$), 7.30 – 7.24 (3H, m, C$\underline{H}_{Ar}$), 3.73 (6H, s, C$\underline{H}_3$), 3.65 (1H, t, *J* = 7.3 Hz, C$\underline{H}$CH$_2$), 2.93 (2H, t, *J* = 7.3 Hz, SeC$\underline{H}_2$), 2.28 (2H, q, *J* = 7.3 Hz, CHC$\underline{H}_2$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3 (s, $\underline{C}$O), 132.9 (d, $\underline{C}H_{Ar}$), 129.4 (s, $\underline{C}_{Ar}$), 129.1 (d, $\underline{C}H_{Ar}$), 127.1 (d, $\underline{C}H_{Ar}$), 52.6 (q, $\underline{C}H_3$), 51.1 (d, CO$\underline{C}$H), 29.2 (t, Se$\underline{C}H_2$), 25.0 (t, CH$\underline{C}H_2$) ppm.

LRMS (EI) *m/z* 316 (43%) $[M]^{+\cdot}$, 159 (100%) $[M–SeC_6H_5]^{+\cdot}$.

HRMS (EI) For $C_{13}H_{16}O_4Se$ calculated 316.0214, found 316.0208 Da.

2.15 - Dimethyl 2-(3-methylbut-2-en-1-yl)-2-(2-(phenylselanyl)ethyl)malonate



$C_{18}H_{24}O_4Se$
M.W. = 383.34 g/mol

To a stirred suspension of NaH (2.28 g, 57.0 mmol) in THF (50 mL) under Ar at rt was added malonate **2.14** (15.0 g, 47.6 mmol) in THF (70 mL) dropwise over 15 min. After 1 h prenyl bromide (**2.02**) (6.71 mL, 52.3 mmol) in THF (70 mL) was added dropwise over 1 h before stirring overnight. NH_4Cl (90 mL) was added and extracted with EtOAc (3 x 90 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:petrol, 1:5) gave the title compound (**2.15**) (15.9 g, 41.5 mmol, 87%) as a pale yellow oil.

FT-IR (neat) ν_{max} 2951 (w, C-H), 1729 (s, C=O), 1161 (m, C-OMe) cm^{-1}.

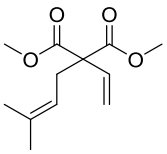
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 – 7.42 (2H, m, C$\underline{H}_{Ar}$), 7.26 – 7.21 (3H, m, C$\underline{H}_{Ar}$), 4.85 (1H, finely coupled t, *J* = 7.7 Hz, C$\underline{H}$=C), 3.68 (6H, s, OC$\underline{H}_3$), 2.80–2.70 (2H, m, SeC$\underline{H}_2$), 2.62 – 2.57 (2H, m, C$\underline{H}_2$CH), 2.33 – 2.19 (2H, m, SeCH$_2$C$\underline{H}_2$), 1.64 (3H, s, CC$\underline{H}_3$), 1.56 (3H, s, CC$\underline{H}_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, (s, $\underline{C}O$), 135.9 (s, $\underline{C}_{Ar}$), 132.5 (d, $\underline{C}H_{Ar}$), 129.8 (s, $\underline{C}=CH_2$), 129.0 (d, $\underline{C}H_{Ar}$), 126.9 (d, $\underline{C}H_{Ar}$), 117.1 (d, C=$\underline{C}$H), 58.2 (s, OC$\underline{C}$), 52.4 (q, OC$\underline{C}H_3$), 33.6 (t, C=CH$\underline{C}H_2$), 31.4 (t, Se$\underline{C}$H), 25.9 (q, $\underline{C}H_3$C), 21.8 (t, $SeCH_2\underline{C}H_2$), 17.8 (q, $\underline{C}H_3$C) ppm.

LRMS (EI) *m/z* 384 (32%) $[M]^{+\cdot}$, 227 (85%) $[M-SeC_6H_5]^{+\cdot}$.

HRMS (EI) For $C_{18}H_{24}O_4Se$ calculated 384.0840, found 384.0831 Da.

2.03 - Dimethyl 2-(3-methylbut-2-en-1-yl)-2-vinylmalonate



$C_{12}H_{18}O_4$
M.W. = 226.27 g/mol

To a stirred solution of malonate **2.15** (928 mg, 2.42 mmol) in THF (11 mL) at rt was added H_2O_2 (30%, 0.30 mL, 2.66 mmol). The resultant solution was stirred overnight, before removing the solvent under reduced pressure. Purification by column chromatography (EtOAc:petrol, 1:5) gave the title compound (**2.03**) (480 mg, 2.12 mmol, 88%) as a light yellow oil.

FT-IR (neat) ν_{max} 2954 (w, C=CH_2), 1732 (s, C=O), 1175 (m, C-OMe) cm^{-1}.

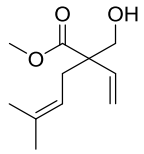
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.28 (1H, dd, *J* = 11.0, 17.6 Hz, CH_2=C$\underline{H}$), 5.30 (1H, d, *J* = 11.0 Hz, C$\underline{H}H_{cis}$=CH), 5.17 (1H, d, *J* = 17.6 Hz, C$\underline{H}H_{trans}$=CH), 4.99 (1H, finely coupled t, *J* = 7.3 Hz, C=C$\underline{H}$), 3.74 (6H, s, OC$\underline{H}_3$), 2.78 (2H, d, *J* = 7.3 Hz, CC$\underline{H}_2$), 1.68 (3H, s, CC$\underline{H}_3$), 1.61 (3H, s, CC$\underline{H}_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7 (s, $\underline{C}O$) 135.6 (s, $\underline{C}$=CH) 134.7 (d, CH_2=$\underline{C}$H) 117.5 (d, C=$\underline{C}$H) 116.8 (t, $\underline{C}H_2$=CH) 60.2 (s, $\underline{C}$CO) 52.6 (q, O$\underline{C}H_3$) 33.8 (t, C$\underline{C}H_2$) 25.9 (q, C$\underline{C}H_3$) 17.9 (q, C$\underline{C}H_3$) ppm.

LRMS (CI) *m/z* 227 $[M+H]^+$.

HRMS (ES$^+$) For $C_{12}H_{19}O_4$ calculated 227.1283, found 227.1284 Da.

2.20 - (±)-Methyl 2-(hydroxymethyl)-5-methyl-2-vinylhex-4-enoate



$C_{11}H_{18}O_3$
M.W. = 198.26 g/mol

By adaptation of the procedure by Ayers *et al.*,[91] to a stirred solution of vinylmalonate **2.03** (222 mg, 0.98 mmol) in THF (5 mL) under Ar at –78 °C was added Li(*t*-BuO)$_3$AlH (1.25 g, 4.92 mmol) in THF (5 mL) dropwise over 15 min. The solution was allowed to slowly warm in a dry ice bath and stirred at rt for 3 days. $NaHSO_4$ (2 mL) was then carefully added, followed by EtOAc (20 mL). The suspension was dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:petrol, 1:10→1:2) gave the title compound (**2.20**) (126 mg, 0.64 mmol, 65%) as a clear oil.

FT-IR (neat) ν_{max} 3435 (br, O-H), 2917 (m, C-H), 1723 (s, C=O), 1636 (m, C=C), 1225 (s, O-C) cm^{-1}.

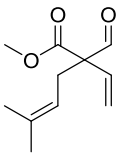
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.96 (1H, dd, *J* = 17.9, 11.0 Hz, CH_2=C<u>H</u>), 5.27 (1H, d, *J* = 11.0, 0.7 Hz, CH=C<u>H</u>H$_{cis}$), 5.19 (1H, m, CH=CH<u>H</u>$_{trans}$), 5.07 (1H, finely coupled t, *J* = 7.3 Hz, C=C<u>H</u>), 3.85 – 3.70 (5H, m, OC<u>H</u>$_3$, C<u>H</u>$_2$OH), 2.50 (1H, dd, *J* = 7.3 Hz, 14.4. CC<u>H</u>H), 2.40 (1H, dd, *J* = 7.3, 14.4 Hz, CCH<u>H</u>), 2.29 (1H, t, *J* = 7.0 Hz, O<u>H</u>), 1.71 (3H, s, CC<u>H</u>$_3$), 1.63 (3H, s, CC<u>H</u>$_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2 (s, <u>C</u>O), 137.3 (d, CH_2=<u>C</u>H), 135.2 (s, <u>C</u>=CH), 118.3 (d, C=<u>C</u>H), 116.2 (t, <u>C</u>H$_2$=CH), 65.4 (t, <u>C</u>H$_2$OH), 54.5 (s, <u>C</u>CO), 52.1 (q, O<u>C</u>H$_3$), 32.5 (t, C<u>C</u>H$_2$), 26.0 (q, C<u>C</u>H$_3$), 17.9 (q, C<u>C</u>H$_3$) ppm.

LRMS (CI) *m/z* 199 [M+H]$^+$.

HRMS (ES$^+$) For $C_{11}H_{18}O_3Na$ calculated 221.1148, found 221.1149 Da.

2.19 - (±)-Methyl 2-formyl-5-methyl-2-vinylhex-4-enoate



$C_{11}H_{16}O_3$
M.W. = 196.24 g/mol

To a stirred solution of alcohol **2.20** (1.14 g, 5.75 mmol) in CH_2Cl_2 (35 mL) under Ar at rt was added Dess-Martin periodinane (3.20 g, 7.48 mmol) in six portions. After 2 h $NaHCO_3$ (25 mL) was added and extracted with CH_2Cl_2 (3 x 40 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (CH_2Cl_2) gave the title compound (**2.19**) (986 mg, 5.02 mmol, 88%) as a clear oil.

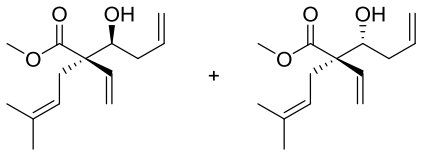
FT-IR (neat) ν_{max} 2917 (w, C-H), 1721 (s, C=O), 1631 (m, C=C), 1227 (s, C-OMe) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.63 (1H, s, C<u>H</u>O), 6.03 (1H, dd, *J* = 17.6, 10.6 Hz, C<u>H</u>=CH_2), 5.41 (1H, d, *J* = 10.6 Hz, CH=C<u>H</u>H_{cis}), 5.21 (1H, d, *J* = 17.6 Hz, CH=CH<u>H</u>$_{trans}$), 5.03 (1H, finely coupled t, *J* = 7.3 Hz, C=C<u>H</u>), 3.78 (3H, s, OC<u>H</u>$_3$), 2.77 – 2.61 (2H, m, CC<u>H</u>$_2$), 1.68 (3H, s, CC<u>H</u>$_3$), 1.63 (3H, s, CC<u>H</u>$_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 196.4 (d, <u>C</u>HO), 170.8 (s, <u>C</u>OOCH_3), 135.8 (s, <u>C</u>=CH), 132.9 (d, CH_2=<u>C</u>H), 119.2 (t, <u>C</u>H_2=CH), 117.3 (d, C=<u>C</u>H), 64.3 (s, <u>C</u>CO), 52.5 (q, O<u>C</u>H_3), 31.7 (t, C<u>C</u>H_2), 25.9 (q, C<u>C</u>H_3), 17.9 (q, C<u>C</u>H_3) ppm.

LRMS (CI) *m/z* 197 $[M+H]^+$.

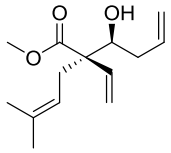
2.18a and 2.18b - (±)-Methyl (*R*)-2-((*S*)-1-hydroxybut-3-en-1-yl)-5-methyl-2-vinylhex-4-enoate and (±)-Methyl (*R*)-2-((*R*)-1-hydroxybut-3-en-1-yl)-5-methyl-2-vinylhex-4-enoate



$C_{14}H_{22}O_3$
M.W. = 238.32 g/mol

To a stirred solution of aldehyde **2.19** (222 mg, 1.13 mmol) in Et_2O (16 mL) under argon, was added allylmagnesium bromide (1 M Et_2O sol., 2.26 mL, 2.26 mmol) dropwise over 10 min at −78 °C. The resultant solution was allowed to slowly warm to rt in a dry ice bath, and stirred overnight. NH_4Cl (15 mL) was then added, and extracted with Et_2O (3 x 25 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Crude dr ca. 1.2:1. Purification by column chromatography (EtOAc:petrol, 1:20→1:3) gave the separated diastereoisomers (**2.18a** = 102 mg, 0.42 mmol, 38%. **2.18b** = 64 mg, 0.27 mmol, 23 %. Total = 0.69 mmol, 61%) as clear oils.

2.18a -(±)-Methyl (*R*)-2-((*S*)-1-hydroxybut-3-en-1-yl)-5-methyl-2-vinylhex-4-enoate



$C_{14}H_{22}O_3$
M.W. = 238.32 g/mol

FT-IR (neat) ν_{max} 3502 (br, O-H), 2916 (w, C-H), 1718 (s, C=O), 1639 (m, C=C), 1222 (s, O-C) cm^{-1}.

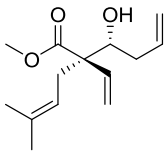
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.12 (1H, dd, *J* = 18.1, 10.9 Hz, CC<u>H</u>=CH_2), 5.88 (1H, m, CH_2=C<u>H</u>CH_2), 5.34 (1H, d, *J* = 10.9 Hz, CCH=C<u>H</u>H_{cis}), 5.19 (1H, d, *J* = 18.1 Hz, CCH=CH<u>H</u>$_{trans}$), 5.15 – 5.05 (2H, m, CH_2CH=C<u>H</u>$_2$), 5.01 (1H, finely coupled t, *J* = 7.3 Hz, C=C<u>H</u>), 3.93 (1H, ddd, *J* = 10.2, 5.4, 2.4 Hz, C<u>H</u>OH), 3.72 (3H, s, OC<u>H</u>$_3$), 2.72 (1H, d, *J* = 5.4 Hz, CHO<u>H</u>), 2.52 (2H, d, *J* = 7.3 Hz, C=CHC<u>H</u>$_2$), 2.27 (1H, m, CH_2=CHCH<u>H</u>), 2.04 (1H, m, CH_2=CHC<u>H</u>H), 1.68 (3H, s, CC<u>H</u>$_3$), 1.62 (3H, s, CC<u>H</u>$_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 175.4 (s, C=O), 135.9 (d, CH_2=CH), 135.5 (d, CH_2=CH), 134.5 (s, C=CH), 118.5 (d, C=CH), 117.2 (t, CH=CH_2), 116.7 (t, CH=CH_2), 74.4 (d, CHOH), 57.3 (s, CCO), 52.0 (q, OCH_3), 36.3 (t, CH_2=CHCH_2), 31.6 (t, CCH_2), 25.9 (q, CCH_3), 17.9 (q, CCH_3) ppm.

LRMS (ES$^+$) *m/z* 239 $[M+H]^+$.

HRMS (ES$^+$) For $C_{14}H_{22}O_3Na$ calculated 261.1461, found 261.1463 Da.

2.18b - (±)-Methyl (*R*)-2-((*R*)-1-hydroxybut-3-en-1-yl)-5-methyl-2-vinylhex-4-enoate



$C_{14}H_{22}O_3$
M.W. = 238.32 g/mol

FT-IR (neat) ν_{max} 3498 (br, O-H), 3078 (w, =C-H), 2917 (m, C-H), 1728 (s, C=O), 1640 (m, C=C), 1221 (s, O-C) cm^{-1}.

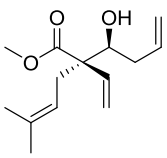
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.04 (1H, dd, *J* = 17.7, 10.9 Hz, CCH=CH_2), 5.86 (1H, m, CH_2=CHCH_2), 5.36 (1H, d, *J* = 10.9 Hz, CCH=CHH_{cis}), 5.21 (1H, d, *J* = 17.7 Hz, CCH=CHH_{trans}), 5.13 – 5.01 (3H, m, CH_2=CHCH_2, C=CH), 3.90 (1H, m, CHOH), 3.71 (3H, s, OCH_3), 2.59 (2H, d, *J* = 7.2 Hz, C=CHCH_2), 2.30 (1H, m, CH_2=CHCHH), 2.18 (1H, d, *J* = 7.9 Hz, OH), 2.05 (1H, m, CH_2=CHCHH), 1.68 (3H, s, CCH_3), 1.63 (3H, s, CCH_3) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 175.4 (s, C=O), 135.9 (d, CH_2=CH), 135.5 (d, CH_2=CH), 134.5 (s, CH_3C), 118.5 (d, CH_3C=CH), 117.2 (t, CH=CH_2), 116.8 (t, CH=CH_2), 74.4 (d, CHOH), 57.3 (s, CCO), 52.1 (q, OCH_3), 36.3 (t, CH_2=CHCH_2), 31.6 (t, CCH_2), 25.9 (q, CH_3), 17.9 (q, CH_3) ppm.

LRMS (CI) *m/z* 239 $[M+H]^+$, 169 $[(M-C_4H_7O)+2H]^+$.

HRMS (ES$^+$) For $C_{14}H_{22}O_3Na$ calculated 261.1461, found 261.1466 Da.

2.18a - (±)-Methyl (*R*)-2-((*S*)-1-hydroxybut-3-en-1-yl)-5-methyl-2-vinylhex-4-enoate

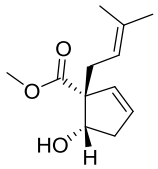


$C_{14}H_{22}O_3$
M.W. = 238.33 g/mol

By adaptation of the procedure by Linclau *et al.*,[99] to a stirred suspension of Mg (37 mg, 1.53 mg-atom) in Et_2O (4 mL) under Ar at rt was added 1,2-dibromoethane (0.13 mL, 1.53 mmol). After 30 min the solvent was removed under reduced pressure, and the residue was resuspended in CH_2Cl_2 (3 mL) under Ar and cooled to −78 °C. To this was added the aldehyde **2.19** (100 mg, 0.51 mmol) in CH_2Cl_2 (3.5 mL) over 4 min. After 30 min at −78 °C, allyltributylstannane (95%, 0.16 mL, 0.50 mmol) in CH_2Cl_2 (4 mL) was added over 4 min. After 30 min at −78 °C the suspension was warmed to −25 °C and stirred for 2.5 h. $NaHCO_3$ (10 mL) was added and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with brine (20 mL) then dried ($MgSO_4$) and concentrated under reduced pressure giving a crude dr of ca. 15:1 of diastereoisomers **2.18a**:**2.18b**. Purification by column chromatography (EtOAc:petrol, 1:3) gave the title compound (**2.18a**) (51 mg, 0.21 mmol, 42%) as a clear oil as a single diastereoisomer.

Data as previously presented.

2.17a - (±)-Methyl (1*R*,5*S*)-5-hydroxy-1-(3-methylbut-2-en-1-yl)cyclopent-2-ene-1-carboxylate



$C_{12}H_{18}O_3$
M.W. = 210.27 g/mol

To a stirred solution of alcohol **2.18a** (199 mg, 0.84 mmol) in CH_2Cl_2 (30 mL) under Ar at rt, was added Grubbs' second generation catalyst (**1.140**) (71 mg, 0.084 mmol) in CH_2Cl_2 (20 mL). After 3 h, the solvent was removed under reduced pressure. Purification by column chromatography twice (EtOAc:petrol, 1:3) gave the title compound (**2.17a**) (125 mg, 0.59 mmol, 71%) as a pale brown oil.

FT-IR (neat) ν_{max} 3458 (br, O-H), 2917 (m, C-H), 1718 (s, C=O), 1227 (s, O-C) cm^{-1}.

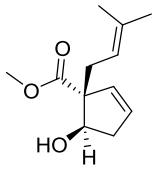
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (1H, m, C<u>H</u>=CHCH$_2$), 5.79 (1H, m, CH=C<u>H</u>CH$_2$), 5.07 (1H, m, C=C<u>H</u>), 4.25 (1H, td, *J* = 6.1, 3.0 Hz, C<u>H</u>OH), 3.73 (3H, s, OC<u>H$_3$</u>), 2.88 (1H, d, *J* = 6.1 Hz, O<u>H</u>), 2.71 (1H, ddt, *J* = 17.2, 6.1, 2.3 Hz, C<u>H</u>HCH=CH), 2.47 – 2.36 (2H, m, CH<u>H</u>CH=CH, C<u>H</u>HCH=C), 2.31 (1H, dd, *J* = 14.2, 8.1 Hz, CH<u>H</u>CH=C), 1.70 (3H, s, CC<u>H$_3$</u>), 1.60 (3H, s, CC<u>H$_3$</u>) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9 (s, <u>C</u>OOCH$_3$) 134.8 (s, <u>C</u>=CH), 132.2 (d, <u>C</u>H=CH), 130.4 (d, CH=<u>C</u>H), 118.8 (d, C=<u>C</u>H), 77.6 (d, <u>C</u>HOH), 64.5 (s, <u>C</u>CO), 51.8 (q, O<u>C</u>H$_3$), 40.4 (t, <u>C</u>H$_2$CH=CH), 35.0 (t, C=CH<u>C</u>H$_2$), 25.9 (q, C<u>C</u>H$_3$), 17.8 (q, C<u>C</u>H$_3$) ppm.

LRMS (CI) *m/z* 211 $[M+H]^+$.

HRMS (ES^+) For $C_{12}H_{18}O_3Na$ calculated 233.1148, found 233.1148 Da.

2.17b - (±)-Methyl (1*R*,5*R*)-5-hydroxy-1-(3-methylbut-2-en-1-yl)cyclopent-2-ene-1-carboxylate



$C_{12}H_{18}O_3$
M.W. = 210.27 g/mol

To a stirred solution of alcohol **2.18b** (80 mg, 0.34 mmol) in CH_2Cl_2 (12 mL) under Ar at rt was added Grubbs' second generation catalyst (**1.140**) (29 mg, 0.034 mmol) in CH_2Cl_2 (8 mL). After 4.5 h the solvent was removed under reduced pressure. Purification by column chromatography (EtOAc:petrol, 1:3) gave the title compound (**2.17b**) (41 mg, 0.19 mmol, 57%) as a pale brown oil.

FT-IR (neat) ν_{max} 3435 (br., O-H), 2952 (w, C-H), 1725 (s, C=O), 1641 (w, C=C), 1180 (s, O-C) cm^{-1}.

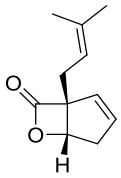
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 – 5.72 (2H, m, C<u>H</u>=C<u>H</u>), 5.11 (1H, finely coupled t, *J* = 7.1 Hz, C=C<u>H</u>), 4.61 (1H, td, *J* = 7.1, 4.5 Hz, C<u>H</u>OH), 3.70 (3H, s, OC<u>H</u>$_3$), 2.71 (1H, m, CH=CHC<u>H</u>H), 2.52 (1H, dd, *J* = 14.1, 7.1 Hz, C=CHC<u>H</u>H), 2.40 (1H, dd, *J* = 14.1, 7.1 Hz, C=CHCH<u>H</u>), 2.32 (1H, m, CH=CHCH<u>H</u>), 2.13 (1H, d, *J* = 4.5 Hz, CHO<u>H</u>), 1.70 (3H, s, CC<u>H</u>$_3$), 1.61 (s, 3H, CC<u>H</u>$_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 176.0 (s, <u>C</u>OOCH$_3$), 134.5 (s, <u>C</u>=CH), 132.5 (d, <u>C</u>H=CH), 129.2 (d, CH=<u>C</u>H), 119.4 (d, C=<u>C</u>H), 76.3 (d, <u>C</u>HOH), 61.9 (s, <u>C</u>CO), 51.8 (q, O<u>C</u>H$_3$), 39.2 (t, <u>C</u>H$_2$CH), 30.5 (t, C<u>C</u>H$_2$), 25.9 (q, C<u>C</u>H$_3$), 17.8 (q, C<u>C</u>H$_3$) ppm.

LRMS (CI) *m/z* 211 $[M+H]^+$.

HRMS (ES^+) For $C_{12}H_{18}O_3Na$ calculated 233.1148, found 233.1151 Da.

2.16 - (±)-(1*R*,5*S*)-1-(3-Methylbut-2-en-1-yl)-6-oxabicyclo[3.2.0]hept-2-en-7-one



$C_{11}H_{14}O_2$
M.W. = 178.23 g/mol

To a stirred solution of ester **2.17a** (157 mg, 0.75 mmol) in MeOH (8 mL), was added NaOH (1 M, 0.75 mL, 0.75 mmol) at 0 °C. The solution was warmed to 60 °C and stirred overnight before removing the solvent under reduced pressure. The residue was taken into H_2O (5 mL), acidified to ~pH 2 with HCl (2 N), and extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to provide the crude acid.

In a separate flask, the aforementioned crude acid was taken into pyridine (11 mL), under argon, before addition of *p*-TsCl (200 mg, 1.05 mmol) at 0 °C. After stirring at this temperature for 1 h, the flask was sealed and placed into a fridge overnight, before cooling to 0 °C and stirring for a further 1 h. ~10 mL of ice was added before extracting with EtOAc (3 x 15 mL). The combined organic extracts were washed with $NaHCO_3$ (10 mL), H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography twice (pentane:Et_2O, 3:1) gave the title compound (**2.16**) (45 mg, 0.25 mmol, 34%) as a clear oil.

FT-IR (neat) ν_{max} 2915 (w, C-H), 1811 (s, C=O), 1673 (w, C=C), 1111 (m, O-C) cm^{-1}.

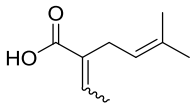
^{1}H NMR (400MHz, $CDCl_3$) δ 5.93 (1H, m, CCHC<u>H</u>), 5.70 (1H, m, CC<u>H</u>CH), 5.12 (1H, t, *J* = 7.1 Hz, $CH_3CC\underline{H}$), 4.78 (1H, d, *J* = 5.1 Hz, C<u>H</u>OC), 2.86 – 2.69 (2H, m, CH=CHC<u>H</u>$_2$), 2.64 (1H, dd, *J* = 15.2, 7.1 Hz, C=CHC<u>H</u>$_2$), 2.45 (1H, dd, *J* = 15.2, 7.1 Hz, C=CHC<u>H</u>$_2$), 1.73 (3H, s, C<u>H</u>$_3$), 1.65 (3H, s, C<u>H</u>$_3$) ppm.

^{13}C NMR (101MHz, $CDCl_3$) δ 173.0 (s, <u>C</u>=O), 135.9 (s, <u>C</u>=CH), 132.5 (d, CH=<u>C</u>H), 128.8 (d, <u>C</u>H=CH), 117.3 (d, C=<u>C</u>H), 78.4 (d, <u>C</u>HOH), 75.6 (s, <u>C</u>CO), 37.5 (t, CH=CH<u>C</u>H$_2$), 27.5 (t, C=CH<u>C</u>H$_2$), 25.8 (q, C<u>C</u>H$_3$), 18.0 (q, C<u>C</u>H$_3$) ppm.

LRMS (CI) *m/z* 196 $[M+NH_4]^+$, 179 $[M+H]^+$, 135 $[M-CO_2+H]^+$.

HRMS (ES^+) For $C_{11}H_{14}NaO_2$ calculated 201.0886, found 201.0886 Da.

2.25 - 2-Ethylidene-5-methylhex-4-enoic acid



$C_9H_{14}O_2$
M.W. = 154.21 g/mol

To a stirred solution of alcohol **2.18b** (40 mg, 0.16 mmol) in MeOH (2 mL) at 0 °C was added NaOH (4N, 0.26 mL, 1.05 mmol). The solution was warmed to rt, and stirred overnight. The solvent was removed under reduced pressure before adding H_2O (2 mL) and washing with EtOAc (4 mL). The aq. phase was then acidified to ~pH 2 with HCl (2N) and extracted with EtOAc (3 x 8 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc: petrol, 1:5) gave the title compound (**2.25**) (16 mg, 0.10 mmol, 63%) as a white solid.

MP 47–49 °C (*solvent*: Et_2O/*n*-hexane).

FT-IR (neat) ν_{max} 2965 (w, =C-H), 2923 (w, C-H), 1677 (C=O), 1633 (s, C=C) 1233 (s, O-C) cm^{-1}.

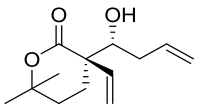
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (1H, q, *J* = 7.0 Hz, C=C<u>H</u>CH_3), 5.05 (1H, t, *J* = 7.0 Hz, C=C<u>H</u>CH_2), 3.02 (2H, d, *J* = 7.0 Hz, CC<u>H</u>$_2$), 1.85 (3H, d, *J* = 7.0 Hz, CHC<u>H</u>$_3$), 1.71 (3H, s, CC<u>H</u>$_3$), 1.69 (3H, s, CC<u>H</u>$_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9 (s, <u>C</u>=O), 140.0 (d, C=<u>C</u>HCH$_3$), 132.4 (s, <u>C</u>=CH), 132.0 (s, <u>C</u>=CH), 121.3 (d, C=<u>C</u>HCH$_2$), 25.7 (q, C<u>C</u>H$_3$), 25.2 (q, CH<u>C</u>H$_3$), 17.8 (t, CH<u>C</u>H$_2$), 14.5 (q, C<u>C</u>H$_3$) ppm.

LRMS (ES$^-$) *m/z* 153 [M–H]$^-$.

HRMS (ES$^-$) For $C_9H_{13}O_2$ calculated 153.0921, found 153.0919 Da.

2.28 - (±)-(*R*)-3-((*S*)-1-Hydroxybut-3-en-1-yl)-6,6-dimethyl-3-vinyltetrahydro-*2H*-pyran-2-one



$C_{13}H_{20}O_3$
M.W. = 224.30 g/mol

A stirred solution of ester **2.18b** (23 mg, 0.097 mmol) in HCl (1.5 M, 1.5 mL) was heated to 65°C for 18 h, before extracting with EtOAc (3 x 5 mL). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:petrol, 1:2) gave the title compound (**2.28**) (19 mg, 0.085 mmol, 88%) as a clear oil.

FT-IR (neat) ν_{max} 3430 (br, O-H), 2977 (w, C-H), 1694 (s, C=O), 1634 (w, C=C), 1118 (s, O-C) cm^{-1}.

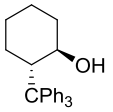
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (1H, m, CH_2C<u>H</u>=CH_2), 5.72 (1H, dd, *J* = 17.5, 10.8 Hz, CC<u>H</u>=CH_2), 5.33 (1H, d, *J* = 10.8 Hz, CCH=C<u>H</u>H$_{cis}$), 5.28 (1H, d, *J* = 17.5 Hz, CCH=CH<u>H</u>$_{trans}$), 5.17 – 5.10 (2H, m, CH_2CH=C<u>H</u>$_2$), 4.12 (1H, ddd, *J* = 10.7, 5.0, 2.1 Hz, C<u>H</u>O), 2.44 (1H, d, *J* = 5.0 Hz, O<u>H</u>), 2.35 – 2.24 (2H, m, C<u>H</u>HCHO, CH_3CCH_2C<u>H</u>H), 2.05 (1H, m, CH<u>H</u>CHO), 1.90 (1H, m, CH_3CC<u>H</u>H), 1.80 – 1.68 (2H, m, CH_3CCH<u>H</u> CH_3CCH_2CH<u>H</u>), 1.42 (3H, s, C<u>H</u>$_3$), 1.40 (3H, s, C<u>H</u>$_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8 (s, C=O), 138.0 (d, $CCH=CH_2$), 135.4 (d, $CH_2CH=CH_2$), 117.9 (t, $CCH=CH_2$), 117.6 (t, $CH_2CH=CH_2$), 82.7 (s, CH_3CO), 75.2 (d, CHO), 54.4 (s, CCHO), 34.9 (t, CH_2CHO), 31.1 (t, CH_3CCH_2), 30.3 (q, CH_3), 27.2 (q, CH_3), 21.0 (t, $CH_3CCH_2CH_2$) ppm.

LRMS (ES^+) *m/z* 225 $[M+Na]^+$.

HRMS (ES^+) For $C_{13}H_{20}O_3Na$ calculated 247.1305, found 247.1306 Da.

1.130 - (±)-(1*R*,2*S*)-2-Tritylcyclohexan-1-ol



$C_{25}H_{26}O$
M.W. = 342.47 g/mol

Following a procedure by Peddle *et al.*,[69] to a stirred solution of $HCPh_3$ (**2.35**) (40.0 g, 164 mmol) in THF (250 mL) under Ar at –78 °C was added *n*-BuLi (2 M in hexane, 86 mL, 172 mmol) *via* cannula over 30 min. The solution was warmed to rt (initially maintaining temperature between 5 and 20 °C with an ice bath) and stirred for 1.5 h, before cooling to 0 °C. Cyclohexene oxide (**2.36**) (24.8 g, 246 mmol) was added over 20 min before warming to rt and stirring for 16 h. H_2O (250 mL) was added and extracted with EtOAc (3 x 300 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Trituration with hexane until a white solid persisted gave the title compound (**1.130**) (38.3 g, 112 mmol, 68%) as a white solid. The analytical data acquired was in accordance with previously reported values.[69]

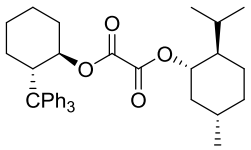
MP 164–166 °C (*solvent*: EtOH) (Lit. MP: 168-170 °C)[69].

FT-IR (neat) ν_{max} 3458 (br, O-H), 3052 (w, =C-H), 2919 (w, C-H), 1594 (w, C=C) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.09 (15H, m, CH_{Ar}), 3.28 (1H, m, CC_{Ar}), 3.09 (1H, td, *J* = 9.9, 3.3 Hz, CHOH), 2.06 (1H, m, CCHCHH), 1.93 (1H, m, OCHCHH), 1.76 – 1.35 (5H, m, OCHCHH OH, $OCHCH_2CHH$, $CCHCH_2CH_2$), 1.09 (1H, apparent qt, *J* = 13.1, 4.1 Hz, $OCHCH_2CHH$), 0.50 (1H, m, CCHCHH) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 129.7 (s, $\underline{C}_{Ar}$), 127.7 (d, $\underline{C}H_{Ar}$), 125.7 (d, $\underline{C}H_{Ar}$), 73.6 (d, $\underline{C}$HOH), 60.7 (s, $\underline{C}Ph_3$), 48.8 (d, C$\underline{C}$H), 37.0 (t, $\underline{C}H_2$CHOH), 28.9 (t, $\underline{C}H_2$CHC), 26.2 (t, $\underline{C}H_2CH_2$CHC), 25.3 (t, $\underline{C}H_2CH_2$CHOH) ppm.

2.37 - (1*S*, 2*R*, 5*S*)-2-Isopropyl-5-methylcyclohexyl ((1*R*, 2*S*)-2-tritylcyclohexyl) oxalate



$C_{37}H_{44}O_4$
M.W. = 552.74 g/mol

To a stirred solution of oxalyl chloride (21.4 mL, 253 mmol) in CH_2Cl_2 (150 mL) under Ar at 0 ˚C was added (+)-menthol (17.3 g, 111 mmol) in CH_2Cl_2 (150 mL) *via* cannula over 30 min. After 1 h, the solution was warmed to rt and stirred for a further 16 h. The solvent was removed under reduced pressure and the residue was taken into CH_2Cl_2 (150 mL) under Ar at rt. (±)-TTC (**1.130**) (34.5 g, 101 mmol) and pyridine (20.5 mL, 253 mmol) in CH_2Cl_2 (90 mL) was then added. After 16 h NH_4Cl (150 mL) was added, and then washed with HCl (2 N, 3 x 70 mL), $NaHCO_3$ (100 mL), and brine (70 mL). The organic solution was dried ($MgSO_4$), and concentrated under reduced pressure. The residue was taken into MeOH (100 mL), stirred rapidly at 0 ˚C and filtered to give a 1:1 mixture of diastereoisomers. The precipitate was taken into MeOH (300 mL) and heated to reflux for 30 min, before filtering, and washing with hot MeOH (250 mL). The filtrate was collected, and the recrystallisation process was repeated 5 more times, to give the title compound (**2.37**) (11.7 g, 21.2 mmol, 21%) as a white solid at +99% ee by HPLC (1% IPA in hexane, OD-H column, 0.5 mL/min). The analytical data acquired was in accordance with previously reported values.[70]

MP 199–201 ˚C (*solvent*: MeOH).

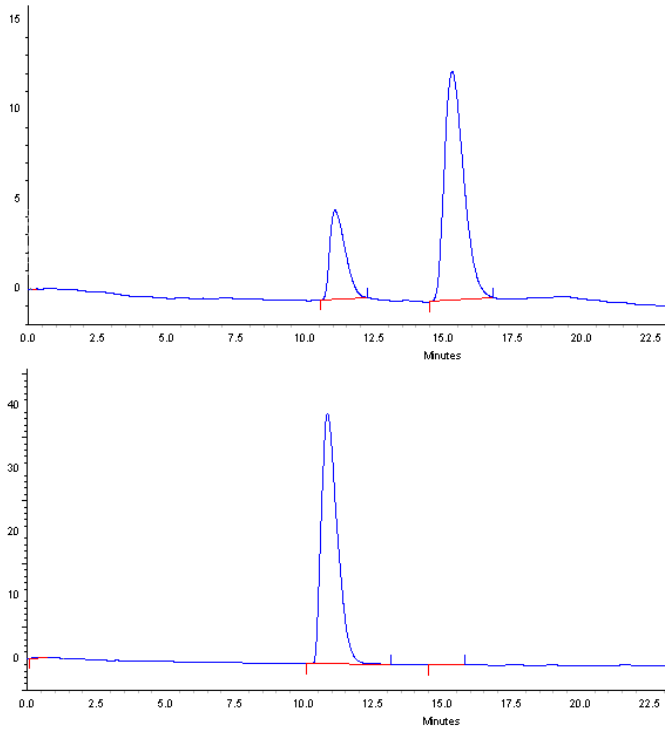
[α] –9.4 (c = 1.14).

FT-IR (neat) ν_{max} 3057 (w, C=C), 2945 (m, C-H), 1732 (s, C=O), 1595 (w, C=C), 1492 (w, C=C) cm^{-1}.

.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.06 (15H, m, C$\underline{H}_{Ar}$), 4.65 (1H, td, *J* = 10.9, 4.5 Hz, OC$\underline{H}$CHCH_3), 4.15 (1H, td, *J* = 10.2, 3.9 Hz, OC$\underline{H}$CHC), 3.60 (1H, m,

PhCC<u>H</u>), 2.13 (1H, d, *J* = 13.7 Hz, CCHC<u>H</u>H), 2.01 (1H, m, OCHC<u>H</u>H), 1.85 – 1.63 (7H, m, $CH_3CHC\underline{H}H$, $C\underline{H}HCH_2CHC$, $C\underline{H}HCH_2CHO$, $OCC\underline{H}HCH$, $CH_3CHCHCH\underline{H}$, $OCHCH\underline{H}$, $OCHC\underline{H}CH_3$, $OCHCH_2C\underline{H}$), 1.51 – 1.17 (4H, m, $CH\underline{H}CH_2CHC$, $CH\underline{H}CH_2CHO$, $C\underline{H}(CH_3)_2$), 1.09 – 0.84 (10H, m, $CH_3CHC\underline{H}H$, $CH(C\underline{H}_3)_2$, $CCHCH\underline{H}$, $OCCH\underline{H}CH$, $CH_3CHCHCH\underline{H}$), 0.75 (3H, d, *J* = 7.0 Hz, $CHC\underline{H}_3$) ppm.

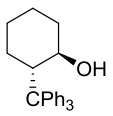
^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8 (s, <u>C</u>=O), 157.7 (s, <u>C</u>=O), 129.5 (s, $\underline{C}_{Ar}$), 127.4 (d, $\underline{C}H_{Ar}$), 125.6 (d, $\underline{C}H_{Ar}$), 78.4 (d, <u>C</u>HO TTC), 77.0 (d, <u>C</u>HO menthol), 60.8 (s, <u>C</u>Ph), 46.3 (d, <u>C</u>HCPh), 46.2 (d, $\underline{C}H(CH_3)$), 40.0 (t, $OC\underline{C}H_2CH$), 34.0 (t, $CH_3CHCH\underline{C}H_2$), 32.7 (t, $OCH\underline{C}H_2$), 31.3 (d, $OCH\underline{C}HCH_3$), 28.9(t, $CCH\underline{C}H_2$), 26.0 (d, $OCHCH_2\underline{C}H$), 25.9 (t, $\underline{C}H_2CH_2CHC$), 24.7 (t, $\underline{C}H_2CH_2CHO$), 23.2 (t, $CH_3CH\underline{C}H_2$), 22.0 (q, $CH(\underline{C}H_3)$), 20.6 (q, $CH(\underline{C}H_3)$), 16.2 (q, $CH_2CH\underline{C}H_3$) ppm.



Retention Time	Area	Area %	Height	Height %
0.653	15182	0.06	424	0.06
10.850	26693650	99.67	664503	99.65
14.983	72966	0.27	1911	0.29

Totals				
	26781798	100.00	666838	100.00

1.130 - (1*R*,2*S*)-2-Tritylcyclohexanol



$C_{25}H_{26}O$
M.W. = 342.47 g/mol

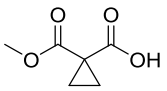
To a stirred solution of oxylate **2.37** (11.4 g, 20.6 mmol) in MeOH (155 mL) and H_2O (31 mL), was added KOH (+85%, 3.40 g, 51.5 mmol) at rt. The suspension was heated to reflux and stirred for 16 h before the solvent was removed under reduced pressure. The residue was taken into H_2O (50 mL) and extracted with EtOAc (5 x 125 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was taken into hexane (100 mL), before filtering and collecting the filtrate. This procedure was repeated, before concentrating under reduced pressure, giving the title compound (**1.130**) (6.60 g, 19.3 mmol, 94%) as a white solid.

MP 176–178 °C (*solvent*: EtOH).

[α] 25.0 (c = 1.10).

Analysis consistent with (±)-**1.130**.

2.38 - 1-(Methoxycarbonyl)cyclopropane-1-carboxylic acid



$C_6H_8O_4$
M.W. = 144.13 g/mol

To a stirred solution of cyclopropylmalonate **2.13** (10.0 g, 63.2 mmol) in methanol (100 mL) at 0 °C was added NaOH (1 N, 63.2 mL, 63.2 mmol). After 20 min the solution was warmed to rt and stirred for 24 h. The solvent was then removed under reduced pressure, and the aq. phase was washed with $CHCl_3$ (3 x 60 mL), acidified to ~pH 3 with HCl (2 N) and extracted with EtOAc (3 x 150 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give the title compound (**2.38**) (8.25 g, 57.2 mmol, 91%) as a white solid. The analytical data acquired was in accordance with previously reported values.[217]

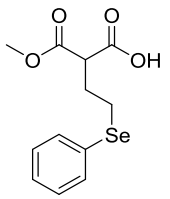
MP 50–52 °C (*solvent*: MeOH).

FT-IR (neat) ν_{max} 2960 (w, C-H),1728 (s, C=O), 1674 (s, C=O), 1149 (s, O-C) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.78 (3H, s, C<u>H</u>$_3$), 1.84 (2H, m, C<u>H</u>$_2$), 1.76 (2H, m, C<u>H</u>$_2$ ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 176.2 (s, <u>C</u>OOH), 170.6 (s, <u>C</u>OOCH$_3$), 53.3 (q, O<u>C</u>H$_3$), 25.0 (s, <u>C</u>CH$_2$), 22.0 (t, <u>C</u>H$_2$) ppm.

2.39 - (±)-2-(Methoxycarbonyl)-4-(phenylselanyl)butanoic acid



$C_{12}H_{14}O_4Se$
M.W. = 301.20 g/mol

To a stirred solution of PhSeSePh (1.95 g, 6.12 mmol) in DMF (30 mL) under Ar at rt was added $NaBH_4$ (301 mg, 7.96 mmol) in 4 portions. Once clear (~10 min), cyclopropylmalonicacid **2.38** (1.50 g, 10.4 mmol) in DMF (15 mL) was added dropwise before stirring overnight. HCl (2 M, 25 mL) and H_2O (350 mL) were added before extracting with Et_2O (4 x 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:petrol:AcOH 100:100:2) gave the title compound (**2.39**) (1.44 g, 4.78 mmol, 46%) as a pale orange oil.

FT-IR (neat) ν_{max} 2950 (w, C-H), 1709 (s, C=O), 1578 (m, C=C), 1201 (s, O-C), 1164 (s, O-C) cm^{-1}.

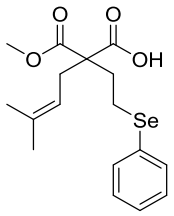
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.49 (2H, m, C<u>H</u>$_{Ar}$), 7.31 – 7.26 (3H, m, C<u>H</u>$_{Ar}$), 3.75 (3H, s, OC<u>H</u>$_3$), 3.69 (1H, t, *J* = 7.2 Hz, C<u>H</u>CO), 3.01 – 2.88 (2H, m, SeC<u>H</u>$_2$), 2.35 – 2.22 (2H, m, CHC<u>H</u>$_2$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5 (s, $\underline{C}$=O), 169.2 ($\underline{C}$=O), 133.0 ($\underline{C}H_{Ar}$), 129.2 ($\underline{C}H_{Ar}$), 127.3 ($\underline{C}H_{Ar}$), 52.8 (O$\underline{C}H_3$), 50.9 ($\underline{C}$HCO), 29.2 (Se$\underline{C}H_2$), 24.9 (CH$\underline{C}H_2$) ppm.

LRMS (ES^-) *m/z* 301 $[M-H]^-$.

HRMS (ES^+) For $C_{12}H_{14}NaO_4Se$ calculated 324.9950, found 324.9954 Da.

2.40 - (±)-2-(Methoxycarbonyl)-5-methyl-2-(2-(phenylselanyl)ethyl)hex-4-enoic acid



$C_{17}H_{22}O_4Se$
M.W. = 369.31 g/mol

To a stirred solution of DIPA (0.82 mL, 5.84 mmol) in THF (5.6 mL) under Ar at −78 °C was added *n*-BuLi (2 N, 2.92 mL, 5.84 mmol) dropwise over 5 min. After 30 min the mono-acid **2.39** (800 mg, 2.66 mmol) in THF (8 mL) was added dropwise over 20 min before stirring at −78 °C for a further 1 h. Prenyl bromide (**2.02**) (1.36 mL, 10.6 mmol) was then added. After 2 h the solution was warmed to rt and after 2 days, HCl (2 N, 15 mL) was added followed by Et_2O (120 mL). The organic phase was separated and washed with HCl (2 N, 30 mL), $Na_2S_2O_3$ (0.1 M, 40 mL) and brine (40 mL). The organic extract was dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:petrol, 1:2) gave the title compound (**2.40**) (635 mg, 1.72 mmol, 65%) as a light orange oil.

FT-IR (neat) ν_{max} 2928 (w, C-H), 1731 (s, C=O), 1706 (s, C=O), 1579 (w, C=C), 1163 (m, O-C) cm^{-1}.

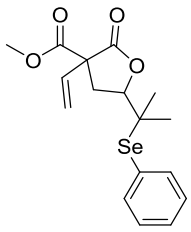
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.45 (2H, m, C$\underline{H}_{Ar}$), 7.29 – 7.24 (3H, m, C$\underline{H}_{Ar}$), 4.91 (1H, finely coupled t, *J* = 7.5 Hz, C=C$\underline{H}$), 3.74 (3H, s, OC$\underline{H}_3$), 2.87 – 2.70 (2H, m, SeC$\underline{H}_2$), 2.70 – 2.56 (2H, m, C$\underline{H}_2$CH=C), 2.39 – 2.23 (2H, m, CC$\underline{H}_2$CH$_2$), 1.67 (3H, s, CC$\underline{H}_3$), 1.58 (3H, s, CC$\underline{H}_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8 (s, C=O), 173.1 (s, C=O), 136.7 (s, C=CH), 132.5 (d, CH_{Ar}), 129.6 (s, C_{Ar}), 129.1 (d, CH_{Ar}), 127.0 (d, C=CH), 116.7 (s, C_{Ar}), 58.3 (s, CC=O), 52.9 (q, OCH_3), 34.9 (t, CH_2CH=C), 33.5 (t, $SeCH_2$), 25.9 (q, CCH_3), 21.9 (t, CCH_2CH_2), 17.8 (q, CCH_3) ppm.

LRMS (ES^-) *m/z* 355 $[M-CH_3]^-$.

HRMS (ES^+) For $C_{17}H_{22}NaO_4Se$ calculated 393.0576, found 393.0583 Da.

2.42 - Methyl 2-oxo-5-(2-(phenylselanyl)propan-2-yl)-3-vinyltetrahydrofuran-3-carboxylate



$C_{17}H_{20}O_4Se$
M.W. = 367.30 g/mol

To a stirred solution of the prenyl acid **2.40** (62 mg, 0.17 mmol) in THF (0.75 mL) at rt was added H_2O_2 (30% aq., 0.02 mL, 0.17 mmol). After stirring overnight the solvent was removed under reduced pressure. Purification by column chromatography (EtOAc:petrol 1:3) gave a 1:1 mixture of diastereoisomers of the title compound (**2.42**) (34 mg, 0.092 mmol, 54%) as a clear oil. A second column (EtOAc:petrol, 1:3) allowed for a small quantity of one diastereoisomer to be isolated for analysis.

FT-IR (neat) ν_{max} 2957 (w, C-H), 1775 (s, C=O, 5 membered lactone), 1732 (s, C=O), 1637 (w, C=C), 1176 (s, C-OMe) cm^{-1}.

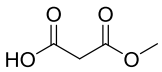
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.63 (2H, m, CH_{Ar}), 7.41 (1H, m, CH_{Ar}), 7.37 – 7.31 (2H, m, CH_{Ar}), 6.30 (1H, dd, *J* = 17.2, 6.6 Hz, $CH=CH_2$), 5.39 (1H, d, *J* = 6.6 Hz, CH=CHH_{cis}) 5.34 (1H, d, *J* = 17.2 Hz, CH=CHH_{trans}), 4.44 (1H, dd, *J* = 10.6, 5.6 Hz, CCH_2CH), 3.79 (3H, s, OCH_3), 3.02 (1H, dd, *J* = 13.1, 5.6 Hz, CCHH), 2.38 (1H, dd, *J* = 13.1, 10.6 Hz, CCHH), 1.44 (3H, s, CCH_3), 1.38 (3H, s, CCH_3) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1(s, $\underline{C}OOC$), 168.8 (s, $\underline{C}OOCH_3$), 138.4 (d, $\underline{C}H_{Ar}$), 133.5 (d, $\underline{C}H{=}CH_2$), 129.2 (d, $\underline{C}H_{Ar}$), 129.0 (d, $\underline{C}H_{Ar}$), 126.0 (s, $\underline{C}_{Ar}$), 117.8 (t, $CH{=}\underline{C}H_2$), 84.6 (d, $\underline{C}HO$), 58.8 (s, $\underline{C}CO$), 53.6 (q, $O\underline{C}H_3$), 46.4 (s, $CH\underline{C}Se$), 34.7 (t, $C\underline{C}H_2$), 27.0 (q, $C\underline{C}H_3$), 23.6 (q, $C\underline{C}H_3$) ppm.

LRMS (EI) *m/z* 368 (2%) $[M]^{+\cdot}$.

HRMS (ES^+) For $C_{17}H_{20}O_4SeNa$ calculated 391.0420, found 391.0423 Da.

Monomethyl malonate



$C_4H_6O_4$
M.W. = 118.09 g/mol

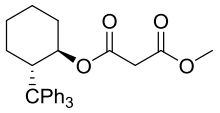
To a stirred solution of dimethyl malonate (**2.05**) (10.0 g, 75.7 mmol) in MeOH (200 mL) at rt, was added KOH (>85%, 5.00 g, 75.7 mmol). After 16 h, the solution was warmed to 65 °C and stirred for 4.5 h. The solvent was removed under reduced pressure and the residue was taken into H_2O (100 mL), and NaOH (2 M, 1 mL) was added, before washing with EtOAc (20 mL). The aq. phase was acidified with HCl (1N) to ~pH 2, and extracted with EtOAc (4 x 120 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give the title compound (8.70 g, 73.7 mmol, 98%) as a clear oil. The analytical data acquired was in accordance with previously reported values.[218]

FT-IR (neat) ν_{max} 3479 (br, OH), 2958 (m, C-H), 1711 (s, C=O), 1151 (s, O-C) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (1H, br s, $O\underline{H}$), 3.80 (3H, s, $C\underline{H_3}$), 3.46 (2H, s, $C\underline{H_2}$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1 (s, $\underline{C}{=}O$), 167.3 (s, $\underline{C}{=}O$), 52.8 (q, $\underline{C}H_3$), 40.5 (t, $\underline{C}H_2$) ppm.

2.48 - Methyl ((1*R*,2*S*)-2-tritylcyclohexyl) malonate



$C_{29}H_{30}O_4$
M.W. = 442.55 g/mol

To a stirred solution of monomethyl malonate (4.70 g, 39.8 mmol) in CH_2Cl_2 (90 mL) under argon at rt was added oxalyl chloride (6.70 mL, 79.5 mmol) in CH_2Cl_2 (25 mL) over 25 min. To this was added DMF (0.43 mL, 5.57 mmol) and stirred at rt for 16 h before removing the solvent under reduced pressure. The residue was taken into CH_2Cl_2 (80 mL) under Ar at 0 °C, and added to a solution of (+)-**1.130** (6.34 g, 18.5 mmol), Et_3N (5.15 mL, 37.0 mmol) and DMAP (0.45 g, 3.68 mmol) in CH_2Cl_2 (120 mL) over 30 min. The solution was heated to reflux for 20 h, before addition of H_2O (100 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 150 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (petrol:CH_2Cl_2, 1:1→CH_2Cl_2) gave the title compound (**2.48**) (6.23 g, 14.1 mmol, 76%) as a white solid.

MP 61–62 °C (*solvent*: CH_2Cl_2).

[α] 36.5 (c = 1.06).

FT-IR (neat) ν_{max} 3055 (w, =C-H), 2942 (w, C-H), 1728 (s, C=O), 1595 (w, C=C), 1493 (m, C=C), 1147 (s, O-C) cm^{-1}.

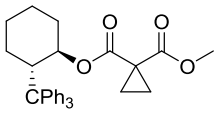
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 6.96 (15H, m, C$\underline{H}_{Ar}$), 4.26 (1H, td, *J* = 10.3, 4.0 Hz, OC$\underline{H}$), 3.69 (3H, s, OC$\underline{H}_3$), 3.52 (1H, m, CC$\underline{H}$), 2.62 (1H, d, *J* = 16.0 Hz, C$\underline{H}$HC=O), 2.56 (1H, d, *J* = 16.0 Hz, CH$\underline{H}$C=O), 2.18 – 2.02 (2H, m, OCHC$\underline{H}$H & CCHC$\underline{H}$H), 1.76 – 1.61 (2H, m, CCHCH$_2$C$\underline{H}$H, OCHCH$_2$C$\underline{H}$H), 1.59 – 1.37 (2H, m, CCHCH$_2$CH$\underline{H}$ & OCHC$\underline{H}$H), 1.15 (1H, m, OCHCH$_2$CH$\underline{H}$), 0.59 (1H, m, CCHC$\underline{H}$H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0 (s, $\underline{C}$=O), 165.3 (s, $\underline{C}$=O), 128.8 (d, $\underline{C}H_{Ar}$), 127.2 (d, $\underline{C}H_{Ar}$), 125.2 (d, $\underline{C}H_{Ar}$), 76.3 (d, O$\underline{C}$H), 60.7 (s, $\underline{C}Ph_3$), 52.2 (q, $\underline{C}H_3$), 46.1 (d, C$\underline{C}$H), 40.6 (t, $\underline{C}H_2$C=O), 33.0 (t, OCH$\underline{C}H_2$), 28.9 (t, CCH$\underline{C}H_2$), 25.8 (t, CCHCH$_2\underline{C}H_2$), 24.7 (t, OCHCH$_2\underline{C}H_2$) ppm.

LRMS (ES$^+$) *m/z* 506 [M+CH_3CN+Na]$^+$, 465 [M+Na]$^+$.

HRMS (ES$^+$) For $C_{29}H_{30}O_4Na$ calculated 465.2036, found 465.2042 Da.

2.46 - Methyl ((1*R*,2*S*)-2-tritylcyclohexyl) cyclopropane-1,1-dicarboxylate



$C_{31}H_{32}O_4$
M.W. = 468.58 g/mol

To a stirred solution of malonate **2.48** (6.10 g, 13.78 mmol) in DMF (17 mL), was added K_2CO_3 (4.76 g, 34.5 mmol), dibromoethane (1.54 mL, 17.9 mmol) then TBAB (23 mg, 0.07 mmol) at rt. The solution was heated to 50 °C, and stirred for 24 h before adding H_2O (100 mL). The aq. phase was extracted with Et_2O (3 x 50 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:petrol, 1:5) gave the title compound (**2.46**) (5.77 g, 12.5 mmol, 89%) as a white solid.

[α] 32.5 (c = 1.06)

MP 47–49 °C (*solvent*: CH_2Cl_2).

FT-IR (neat) ν_{max} 3055 (w, =C-H), 2944 (w, C-H), 1718 (s, C=O), 1595 (w, C=C), 1493 (w, C=C), 1118 (m, O-C) cm^{-1}.

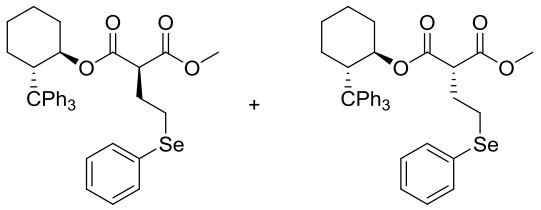
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 6.95 (15H, m, C$\underline{H}_{Ar}$), 4.18 (1H, td, *J* = 10.1, 3.8 Hz, C$\underline{H}$O), 3.72 (3H, s, OC$\underline{H}_3$), 3.56 (1H, m, C$\underline{H}$CPh), 2.13 (1H, m, C$\underline{H}$HCHC), 1.98 (1H, m, C$\underline{H}$HCHO), 1.74 – 1.61 (2H, m, C$\underline{H}$HCH$_2$CHC, C$\underline{H}$HCH$_2$CHO), 1.51 (1H, m, CH$\underline{H}$CHO), 1.42 (1H, m, CH$\underline{H}$CH$_2$CHC), 1.21 – 1.10 (2H, m, CH$_2$CH$_2$CHO, C$\underline{H}$HCH$_2$), 1.03 – 0.96 (2H, m, CH$_2$C$\underline{H}_2$), 0.77 – 0.65 (2H, m, CH$\underline{H}$CHC, CH$\underline{H}$CH$_2$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4 (s, $\underline{C}$=O), 168.0 (s, $\underline{C}$=O), 128.7 (s, $\underline{C}_{Ar}$), 127.3 (d, $\underline{C}H_{Ar}$), 125.4 (d, $\underline{C}H_{Ar}$), 76.5 (d, $\underline{C}$HOH), 60.9 (s, CPh), 52.2 (q, O$\underline{C}H_3$), 45.8 (d, $\underline{C}$HCPh), 32.7 (t, $\underline{C}H_2$CHO), 28.7 (t, $\underline{C}H_2$CHC), 28.2 (s, $\underline{C}$C=O), 25.8 (t, $\underline{C}H_2CH_2$CHC), 24.6 (t, $\underline{C}H_2CH_2$CHO), 16.1 (t, $\underline{C}H_2CH_2$), 15.3 (t, $CH_2\underline{C}H_2$) ppm.

LRMS (ES$^+$) *m/z* 532 [M+CH_3CN+Na]$^+$, 491 [M+Na]$^+$.

HRMS (ES$^+$) For $C_{31}H_{32}O_4Na$ calculated 491.2193, found 491.2201 Da.

2.49 - Methyl ((1*R*,2*S*)-2-tritylcyclohexyl) (*R*)-2-(2-(phenylselanyl)ethyl)malonate and 1-Methyl 3-((1*R*,2*S*)-2-tritylcyclohexyl) (*S*)-2-(2-(phenylselanyl)ethyl)malonate



$C_{37}H_{38}O_4Se$
M. W. = 625.67 g/mol

To a stirred solution of PhSeSePh (2.12 g, 6.79 mmol) in MeOH (40 mL) under Ar at rt was added $NaBH_4$ (0.65 g, 17.1 mmol) portionwise over 45 min. The solution was stirred at rt for 10 min until clear. To this was added MeOH (40 mL) followed by malonate **2.46** (5.77 g, 12.3 mmol). The solution was heated to reflux for 24 h before adding HCl (2 N, 30 mL) and extracting with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (CH_2Cl_2;petrol, 2:1→CH_2Cl_2) gave the title compound (**2.49**) (6.00 g, 9.59 mmol, 78%) as a ca. 2:1 mixture of diastereoisomers as a white solid.

[α] 10.3 (c = 1.00).

MP 120–122 °C (*solvent*: CH_2Cl_2).

FT-IR (neat) ν_{max} 3053 (w, =C-H), 2946 (w, C-H), 1741 (s, C=O), 1720 (s, C=O), 1578 (w, C=C), 1492 (w, C=C), 1163 (s, O-C) cm^{-1}.

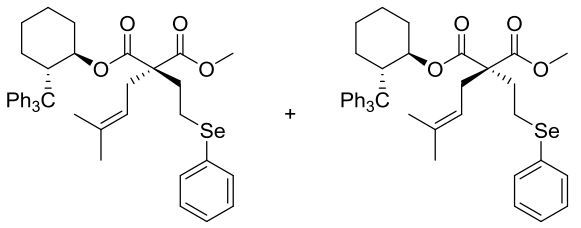
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.50 (2H, m, C$\underline{H}_{Ar}$), 7.45 – 6.92 (18H, m, C$\underline{H}_{Ar}$), 4.28 + 4.13 (1H, td, *J* = 10.2, 4.0 Hz, td, *J* = 10.2, 3.8 Hz, C$\underline{H}$OH), 3.68 (3H, s, OC$\underline{H}_3$), 3.58 – 3.49 (1H, m, CC$\underline{H}$), 2.85 – 2.59 (3H, m, OCC$\underline{H}$ SeC$\underline{H}_2$), 2.14 (1H, m, CCHC$\underline{H}$H), 2.06 – 1.88 (3H, m, OCCHC$\underline{H}_2$ OCHC$\underline{H}$H), 1.68 (2H, apparent t, *J* = 12.8 Hz, CCHCH$_2$C$\underline{H}$H, OCHCH$_2$C$\underline{H}$H), 1.54 – 1.36 (2H, m, CCHCH$_2$CH$\underline{H}$ OCHCH$\underline{H}$), 1.22 – 1.09 (1H, m, OCHCH$_2$CH$\underline{H}$), 0.66 (1H, m, CCHCH$\underline{H}$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.2 + 168.9 (s, C=O), 167.9 + 167.2 (s, C=O), 132.7 + 132.5 (d, CH_{Ar}), 129.7 + 129.7 (s, C_{Ar}), 129.1 (d, CH_{Ar}), 128.7 (s, C_{Ar}), 127.1 + 127.0 (d, CH_{Ar}), 126.9 (d, CH_{Ar}), 76.8 + 76.2 (d, OCH), 60.8 (s, CPh), 52.3 + 52.2 (q, OCH_3), 51.3 + 51.1 (d, OCCH), 45.8 + 45.7 (d, CHCPh), 32.8 + 32.6 (t, CH_2CHO), 29.3 + 28.8 (t, CH_2CH_2Se), 28.7 + 28.6 (t, CH_2CHC), 25.8 (t, CH_2CH_2CHC), 24.8 + 24.6 (t, $SeCH_2$), 24.5 (t, CH_2CH_2CHO) ppm.

LRMS (ES^+) 649 $[M+Na]^+$.

HRMS (ES^+) For $C_{37}H_{38}O_4SeNa$ calculated 649.1830, found 649.1836 Da.

2.50 - Methyl ((1*R*,2*S*)-2-tritylcyclohexyl) (*R*)-2-(3-methylbut-2-en-1-yl)-2-(2-(phenylselanyl)ethyl)malonate and Methyl ((1*R*,2*S*)-2-tritylcyclohexyl) (*S*)-2-(3-methylbut-2-en-1-yl)-2-(2-(phenylselanyl)ethyl)malonate



$C_{42}H_{46}O_4Se$
M.W. = 693.77 g/mol

To a stirred solution of DIPA (1.20 mL, 8.79 mmol) in THF (30 mL) under Ar at −78 °C was added *n*-BuLi (2.5 M, 3.20 mL, 7.99 mmol) over 20 min. The solution was stirred at −78 °C for 45 min before addition of malonate **2.49** (5.00 g, 7.99 mmol) in THF (30 mL) dropwise over 45 min. The solution was stirred at −78 °C for 1 h, before addition of prenyl bromide (1.02 ml, 8.79 mmol) over 5 min. The solution was allowed to slowly warm to rt in a cardice bath and stirred for 18 h. H_2O (20 mL) was added and extracted with CH_2Cl_2 (3 x 40 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography twice (CH_2Cl_2:petrol, 1:2→CH_2Cl_2) gave the title compound (**2.50**) (3.92 g, 5.65 mmol, 71%) as a ca. 1:5 mixture of diastereoisomers as a white solid.

[α] −37.2 (c = 1.00).

MP 70–71 °C (*solvent*: CH_2Cl_2/*n*-hexane).

FT-IR (neat) ν_{max} 3055 (w, =C-H), 2934 (w, C-H), 1724 (s, C=O), 1157 (m, O-C) cm^{-1}.

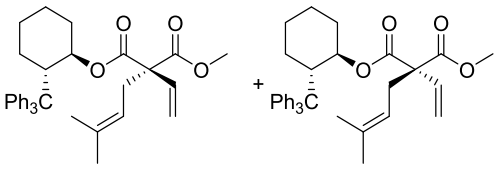
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.45 (2H, m, C$\underline{H}_{Ar}$), 7.43 – 6.94 (18H, m, C$\underline{H}_{Ar}$), 4.81 + 4.73 (1H, finely coupled t, *J* = 7.1 Hz, distorted t, *J* = 6.2 Hz, C=C$\underline{H}$), 4.17 (1H, td, *J* = 9.3, 3.3 Hz, OC$\underline{H}$), 3.65 + 3.63 (3H, 2 x s, OC$\underline{H}_3$), 3.53 (1H, m, PhCC$\underline{H}$), 2.75 – 2.51 (2H, m, SeC$\underline{H}_2$), 2.33 (1H, m, C=CHC$\underline{H}$H), 2.20 – 1.94 (3H, m, C=CHCH$\underline{H}$, CCHC$\underline{H}$H & CCH$\underline{H}$), 1.83 (1H, m, OCHC$\underline{H}$H), 1.69 – 1.52 (9H, m, CC$\underline{H}_3$, CC$\underline{H}_3$, OCHCH$_2$C$\underline{H}$H, CCHCH$_2$C$\underline{H}$H & CCH$\underline{H}$), 1.47 – 1.33 (2H, m, OCHCH$\underline{H}$ & CCHCH$_2$CH$\underline{H}$), 1.16 (1H, m, OCHCH$_2$C$\underline{H}$H), 0.84 (1H, m, CCHCH$\underline{H}$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8 (s, $\underline{C}$=O), 170.0 (s, $\underline{C}$=O), 135.2 (s, $\underline{C}_{Ar}$), 132.7 + 132.5 (d, $\underline{C}H_{Ar}$), 130.3 (s, $\underline{C}$=CH), 129.0 (d, $\underline{C}H_{Ar}$), 128.4 + 127.9 (d, $\underline{C}H_{Ar}$), 126.9 + 126.8 (d, $\underline{C}H_{Ar}$), 117.6 + 117.4 (d, C=$\underline{C}$H), 77.4 (d, O$\underline{C}$H), 61.0 (s, $\underline{C}Ph_3$), 58.2 + 57.9 (s, $\underline{C}$CO), 52.1 (q, O$\underline{C}H_3$), 45.2 (d, C$\underline{C}$H), 32.8 + 32.6 (t, Se$\underline{C}H_2$), 31.9 (t, OCH$\underline{C}H_2$), 30.6 (t, $\underline{C}H_2$CH=C), 28.2 (t, CCH$\underline{C}H_2$), 26.0 (q, C$\underline{C}H_3$), 25.4 (t, CCHCH$_2$C$\underline{H}_2$), 24.1 + 24.1 (t, OCHCH$_2$C$\underline{H}_2$), 22.0 (t, Se$\underline{C}H_2$), 18.0 (q, C$\underline{C}H_3$) ppm.

LRMS (ES$^+$) *m/z* 717 $[M+Na]^+$.

HRMS (ES$^+$) For $C_{42}H_{46}O_4SeNa$ calculated 717.2457, found 717.2472 Da.

2.51a and 2.51b - Methyl ((1*R*,2*S*)-2-tritylcyclohexyl) (*R*)-2-(3-methylbut-2-en-1-yl)-2-vinylmalonate and Methyl ((1*R*,2*S*)-2-tritylcyclohexyl) (*S*)-2-(3-methylbut-2-en-1-yl)-2-vinylmalonate

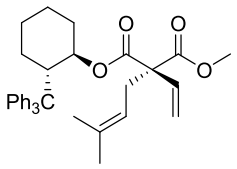


$C_{36}H_{40}O_4$
M.W. = 536.70 g/mol

To a stirred solution of prenylated derivative **2.50** (1:5 mixture of diastereoisomer, 3.70 g, 5.33 mmol) in THF (25 mL) at rt was added H_2O_2 (30%, 0.67 mL, 5.87 mmol). The solution was stirred for 3.5 h before removing the solvent under reduced pressure. Purification by column chromatography twice (CH_2Cl_2:petrol, 1:2→CH_2Cl_2) gave the title

compounds (**2.51a** and **2.51b**) (Major diastereoisomer **2.51a** 2.27 g, 4.23 mmol, 79%. Minor diastereoisomer **2.51b** 380 mg, 0.71 mmol, 13%) as white solids.

2.51a - Methyl ((1*R*,2*S*)-2-tritylcyclohexyl) (*R*)-2-(3-methylbut-2-en-1-yl)-2-vinylmalonate



$C_{36}H_{40}O_4$
M.W. = 536.70 g/mol

[α] –22.0 (c = 0.88)

MP 55–57 °C (*solvent*: CH_2Cl_2).

FT-IR (neat) ν_{max} 3056 (w, =C-H), 2935 (w, C-H), 1728 (s, C=O), 1595 (C=C), 1493 (w, C=C), 1230 (m, O-C) cm^{-1}.

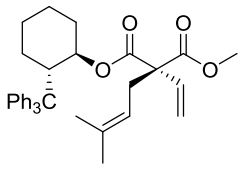
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.03 (15H, m, C<u>H</u>$_{Ar}$), 5.25 (1H, dd, *J* = 17.6, 10.5 Hz, C<u>H</u>=CH$_2$), 5.11 – 5.02 (2H, m, CH=C<u>H</u>$_2$), 4.86 (1H, t, *J* = 6.9 Hz, C<u>H</u>=C), 4.04 (1H, td, *J* = 9.8, 3.3 Hz, C<u>H</u>O), 3.70 (3H, s, OC<u>H</u>$_3$), 3.55 (1H, apparent t, *J* = 9.6 Hz, C<u>H</u>CAr), 2.60 (2H, d, *J* = 7.0 Hz, C<u>H</u>$_2$CH=C), 2.13 (1H, apparent d, *J* = 13.7 Hz, ArCCHC<u>H</u>H), 1.91 (1H, m, OCHCH<u>H</u>), 1.68 – 1.62 (5H, m, CC<u>H</u>$_3$ & OCHCH$_2$C<u>H</u>H, ArCHCH$_2$C<u>H</u>H), 1.60 (3H, s, CC<u>H</u>$_3$), 1.48 – 1.33 (2H, m, OCHCH<u>H</u> & ArCCHCH$_2$CH<u>H</u>), 1.17 (1H, m, OCHCH$_2$CH<u>H</u>), 0.85 (1H, m, ArCCHCH<u>H</u>) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4 (s, <u>C</u>=O), 168.7 (s, <u>C</u>=O), 134.7 (s, CH=<u>C</u>), 134.0 (d, <u>C</u>H=CH$_2$), 128.4 (d, <u>C</u>H$_{Ar}$), 127.7 (d, <u>C</u>H$_{Ar}$), 125.0 (d, <u>C</u>H$_{Ar}$), 117.9 (d, <u>C</u>H=C), 116.4 (t, CH=<u>C</u>H$_2$), 61.0 (s, <u>C</u>Ar), 59.7 (s, <u>C</u>C=O), 52.2 (q, O<u>C</u>H$_3$), 45.4 (d, ArC<u>C</u>H), 32.0 (t, OCH<u>C</u>H$_2$), 32.0 (t, <u>C</u>H$_2$CH=C), 28.4 (t, CCH<u>C</u>H$_2$), 25.9 (q, C<u>C</u>H$_3$), 25.7 (t, CCHCH$_2$<u>C</u>H$_2$), 24.4 (t, OCHCH$_2$<u>C</u>H$_2$), 18.0 (q, C<u>C</u>H$_3$) ppm (<u>C</u>HO covered by chloroform peak).

LRMS (ES$^+$) *m/z* 600 [M+Na+CH_3CN]$^+$, 559 [M+Na]$^+$.

HRMS (ES$^+$) For $C_{36}H_{40}O_4Na$ calculated 559.2819, found 559.2819 Da.

2.51b - Methyl ((1*R*,2*S*)-2-tritylcyclohexyl) (*S*)-2-(3-methylbut-2-en-1-yl)-2-vinylmalonate



$C_{36}H_{40}O_4$
M.W. = 536.70 g/mol

[α] –39.8 (c = 1.03)

MP 53–55 °C (*solvent*: CH_2Cl_2).

FT-IR (neat) ν_{max} 2926 (w, C-H), 1724 (s, C=O), 1635 (w, C=C), 1595 (C=C), 1493 (w, C=C), 1232 (m, O-C) cm^{-1}.

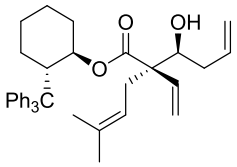
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 6.96 (15H, m, C$\underline{H}_{Ar}$), 5.82 (1H, dd, *J* = 17.7, 11.1 Hz, C$\underline{H}$=CH$_2$), 5.13 (1H, d, *J* = 11.1 Hz, CH=C$\underline{H}\underline{H}_{cis}$), 4.96 (1H, d, *J* = 17.7 Hz, CH=CH$\underline{H}_{trans}$), 4.91 (1H, m, C=C$\underline{H}$), 4.14 (1H, td, *J* = 9.4, 3.5 Hz, C$\underline{H}$O), 3.70 (3H, s, OC$\underline{H}_3$), 3.58 (1H, m, C$\underline{H}$CAr), 2.52 (1H, apparent dd, *J* = 15.4, 7.3 Hz, C=CHC$\underline{H}_2$), 2.17 – 2.04 (2H, m, ArCCHC$\underline{H}$H), 1.80 (1H, m, OCHC$\underline{H}$H), 1.72 – 1.60 (5H, m, CC$\underline{H}_3$, OCHCH$_2$C$\underline{H}$H & ArCHCH$_2$C$\underline{H}$H), 1.56 (3H, s, CC$\underline{H}_3$), 1.49 – 1.35 (2H, m, OCHCH$\underline{H}$ & ArCCHCH$_2$CH$\underline{H}$), 1.20 (1H, m, OCHCH$_2$CH$\underline{H}$), 0.90 (1H, m, ArCHCH$\underline{H}$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4 (s, $\underline{C}$=O), 169.4 (s, $\underline{C}$=O), 134.6 (d, $\underline{C}$H=CH$_2$), 134.3 (s, $\underline{C}_{Ar}$), 128.4 (d, $\underline{C}H_{Ar}$), 127.8 (d, $\underline{C}H_{Ar}$), 125.0 (d, $\underline{C}H_{Ar}$), 118.1 (d, $\underline{C}$H=C), 116.6 (t, CH=$\underline{C}$H$_2$), 77.5 (d, $\underline{C}$HO), 61.0 (s, $\underline{C}$Ar), 60.0 (s, $\underline{C}$C=O), 52.2 (q, O$\underline{C}$H$_3$), 45.4 (d, ArC$\underline{C}$H), 32.3 (t, OCH$\underline{C}$H$_2$), 31.6 (t, $\underline{C}$H$_2$CH=C), 28.1 (t, CCH$\underline{C}$H$_2$), 25.9 (q, C$\underline{C}$H$_3$), 25.4 (t, CCHCH$_2\underline{C}$H$_2$), 24.0 (t, OCHCH$_2\underline{C}$H$_2$), 18.1 (C$\underline{C}$H$_3$) ppm.

LRMS (ES$^+$) *m/z* 600 [M+CH$_3$CN+Na]$^+$, 559 [M+Na]$^+$.

HRMS (ES$^+$) For $C_{36}H_{40}NaO_4$ calculated 559.2819, found 559.2824 Da.

2.52 - (1*R*,2*S*)-2-Tritylcyclohexyl (*R*)-2-((*S*)-1-hydroxybut-3-en-1-yl)-5-methyl-2-vinylhex-4-enoate



$C_{38}H_{44}O_3$
M.W. = 548.75 g/mol

To a stirred solution of malonate **2.51a** (0.75 g, 1.40 mmol) in CH_2Cl_2 (12 mL) under Ar at –78 °C was added DIBAL (1 M, 2.79 mL, 2.79 mmol) dropwise over 40 min. The solution was stirred at –78 °C for 6 h before adding Rochelle salt (10 mL), warming to rt and extracting with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to provide the crude aldehyde.

In a separate flask, by adaptation of the procedure by Linclau *et al.*,[99] Mg (105 mg, 4.32 mg-atom) was suspended in Et_2O (11.5 mL) under Ar at rt and 1,2-dibromoethane (0.37 mL, 4.32 mmol) was added. After stirring at rt for 30 min, the solvent was removed under reduced pressure, and the residue was resuspended in CH_2Cl_2 (8 mL) under Ar and cooled to –78 °C. To this was added the aforementioned crude aldehyde in CH_2Cl_2 (10 mL) over 45 min. After 45 min at –78 °C, allyltributylstannane (0.55 mL, 1.68 mmol) in CH_2Cl_2 (11.5 mL) was added over 45 min. After 1 h at –78 °C the suspension was warmed to –25 °C. $NaHCO_3$ (10 mL) was added and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:petrol, 1:15) gave the title compound (**2.52**) (417 mg, 0.76 mmol, 54%) as a white foam.

[α] –31.9 (c = 1.01)

FT-IR (neat) ν_{max} 3563 (br, OH), 3056 (w, =C-H), 2922 (w, C-H), 1719 (m, C=O), 1639 (w, alkene C=C), 1595 (w, C=C), 1493 (w, C=C), 1173 (m, C-O) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 – 7.03 (15H, m, CH_{Ar}), 5.84 – 5.65 (2H, m, 2 x CH_2=C<u>H</u>), 5.22 (1H, d, *J* = 11.3 Hz, CCH=C<u>H</u>H$_{cis}$), 5.13 – 4.90 (4H, m, C=C<u>H</u> & CCH=CH<u>H</u>$_{trans}$ & CH_2CH=C<u>H</u>$_2$), 4.13 (1H, td, *J* = 9.8, 3.5 Hz, COC<u>H</u>), 3.61 (1H, apparent t, *J* = 9.5 Hz, ArCC<u>H</u>), 3.17 (1H, ddd, *J* = 10.2, 5.0, 2.4 Hz, C<u>H</u>OH), 2.24 – 2.09 (2H, m, C=CHC<u>H</u>$_2$), 2.08 – 1.83 (5H, m, ArCCHC<u>H</u>$_2$C<u>H</u>H

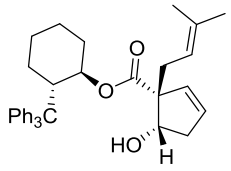
& ArCCHCHH & OCHCHH & CH_2=CHCH_2), 1.73 – 1.63 (7H, m, 2 x CH_3 & OCHCH_2CHH), 1.52 – 1.32 (2H, m, ArCCHCH_2CHH & OCHCHH), 1.1 (1H, m, OCHCH_2CHH), 0.81 (1H, m, ArCCHCHH) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5 (s, C=O), 135.7 (d, CH=CH_2), 133.0 (s, CH=C), 128.5 (d, CH_2=CH), 127.7 (d, C_{Ar}), 125.1 (d, C_{Ar}), 119.6 (d, CH=C), 117.3 (t, CH=CH_2), 116.6 (t, CH=CH_2), 77.1 (d, CHOC), 73.2 (d, CHOH), 61.1 (s, ArC), 56.7 (s, CC=O), 45.5 (d, ArCCH), 36.5 (t, CH_2CH=CH_2), 32.7 (t, OCHCH_2), 29.8 (t, C=CHCH_2), 28.7 (t, CCHCH_2), 25.9 (q, CCH_3), 25.8 (t, CCHCH_2CH_2), 24.7 (t, OCHCH_2CH_2), 18.2 (q, CCH_3) ppm.

LRMS (ES$^+$) *m/z* 612 [M+Na+CH_3CN]$^+$, 571 [M+Na]$^+$.

HRMS (ES$^+$) For $C_{38}H_{44}O_3Na$ calculated 571.3183, found 571.3184 Da.

2.53 - (1*R*,2*S*)-2-Tritylcyclohexyl (1*R*,5*S*)-5-hydroxy-1-(3-methylbut-2-en-1-yl)cyclopent-2-ene-1-carboxylate



$C_{36}H_{40}O_3$
M.W. = 520.70 g/mol

To a stirred solution of Grubbs' second generation catalyst (**1.140**) (49 mg, 0.058 mmol) in CH_2Cl_2 (2.5 mL) under argon at rt was added alcohol **2.52** (316 mg, 0.58 mmol) in CH_2Cl_2 (3.5 mL). After 3 h the solvent was removed under reduced pressure. Purification by column chromatography twice (EtOAc:petrol, 1:10) gave the title compound (**2.53**) (252 mg, 0.48 mmol, 83%) as a white solid.

[α] –3.0 (c = 0.6)

MP 104–106 °C (*solvent*: CH_2Cl_2/*n*-hexane).

FT-IR (neat) ν_{max} 3348 (br, OH), 3055 (w, =C-H), 2926 (m, C-H), 1712 (s, C=O), 1595 (w, C=C), 1493 (m, C=C) cm^{-1}.

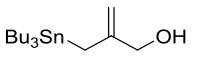
^{1}H NMR (400 MHz, $CDCl_3$) 7.56 – 7.06 (15H, m, C$\underline{H}_{Ar}$), 5.71 (1H, dt, *J* = 5.8, 2.3 Hz, CCH=C$\underline{H}$), 5.41 (1H, m, CC$\underline{H}$=CH), 4.94 (1H, finely coupled t, *J* = 7.1 Hz, C=C$\underline{H}$), 4.22 (1H, td, *J* = 10.0, 3.7 Hz, C$\underline{H}$O), 3.75 (1H, td, *J* = 6.1, 2.7 Hz, C$\underline{H}$OH), 3.62 (1H, m, C$\underline{H}$CPh), 2.57 – 2.48 (2H, m, CH=CHC$\underline{H}$H, O$\underline{H}$), 2.25 – 2.14 (2H, m, CH=CHCH$\underline{H}$, C$\underline{H}$HCHC), 2.01 – 1.89 (2H, m, C$\underline{H}$HCHO, C=CHC$\underline{H}$H), 1.77 (1H, m, C=CHCH$\underline{H}$), 1.72 (3H, s, CC$\underline{H}_3$), 1.70 – 1.62 (2H, m, C$\underline{H}$HCH$_2$CHC, C$\underline{H}$HCH$_2$CHO), 1.58 (3H, s, CC$\underline{H}_3$), 1.52 – 1.39 (2H, m, CH$\underline{H}$CHO, CH$\underline{H}$CH$_2$CHC), 1.16 (1H, m, CH$\underline{H}$CH$_2$CHO), 0.74 (1H, m, CH$\underline{H}$CHC) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7 (s, $\underline{C}$=O), 134.0 (s, $\underline{C}$=CH), 132.8 (d, C$\underline{C}$H=CH), 129.4 (d, CCH=$\underline{C}$H), 128.6 (d, $\underline{C}H_{Ar}$), 127.7 (d, $\underline{C}H_{Ar}$), 125.0 (d, $\underline{C}H_{Ar}$) 119.1 (d, C=$\underline{C}$H), 77.1 (d, $\underline{C}$HOH), 76.7 (d, $\underline{C}$HO), 64.1 (s, $\underline{C}$C=O), 61.1 (s, $\underline{C}$Ph), 45.5 (d, $\underline{C}$HCPh), 40.3 (t, CH=CH$\underline{C}H_2$), 33.6 (t, C=CH$\underline{C}H_2$), 33.1 (t, $\underline{C}H_2$CHO), 28.8 (t, $\underline{C}H_2$CHC), 25.9 (q, C$\underline{C}H_3$), 25.9 (t, $\underline{C}H_2CH_2$CHC), 24.7 (t, $\underline{C}H_2CH_2$CHO), 18.1 (q, C$\underline{C}H_3$) ppm.

LRMS (ES$^+$) *m/z* 584 $[M+Na+CH_3CN]^+$.

HRMS (ES$^+$) For $C_{36}H_{40}O_3Na$ calculated 543.2870, found 543.2871 Da.

2.57 - 2-((Tributylstannyl)methyl)prop-2-en-1-ol



$C_{16}H_{34}OSn$
M.W. = 361.15 g/mol

By adaptation of a procedure by Echavarren *et al.*,[219] a solution of *n*-BuLi (2.3 M in hexane, 13.3 mL, 30.50 mmol) under Ar, was concentrated under reduced pressure *via* a double manifold. After 1 h, the Ar atmosphere was replaced, and Et_2O (20 mL) was added. The solution was cooled to 0 °C and TMEDA (6.10 mL) was added, followed by methallyl alcohol (**2.56**) (1.16 mL, 13.8 mmol) dropwise. After 30 min, THF (6.1 mL) was added at 0 °C and the solution was warmed to rt before stirring for 16 h, slowly producing a red gum. Bu_3SnCl (4.15 mL, 15.3 mmol) was added at rt and after 45 min NH_4Cl (20 mL) was added, and extracted with Et_2O (3 x 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:hexane, 1:9) gave the title compound (**2.57**) (1.65 g,

4.57 mmol, 33%) as a clear oil. The analytical data acquired was in accordance with previously reported values.[219]

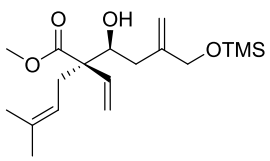
FT-IR (neat) ν_{max} 3319 (br, O-H), 2921 (m, C-H), 1632 (w, alkene C=C), 1044 (m, C-O) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.76 (1H, m, CC$\underline{H}_2$), 4.66 (1H, m, CC$\underline{H}_2$), 3.99 (2H, d, *J* = 5.9 Hz, C$\underline{H}_2$OH), 1.78 (2H, s, C$\underline{H}_2$Sn), 1.58 – 1.42 (6H, m, alkyl C$\underline{H}$), 1.40 – 1.23 (8H, m, alkyl C$\underline{H}$), 0.99 – 0.76 (14H, m, alkyl C$\underline{H}$, O$\underline{H}$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 149.5 (s, $\underline{C}CH_2$), 104.4 (t, C$\underline{C}H_2$), 67.2 (t, $\underline{C}H_2$OH), 29.1 (t, $\underline{C}H_2CH_2$) 27.3 (t, $CH_2\underline{C}H_2$), 15.1 (t, C$\underline{C}H_2$Sn), 13.7 (q, $\underline{C}H_3$), 9.6 (t, $\underline{C}H_2$Sn) ppm.

LRMS (EI) 305 (100%) $[M-C_4H_9]^{+\cdot}$.

2.59 - (±)-Methyl (*R*)-2-((*S*)-1-hydroxy-3-(((trimethylsilyl)oxy)methyl)but-3-en-1-yl)-5-methyl-2-vinylhex-4-enoate



$C_{18}H_{32}O_4Si$
M.W. = 340.53 g/mol

To a stirred solution of stannane **2.57** (577 mg, 1.60 mmol) in THF (5 mL) under Ar at 0 °C was added pyridine (0.13 mL, 1.61 mmol) then TMSCL (0.23 mL, 1.81 mmol) dropwise. The suspension was stirred at 0 °C for 1.5 h, before adding H_2O (4 mL) and extracting with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to give the crude silyl ether **2.58** (594 mg).

In a separate flask, by adaptation of the procedure by Linclau *et al.*,[99] to a stirred suspension of Mg (70 mg, 2.89 mg-atom) in Et_2O (7.5 mL) under Ar at rt was added 1,2-dibromoethane (0.25 mL, 2.89 mmol). After stirring at rt for 30 min, the solvent was removed under reduced pressure, and the residue was resuspended in CH_2Cl_2 (5.1 mL) under Ar and cooled to –78 °C. To this was added the aldehyde **2.19** (189 mg, 0.96 mmol) in CH_2Cl_2 (6.3 mL) over 30 min. After 30 min at –78 °C, the aforementioned crude silyl ether **2.58** (459 mg, ca. 1.06 mmol) in CH_2Cl_2 (7.5 mL) was added over 40

min. After 1.5 h at −78 °C the suspension was warmed to −25 °C over 1 h. $NaHCO_3$ (5 mL) was added and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography twice (EtOAc:petrol, 5:2) gave the title compound (**2.59**) (80 mg, 0.23 mmol, 24%) as a clear oil.

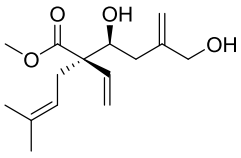
FT-IR (neat) ν_{max} 3430 (br, OH), 2922 (w, C-H), 1727 (m, C=O), 1640 (w, C=C), 1062 (m, C-O) cm^{-1}.

^{1}H NMR (300MHz, $CDCl_3$) δ 6.16 (1H, dd, *J* = 17.9, 11.0 Hz, C<u>H</u>=CH_2), 5.35 (1H, d, *J* = 11.3 Hz, CH=C<u>H</u>H_{cis}), 5.18 (1H, d, *J* = 17.9 Hz, CH=CH<u>H</u>$_{trans}$), 5.12 (1H, s, C=C<u>H</u>H), 5.05 (1H, finely coupled t, *J* = 7.0 Hz, C=C<u>H</u>), 4.95 (1H, s, C=CH<u>H</u>), 4.15 – 3.99 (3H, m, C<u>H</u>OH & C<u>H_2</u>O), 3.72 (3H, s, OC<u>H_3</u>), 3.10 (1H, d, *J* = 4.0 Hz, O<u>H</u>), 2.50 (2H, d, *J* = 7.0 Hz, C<u>H_2</u>CH=C), 2.31 (1H, d, *J* = 14.3 Hz, C<u>H</u>HCHOH), 1.98 (1H, dd, *J* = 14.1, 11.0 Hz, CH<u>H</u>CHOH), 1.69 (3H, s, CC<u>H_3</u>), 1.63 (3H, s, CC<u>H_3</u>), 0.14 (9H, s, Si(C<u>H_3</u>)$_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2 (s, <u>C</u>=O), 145.5 (s, CH_2=<u>C</u>), 136.0 (d, <u>C</u>H=CH_2), 134.2 (s, <u>C</u>=CH), 118.9 (d, C=<u>C</u>H), 116.5 (t, CH=<u>C</u>H_2), 113.1 (t, <u>C</u>H_2=C), 74.4 (d, <u>C</u>HOH), 65.9 (t, <u>C</u>H_2O), 57.6 (s, <u>C</u>C=O), 52.0 (q, O<u>C</u>H_3), 35.8 (t, <u>C</u>H_2C=CH_2), 31.4 (<u>C</u>H_2CH=C), 25.9 (q, C<u>C</u>H_3), 17.9 (q, C<u>C</u>H_3), −0.6 (q, Si<u>C</u>H_3) ppm.

LRMS (ES$^+$) *m/z* 363 [M+Na]$^+$.

2.60 - (±)-Methyl (*R*)-2-((*S*)-1-hydroxy-3-(hydroxymethyl)but-3-en-1-yl)-5-methyl-2-vinylhex-4-enoate



$C_{15}H_{24}O_4$
M.W. = 268.35 g/mol

To a stirred solution of malonate **2.03** (316 mg, 1.40 mmol) in CH_2Cl_2 (12 mL) under Ar, was added DIBAL (1 M, 2.79 mL, 2.79 mmol) dropwise over 40 min at −78 °C. After 3.5 h, Rochelle salt (10 mL) was added, and the suspension was warmed to rt before

extracting with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give the crude aldehyde **2.19**.

In a separate flask, the crude silyl ether **2.58** was prepared by addition of pyridine (0.31 mL, 3.82 mmol) to a stirred solution of stannane **2.57** (1.38 g, 3.82 mmol) in THF (12 mL) under Ar at 0 °C, followed by TMSCl (0.53 mL, 4.20 mmol) dropwise. The suspension was stirred at 0 °C for 1.5 h, before adding H_2O (10 mL) and extracting with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to give the crude silyl ether **2.58** (1.53 g).

Finally, by adaptation of the procedure by Linclau *et al.*,[99] in a separate flask, Mg (105 mg, 4.32 mg-atom) was suspended in Et_2O (11.5 mL) under Ar, and dibromoethane (0.37 mL, 4.32 mmol) was added at rt. After 30 min, the solvent was removed, and the residue was resuspended in CH_2Cl_2 (8 mL) under Ar and cooled to −78 °C. To this was added the aforementioned crude aldehyde **2.19** in CH_2Cl_2 (10 mL) dropwise over 30 min. After 30 min, the crude silyl ether **2.58** (726 mg, 1.68 mmol) in CH_2Cl_2 (11.5 mL) was added dropwise over 30 min at −78 °C. After 1 h, the suspension was warmed to −25 °C, and stirred for a further 2 h. $NaHCO_3$ (10 mL) was then added, before extracting with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:petrol, 1:5→EtOAc) gave the title compound (**2.60**) (71 mg, 0.26 mmol, 19%) as a clear oil.

FT-IR (neat) ν_{max} 3368 (bw, O-H), 2919 (w, C-H), 1721 (s, C=O), 1647 (w, C=C), 1053 (m, C-O) cm^{-1}.

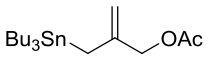
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.12 (1H, dd, *J* = 17.9, 11.3 Hz, C$\underline{H}$=CH_2), 5.36 (1H, d, *J* = 11.3 Hz, CH=C$\underline{H}H_{cis}$), 5.21 (1H, d, *J* = 17.9 Hz, CH=CH$\underline{H}_{trans}$), 5.10 (1H, s, C=C$\underline{H}$H), 5.02 (1H, m, C=CH), 4.93 (1H, s, C=CH$\underline{H}$), 4.16 – 4.02 (3H, m, C$\underline{H}$OH, C$\underline{H_2}$OH), 3.73 (3H, s, OC$\underline{H_3}$), 2.79 – 2.71 (2H, m, CHO$\underline{H}$, CH_2O$\underline{H}$), 2.61 – 2.43 (2H, m, C$\underline{H_2}$CH=C), 2.31 (1H, m, C$\underline{H_2}$CHOH), 2.06 (1H, dd, *J* = 14.3, 10.6 Hz, C$\underline{H_2}$CHOH), 1.69 (3H, s, CC$\underline{H_3}$), 1.63 (3H, s, CC$\underline{H_3}$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 175.6 (s, $\underline{C}$=O), 146.5 (s, $\underline{C}$=CH_2), 135.6 (d, $\underline{C}$H=CH_2), 134.7 (s, $\underline{C}$=CH), 118.3 (d, C=$\underline{C}$H), 117.0 (t, CH=$\underline{C}H_2$), 113.8 (t, C=$\underline{C}H_2$), 74.5 (d, $\underline{C}$HOH), 66.5 (t, $\underline{C}H_2$OH), 57.3 (s, $\underline{C}$CO), 52.2 (q, O$\underline{C}H_3$), 35.9 (t, $\underline{C}H_2$CHOH), 31.6 (t, $\underline{C}H_2$CH=C), 26.0 (q, C$\underline{C}H_3$), 17.9 (q, C$\underline{C}H_3$) ppm.

LRMS (ES$^+$) *m/z* 291 [M+Na]$^+$.

HRMS (ES$^+$) For $C_{15}H_{24}O_4Na$ calculated 291.1567, found 291.1566 Da.

2.65 - 2-((Tributylstannyl)methyl)allyl acetate



$C_{18}H_{36}O_2Sn$
M. W. = 403.19 g/mol

To a stirred solution of tin intermediate **2.57** (1.69 g, 4.70 mmol) in CH_2Cl_2 (25 mL) under Ar at 0 °C was added Et_3N (1.97 mL, 14.1 mmol) then AcCl (0.47 mL, 6.58 mmol) dropwise. The solution was stirred at 0 °C for 30 min before adding H_2O (20 mL) and extracting with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:petrol, 1:10) gave the title compound (**2.65**) (1.71 g, 4.24 mmol, 90%) as a clear oil.

FT-IR (neat) ν_{max} 2922 (m, C-H), 1743 (s, C=O), 1634 (w, C=C) 1223 (s, O-C) cm^{-1}.

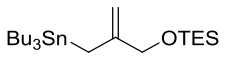
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.75 (1H, s, C=C$\underline{H}$H), 4.71 (1H, s, C=CH$\underline{H}$), 4.43 (2H, s, C$\underline{H_2}$O), 2.10 (3H, s, C$\underline{H_3}$CO), 1.79 (2H, m, CC$\underline{H_2}$Sn), 1.58 – 1.43 (6H, m, C$\underline{H_2}$), 1.37 – 1.26 (6H, m, C$\underline{H_2}$), 0.97 – 0.81 (15H, m, C$\underline{H_3}$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7 (s, $\underline{C}$=O), 144.3 (s, $\underline{C}$=CH_2), 107.5 (t, C=$\underline{C}H_2$), 68.3 (t, $\underline{C}H_2O$), 29.0 (t, $C\underline{C}H_2Sn$), 27.3 (t, $\underline{C}H_2CH_3$), 21.0 (q, $\underline{C}H_3CO$), 15.4 (t, $\underline{C}H_2CH_2Sn$), 13.7 (q, $CH_2\underline{C}H_3$), 9.6 (t, $\underline{C}H_2Sn$) ppm.

LRMS (EI) *m/z* 347 (24%) [M–C_4H_9]$^{+\cdot}$, 177 (91%) [M–$C_{14}H_{27}O_2$]$^{+\cdot}$.

HRMS (ES$^+$) For $C_{18}H_{36}NaO_2Sn^{120}$ calculated 427.1632, found 427.1635 Da.

2.66 - Triethyl((2-((tributylstannyl)methyl)allyl)oxy)silane



$C_{22}H_{48}OSiSn$
M. W. = 475.42 g/mol

To a stirred solution of stannane **2.57** (1.77 g, 4.90 mmol) in CH_2Cl_2 (17 mL) under Ar at 0 °C was added Et_3N (2.05 mL, 14.7 mmol) then TESCl (0.99 mL, 5.88 mmol) over 5 min. The white suspension was stirred at rt for 1 h before adding H_2O (10 mL) and extracting with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:petrol, 1:10) gave the title compound (**2.66**) (2.23 g, 4.69 mmol, 96%) as a clear oil.

FT-IR (neat) ν_{max} 2914 (m, C-H), 1633 (w, alkene C=C), 1074 (m, C-O) cm^{-1}.

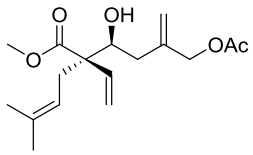
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.80 (1H, m, C=C<u>H</u>H), 4.60 (1H, m, C=CH<u>H</u>), 4.00 – 3.95 (2H, m, C<u>H</u>$_2$O), 1.74 (2H, t, *J* = 29.6 Hz, C<u>H</u>$_2$Sn), 1.53 – 1.44 (6H, m, C<u>H</u>$_2$), 1.37 – 1.27 (6H, m, C<u>H</u>$_2$), 0.98 (9H, d, *J* = 8.0 Hz, SiCH$_2$C<u>H</u>$_3$), 0.94 – 0.84 (15H, m, C<u>H</u>$_2$, C<u>H</u>$_3$), 0.63 (6H, q, *J* = 8.0 Hz, SiC<u>H</u>$_2$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 148.7 (s, <u>C</u>=CH$_2$), 104.0 (t, C=<u>C</u>H$_2$), 66.6 (t, <u>C</u>H$_2$O), 29.1 (t, <u>C</u>H$_2$), 27.4 (t, <u>C</u>H$_2$), 14.6 (t, <u>C</u>H$_2$), 13.7 (t, <u>C</u>H$_2$), 9.5 (q, <u>C</u>H$_3$), 6.8 (t, <u>C</u>H$_2$), 4.5 (q, <u>C</u>H$_3$) ppm.

LRMS (EI) *m/z* 419 (59%) $[M-C_4H_9]^{+\cdot}$, 157 (100%) $[M-C_{19}H_{44}OSi]^{+\cdot}$.

HRMS (EI) For $C_{18}H_{39}OSiSn^{120}$ calculated 419.1792, found 419.1793 Da.

2.67 - (±)-Methyl (*R*)-2-((*S*)-3-(acetoxymethyl)-1-hydroxybut-3-en-1-yl)-5-methyl-2-vinylhex-4-enoate



$C_{17}H_{26}O_5$
M.W. = 310.39 g/mol

By adaptation of the procedure by Linclau *et al.*,[99] to a suspension of Mg (74 mg, 3.06 mg-atom) in Et_2O (8 mL) under Ar, was added dibromoethane (0.26 mL, 3.06 mmol) at rt. After 40 min, the solvent was removed, and the $MgBr_2.OEt_2$ residue was resuspended in CH_2Cl_2 (6 mL) under Ar and cooled to –78 °C. To this was added the aldehyde **2.19** (200 mg, 1.02 mmol) in CH_2Cl_2 (6 mL) dropwise over 30 min. After 30 min, allyltin reagent **2.65** (399 mg, 0.99 mmol) in CH_2Cl_2 (7 mL) was added dropwise over 40 min at –78 °C. After 1 h, the suspension was warmed to –40 °C, and $NaHCO_3$ (15 mL) was added, before extracting with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:petrol, 2:5) gave the title compound **2.67** (100 mg, 0.32 mmol, 31%) as a clear oil.

FT-IR (neat) ν_{max} 3478 (br, O-H), 2914 (m, C-H), 1722 (s, C=O), 1637 (w, C=C), 1225 (s, O-C) cm^{-1}.

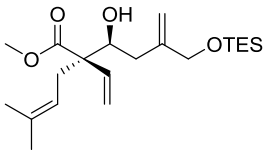
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.13 (1H, dd, *J* = 17.8, 11.2 Hz, C<u>H</u>=CH_2), 5.36 (1H, d, *J* = 11.3 Hz, CH=C<u>H</u>H_{cis}), 5.20 (1H, d, *J* = 17.9 Hz, CH=CH<u>H</u>$_{trans}$), 5.17 – 4.98 (3H, m, C<u>H</u>=C, C<u>H</u>$_2$=C), 4.58 (2H, s, C<u>H</u>$_2$O), 4.06 (1H, ddd, *J* = 10.7, 5.4, 1.8 Hz, C<u>H</u>OH), 3.73 (3H, s, OC<u>H</u>$_3$), 2.80 (1H, d, *J* = 5.5 Hz, CHO<u>H</u>), 2.60 – 2.44 (2H, m, C<u>H</u>$_2$CH=C), 2.27 (1H, m, C<u>H</u>HCHO), 2.09 (3H, s, OCC<u>H</u>$_3$), 2.03 (1H, dd, *J* = 13.5, 10.6 Hz, CH<u>H</u>CHOH), 1.69 (3H, s, CC<u>H</u>$_3$), 1.63 (3H, s, CC<u>H</u>$_3$), ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3 (s, <u>C</u>=O), 170.7 (s, <u>C</u>=O), 141.2 (s, <u>C</u>=CH_2), 135.8 (d, <u>C</u>H=CH_2), 134.6 (s, <u>C</u>=CH), 118.4 (d, C=<u>C</u>H), 116.9 (t, CH=<u>C</u>H_2), 73.3 (d, <u>C</u>HOH), 66.8 (t, <u>C</u>H_2OH), 57.4 (s, <u>C</u>CO), 52.1 (q, O<u>C</u>H_3), 35.7 (t, <u>C</u>H_2CHOH), 31.6 (t, <u>C</u>H_2CH=C), 25.9 (q, CH=C<u>C</u>H_3), 20.9 (q, OC<u>C</u>H_3), 17.9 (q, CH=C<u>C</u>H_3) ppm.

LRMS (ES$^+$) *m/z* 333 $[M+Na]^+$, 311 $[M+H]^+$.

HRMS (ES$^+$) For $C_{17}H_{26}NaO_5$ calculated 333.1672, found 333.1676 Da.

2.68 - (±)-Methyl (*R*)-2-((*S*)-1-hydroxy-3-(((triethylsilyl)oxy)methyl)but-3-en-1-yl)-5-methyl-2-vinylhex-4-enoate



$C_{21}H_{38}O_4Si$
M.W. = 382.61 g/mol

To a stirred solution of vinyl malonate **2.03** (939 mg, 4.15 mmol) in CH_2Cl_2 (22 mL) under Ar, was added DIBAL (1 M in hexanes, 5.98 mL, 5.98 mmol) dropwise over 1 h at –78 °C. After 7 h, another portion of DIBAL (1 M, 2.90 mL, 2.90 mmol) was added dropwise over 45 min. After 1 h at –78 °C, Rochelle salt (100 mL) was added dropwise over 20 min, and the suspension was warmed to rt before diluting in CH_2Cl_2 (100 mL). After stirring at rt for 15 min, the aq. phase was extracted with CH_2Cl_2 (1 x 150 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give the crude aldehyde **2.19** (764 mg).

In a separate flask, by adaptation of the procedure by Linclau *et al.*,[99] Mg (192 mg, 7.91 mg-atom) was suspended in Et_2O (8.1 mL) under Ar, and dibromoethane (0.68 mL, 7.91 mmol) was added. After stirring for 30 min, the solvent was removed, and the residue was suspended in CH_2Cl_2 (5.6 mL) under Ar, and cooled to –78 °C. To this was added the aforementioned crude aldehyde **2.19** (499 mg) in CH_2Cl_2 (6.8 mL) dropwise over 30 min. After 30 min at –78 °C, allyltin **2.66** (1.21 g, 2.55 mmol) was added in CH_2Cl_2 (8.1 mL) dropwise over 30 min. After 5 h at –78 °C, $NaHCO_3$ (15 mL) was added, before warming to rt, and extracting with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:petrol, 1:10) gave the title compound (**2.68**) (413 mg, 1.08 mmol, 40%) as a clear oil.

FT-IR (neat) ν_{max} 3521 (O-H), 2953 (m, C-H), 1728 (m, C=O), 1647 (w, alkene C=C), 1069 (s, C-O) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.16 (1H, dd, *J* = 18.2, 11.6 Hz, C<u>H</u>=CH_2), 5.34 (1H, dd, *J* = 11.6, 1.0 Hz, CH=C<u>H</u>H$_{cis}$), 5.18 (1H, dd, *J* = 18.2, 1.0 Hz, CH=CH<u>H</u>$_{trans}$), 5.13 (1H, d, *J* = 1.0 Hz, C=C<u>H</u>$_2$), 5.05 (1H, finely coupled t, *J* = 7.6 Hz, C<u>H</u>=C), 4.95 (1H, s, C=C<u>H</u>$_2$), 4.14 (1H, d, *J* = 13.1 Hz, C<u>H</u>HCSi), 4.1 (1H, d, *J*

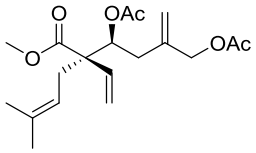
= 13.1 Hz, CHHOSi), 4.04 (1H, ddd, *J* = 11.0, 4.4, 2.3 Hz, CHOH), 3.72 (3H, s, OCH$_3$), 3.12 (1H, d, *J* = 4.5 Hz, OH), 2.56 – 2.44 (2H, m, CH$_2$CH=C), 2.30 (1H, d, *J* = 14.1 Hz, CH$_2$CHO), 2.00 (1H, dd, *J* = 14.1, 11.1 Hz, CH$_2$CHO), 1.69 (3H, d, *J* = 1.0 Hz, CCH$_3$), 1.63 (3H, s, CCH$_3$), 0.98 (9H, t, *J* = 8.1 Hz, CH$_2$CH$_3$), 0.63 (6H, q, *J* = 8.1 Hz, CH$_2$CH$_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.1 (s, C=O), 145.7 (s, C=CH$_2$), 136.0 (d, CH=CH$_2$), 134.1 (s, C=CH), 118.9 (d, CH=C), 116.5 (t, CH=CH$_2$), 112.9 (t, C=CH$_2$), 74.5 (d, CHOH), 66.2 (t, CH$_2$OSi), 57.6 (s, CCH=CH$_2$), 52.0 (q, OCH$_3$), 35.9 (t, CH$_2$CHOH), 31.3 (t, CH$_2$CH=C), 25.9 (q, CCH$_3$), 17.9 (q, CCH$_3$), 6.7 (q, CH$_2$CH$_3$), 4.4 (t, CH$_2$CH$_3$) ppm.

LRMS (ES$^+$) *m/z* 405 [M+Na]$^+$.

HRMS (ES$^+$) For $C_{21}H_{38}NaO_4Si$ calculated 405.2432, found 405.2429 Da.

2.69 - (±)-(4*S*,5*R*)-5-(Methoxycarbonyl)-8-methyl-2-methylene-5-vinylnon-7-ene-1,4-diyl diacetate



$C_{19}H_{28}O_6$
M.W. = 352.43 g/mol

To a stirred solution of alcohol **2.67** (100 mg, 0.32 mmol) in CH_2Cl_2 (4 mL) under Ar at 0 °C was added DMAP (12 mg, 0.10 mmol), Et_3N (0.13 mL, 0.96 mmol) then AcCl (0.03 mL, 0.45 mmol) dropwise. The solution was stirred at 0 °C for 4 h before adding H_2O (2 mL) and extracting with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:petrol, 2:5) gave the title compound (**2.69**) (47 mg, 0.13 mmol, 42%) as a clear oil.

FT-IR (neat) ν_{max} 2928 (w, C-H), 1736 (s, C=O), 1651 (w, alkene C=C), 1223 (s, C-O), 1080 (m, C-O) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 (1H, dd, *J* = 18.0, 11.1 Hz, CH=CH$_2$), 5.46 (1H, dd, *J* = 10.9, 2.5 Hz, CHOAc), 5.39 (1H, dd, *J* = 11.1, 0.6 Hz, CH=CHH$_{cis}$), 5.21

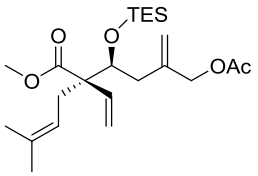
(1H, dd, *J* = 18.0, 0.6 Hz, CH=CH$\underline{H}_{trans}$), 5.08 – 5.01 (2H, m, C=C$\underline{H}$H, C=C$\underline{H}$), 4.97 (1H, s, C=CH$\underline{H}$), 4.65 (1H, d, *J* = 13.3 Hz, C$\underline{H}$HOAc), 4.53 (1H, d, *J* = 13.3 Hz, CH$\underline{H}$OAc), 3.68 (3H, s, OC$\underline{H}_3$), 2.57 – 2.40 (2H, m, C$\underline{H}_2$CHO), 2.30 (1H, m, C=CHC$\underline{H}$H), 2.18 (1H, m, C=CHCH$\underline{H}$), 2.10 (3H, s, C$\underline{H}_3$CO), 1.98 (3H, s, C$\underline{H}_3$CO), 1.70 – 1.68 (3H, m, CC$\underline{H}_3$), 1.63 (3H, s, CC$\underline{H}_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2 (s, $\underline{C}$=O), 170.5 (s, $\underline{C}$=O), 169.8 (s, $\underline{C}$=O), 139.9 (s, $\underline{C}$=CH_2), 135.2 (d, $\underline{C}$H=CH_2), 134.4 (s, $\underline{C}$=CH), 118.5 (d, C=$\underline{C}$H), 117.3 (t, C=$\underline{C}H_2$), 116.2 (t, CH=$\underline{C}H_2$), 74.1 (d, $\underline{C}$HO), 66.3 (t, $\underline{C}H_2O$), 56.5 (s, $\underline{C}$CHO), 52.0 (q, O$\underline{C}H_3$), 34.6 (t, $\underline{C}H_2$CHO), 30.7 (t, $\underline{C}H_2$CH=C), 25.9 (q, C$\underline{C}H_3$), 20.9 (q, $\underline{C}H_3$CO), 20.8 (q, $\underline{C}H_3$CO), 17.9 (q, C$\underline{C}H_3$) ppm.

LRMS (ES$^+$) *m/z* 375 $[M+Na]^+$, 353 $[M+H]^+$.

HRMS (ES$^+$) For $C_{19}H_{28}O_6Na$ calculated 375.1778 found 375.1775 Da.

2.70 - (±)-Methyl (*R*)-2-((*S*)-3-(acetoxymethyl)-1-((triethylsilyl)oxy)but-3-en-1-yl)-5-methyl-2-vinylhex-4-enoate



$C_{23}H_{40}O_5Si$
M.W. = 424.65 g/mol

To a stirred solution of alcohol **2.67** (100 mg, 0.32 mmol) in CH_2Cl_2 (1.5 mL) under Ar at 0 °C was added Et_3N (0.09 mL, 0.64 mmol) then TESOTf (0.09 mL, 0.38 mmol) dropwise. The solution was stirred at rt for 2 h before adding $NaHCO_3$ (2 mL) and extracting with CH_2Cl_2 (3 x 4 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:hexane, 1:10) gave the title compound (**2.70**) (107 mg, 0.25 mmol, 78%) as a clear oil.

FT-IR (neat) ν_{max} 1920 (m, C-H), 1740 (m, C=O), 1650 (w, C=C), 1224 (m, C-O), 1077 (m, C-O) cm^{-1}.

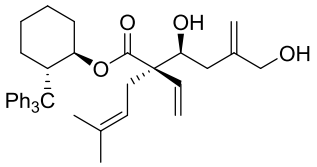
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.15 (1H, dd, *J* = 18.0, 11.2 Hz, C<u>H</u>=CH_2), 5.33 (1H, d, *J* = 11.3 Hz, CH=C<u>H</u>H_{cis}), 5.14 (4H, m, CH=CH<u>H</u>$_{trans}$, C=C<u>H</u>$_2$, C=C<u>H</u>), 4.54 (2H, s, C<u>H</u>$_2$O), 4.29 (1H, dd, *J* = 8.1, 3.4 Hz, C<u>H</u>O), 3.66 (3H, s, OC<u>H</u>$_3$), 2.43 – 2.33 (2H, m, C<u>H</u>$_2$CH), 2.27 (1H, dd, *J* = 14.5, 2.9 Hz, C<u>H</u>HCHO), 2.11 (3H, s, C<u>H</u>$_3$CO), 2.04 (1H, dd, *J* = 14.7, 7.6 Hz, CH<u>H</u>CHO), 1.67 (3H, s, CC<u>H</u>$_3$), 1.61 (3H, s, CC<u>H</u>$_3$), 0.93 (9H, t, *J* = 7.9 Hz, CH_2C<u>H</u>$_3$), 0.55 (6H, q, *J* = 7.9 Hz, C<u>H</u>$_2$$CH_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4 (s, <u>C</u>=O), 170.6 (s, <u>C</u>=O), 140.5 (s, <u>C</u>=CH_2), 136.2 (d, <u>C</u>H=CH_2), 133.5 (s, <u>C</u>=CH), 119.4 (d, C=<u>C</u>H), 116.0 (t, C=<u>C</u>H$_2$), 115.8 (t, CH=<u>C</u>H$_2$), 75.6 (d, <u>C</u>HO), 66.8 (t, <u>C</u>H$_2$O), 59.2 (s, <u>C</u>CHO), 51.6 (q, O<u>C</u>H$_3$), 37.7 (t, <u>C</u>H$_2$CHO), 30.5 (t, <u>C</u>H$_2$CH), 25.9 (q, C<u>C</u>H$_3$), 20.9 (s, <u>C</u>CO), 17.9 (q, C<u>C</u>H$_3$), 7.0 (q, CH_2<u>C</u>H$_3$), 5.4 (t, <u>C</u>H$_2$$CH_3$) ppm.

LRMS (ES$^+$) *m/z* 447 $[M+Na]^+$, 425 $[M+H]^+$.

HRMS (ES$^+$) For $C_{23}H_{40}NaO_5Si$ calculated 447.2537, found 447.2546 Da.

2.74 - (1*R*,2*S*)-2-Tritylcyclohexyl (*R*)-2-((*S*)-1-hydroxy-3-(hydroxymethyl)but-3-en-1-yl)-5-methyl-2-vinylhex-4-enoate



$C_{39}H_{46}O_4$
M.W. = 578.78 g/mol

To a stirred solution of malonate **2.51a** (750 mg, 1.40 mmol) in CH_2Cl_2 (12 mL) under Ar at –78 °C, was added DIBAL (1 M in hexanes, 2.79 mL, 2.79 mmol) dropwise over 40 min. After 6 h, Rochelle salt (10 mL) was added at –78 °C, and the suspension was warmed to rt, before extracting with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give the crude aldehyde.

In a separate flask, by adaptation of the procedure by Linclau *et al.*,[99] Mg (105 mg, 4.32 mg-atom) was suspended in Et_2O (11.5 mL) under Ar, and dibromoethane (0.37 mL, 4.32 mmol) was added at rt. After 30 min, the solvent was removed, and the residue was resuspended in CH_2Cl_2 (8 mL) under Ar, and cooled to –78 °C. To this was

added the aforementioned crude aldehyde in CH_2Cl_2 (10 mL) dropwise over 40 min. After 40 min, allyltin reagent **2.58** (726 mg, ca. 1.68 mmol) in CH_2Cl_2 (11.5 mL) was added dropwise over 40 min at –78 °C. After 1 h, the suspension was warmed to –25 °C, and stirred for a further 3 h. $NaHCO_3$ (10 mL) was then added, before extracting with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography twice (EtOAc:petrol, 1:10→EtOAc, then EtOAc:petrol, 1:2→1:1) gave the title compound (**2.74**) (485 mg, 0.84 mmol, 60%) as a white solid.

[α] –36.5 (c = 0.59).

MP 56–58 °C (*solvent*: CH_2Cl_2).

FT-IR (neat) ν_{max} 3365 (br, O-H), 2929 (w, C-H), 1716 (m, C=O), 1595 (w, C=C), 1493 (m, C=C), 1179 (m, C-O) cm^{-1}.

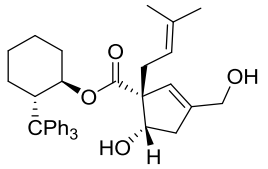
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.22 (15H, m, C$\underline{H}_{Ar}$), 5.53 (1H, dd, *J* = 17.7, 11.1 Hz, C$\underline{H}$=CH_2), 5.20 (1H, d, *J* = 11.1 Hz, CH=C$\underline{H}\underline{H}_{cis}$), 5.08 (1H, s, C=C$\underline{H}$H), 5.02 (1H, d, *J* = 17.7 Hz, CH=CH$\underline{H}_{trans}$), 4.95 (1H, m, C=C$\underline{H}$), 4.86 (1H, s, C=CH$\underline{H}$), 4.18 – 4.00 (3H, m, C$\underline{H}$OC, C$\underline{H}_2$OH), 3.73 (1H, apparent d, *J* = 10.2 Hz, C$\underline{H}$OH), 3.60 (1H, m, PhCC$\underline{H}$), 2.88 – 2.69 (2H, m, CH_2O$\underline{H}$, CHO$\underline{H}$), 2.20 – 2.05 (3H, m, PhCCHC$\underline{H}$H, C$\underline{H}$HCHOH, C$\underline{H}$HCH=C), 2.01 – 1.84 (3H, m, CH$\underline{H}$CHOH, CH$\underline{H}$CH=C, C$\underline{H}$HCHOC), 1.72 (3H, s, CC$\underline{H}_3$), 1.68 – 1.58 (5H, m, PhCHCH_2C$\underline{H}$H, C$\underline{H}$HCH_2CHOC, CC$\underline{H}_3$), 1.51 – 1.36 (2H, m, CH$\underline{H}$CHOC PhCHCH_2CH$\underline{H}$), 1.17 (1H, m, CH$\underline{H}$CH_2CHOC), 0.84 (1H, m, PhCCHCH$\underline{H}$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.0 (s, $\underline{C}$=O), 146.8 (s, $\underline{C}$=CH_2), 135.8 (d, $\underline{C}$H=CH_2), 133.3 (s, $\underline{C}$=CH), 128.5 (d, $\underline{C}H_{Ar}$), 127.9 (d, $\underline{C}H_{Ar}$), 125.2 (s, $\underline{C}_{Ar}$) 119.1 (d, C=$\underline{C}$H), 116.9 (t, CH=$\underline{C}H_2$), 113.6 (t, C=$\underline{C}H_2$), 77.5 (d, $\underline{C}$HOC), 74.1 (d, $\underline{C}$HOH), 66.6 (t, $\underline{C}H_2$OH), 61.0 (s, Ph$\underline{C}$CH), 56.6 (s, $\underline{C}$CHOH), 45.5 (d, PhC$\underline{C}$H), 35.8 (t, $\underline{C}H_2$CHOH), 32.6 (t, $\underline{C}H_2$CHOC), 29.8 (t, $\underline{C}H_2$CH=C), 28.6 (t, PhCCH$\underline{C}H_2$), 26.0 (q, C$\underline{C}H_3$), 25.7 (t, PhCHC$H_2\underline{C}H_2$), 24.5 (t, $\underline{C}H_2CH_2$CHOC), 18.1 (q, C$\underline{C}H_3$) ppm.

LRMS (ES$^+$) *m/z* 601 $[M+Na]^+$.

HRMS (ES$^+$) For $C_{39}H_{47}O_4$ calculated 579.3469, found 579.3460 Da.

2.75 - (1*R*,2*S*)-2-Tritylcyclohexyl (1*R*,5*S*)-5-hydroxy-3-(hydroxymethyl)-1-(3-methyl but-2-en-1-yl)cyclopent-2-ene-1-carboxylate



$C_{37}H_{42}O_4$
M.W. = 550.73 g/mol

To a stirred solution of Grubbs' second generation catalyst (**1.140**) (7.8 mg, 0.009 mmol) in CH_2Cl_2 (1 mL) under Ar at rt, was added allyl alcohol **2.74** (107 mg, 0.18 mmol) in CH_2Cl_2 (1 mL). The solution was warmed to reflux for 24 h, before addition of Grubbs' second generation catalyst (**1.140**) (7.8 mg, 0.009 mmol) in CH_2Cl_2 (1 mL). The solution was stirred at reflux for a further 48 h, before removing the solvent under reduced pressure. Purification by column chromatography (EtOAc:hexane, 1:1) gave the title compound (**2.75**) (38 mg, 0.068 mmol, 38%) as a white solid.

[α] –12.5 (c = 0.80).

MP 82–84 °C (*solvent*: CH_2Cl_2/*n*-hexane).

FT-IR (neat) ν_{max} 3389 (br, O-H), 3055 (=C-H), 2921 (m, C-H), 1690 (m, C=O), 1594 (w, C=C), 1493 (m, C=C) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.01 (15H, m, C<u>H</u>$_{Ar}$), 5.34 (1H, s, C<u>H</u>=CCH$_2$), 4.91 (1H, finely coupled t, *J* = 7.0 Hz, CH$_3$C=C<u>H</u>), 4.26 – 4.13 (3H, m, C<u>H</u>O, C<u>H$_2$</u>OH), 3.75 (1H, td, *J* = 5.9, 2.5 Hz, C<u>H</u>OH), 3.69 (1H, m, C<u>H</u>CPh), 2.55 – 2.47 (2H, m, C<u>H</u>HCHO, CH$_2$O<u>H</u>), 2.23 – 2.13 (2H, m, CH<u>H</u>CHO, C<u>H</u>HCHC), 2.01 – 1.91 (2H, m, C=CHC<u>H</u>H, C<u>H</u>HCHO), 1.81 – 1.61 (7H, m, CC<u>H$_3$</u>, C<u>H</u>HCH$_2$CHC, C<u>H</u>HCH$_2$CHO, C=CHCH<u>H</u>, CHO<u>H</u>), 1.58 (3H, s, CC<u>H$_3$</u>), 1.49 – 1.37 (2H, m, CH<u>H</u>CHO, CH<u>H</u>CH$_2$CHC), 1.16 (1H, m, CH<u>H</u>CH$_2$CHO), 0.72 (1H, m, CH<u>H</u>CHC) ppm.

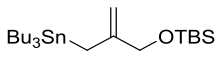
^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7 (s, <u>C</u>=O), 143.0 (s, <u>C</u>=CH), 134.1 (s, <u>C</u>=CH), 128.6 (d, <u>C</u>H$_{Ar}$), 127.8 (d, <u>C</u>H$_{Ar}$), 126.6 (d, <u>C</u>H=CCH$_2$), 125.0 (s, <u>C$_{Ar}$</u>), 119.0 (d, CH$_3$C=<u>C</u>H), 77.2 (d, <u>C</u>HOH), 76.8 (d, <u>C</u>HO), 64.2 (s, <u>C</u>Ph), 61.9 (t, <u>C</u>H$_2$OH), 61.1 (s, <u>C</u>CHOH), 45.5 (d, <u>C</u>HCPh), 40.2 (t, <u>C</u>H$_2$CHOH), 33.8 (t, C=CH<u>C</u>H$_2$),

33.1 (t, $\underline{C}H_2CHO$), 28.9 (t, $\underline{C}H_2CHC$), 25.9 (q, $C\underline{C}H_3$), 25.9 (t, $\underline{C}H_2CH_2CHC$), 24.8 (t, $\underline{C}H_2CH_2CHO$), 18.2 (q, $C\underline{C}H_3$) ppm.

LRMS (ES^+) *m/z* 1124 $[2M+Na]^+$, 573 $[M+Na]^+$.

HRMS (ES^+) For $C_{37}H_{42}O_4Na$ calculated 573.2975, found 573.2978 Da.

2.76 - *t*-Butyldimethyl((2-((tributylstannyl)methyl)allyl)oxy)silane



$C_{22}H_{48}OSiSn$
M. W. = 475.42 g/mol

To a stirred solution of TBSCl (83 mg, 0.55 mmol) and alcohol **2.57** (200 mg, 0.55 mmol) in CH_2Cl_2 (5 mL) under Ar at 0 °C was added imidazole (57 mg, 0.83 mmol). The solution was stirred at rt for 1 h before addition of H_2O (5 mL) and extracting with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:petrol, 1:10) gave the title compound (**2.76**) (250 mg, 0.53 mmol, 96%) as a clear oil.

FT-IR (neat) ν_{max} 2926 (m, C-H), 1638 (w, C=C), 1076 (s, O-C) cm^{-1}.

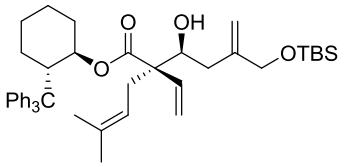
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.80 (1H, m, C=C$\underline{H}$H), 4.60 (1H, m, C=CH$\underline{H}$), 4.00 –3.95 (2H, m, $C\underline{H}_2O$), 1.73 (2H, t, *J* = 29.7 Hz, $C\underline{H}_2Sn$), 1.56 – 1.43 (6H, m, $C\underline{H}_2$), 1.37 – 1.27 (6H, m, $C\underline{H}_2$), 0.96 – 0.84 (24H, m, $SiC(C\underline{H}_3)_3$, $C\underline{H}_3$) 0.08 (6H, s, $SiC\underline{H}_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.7 (s, $\underline{C}=CH_2$), 103.8 (t, $C=\underline{C}H_2$), 66.9 (t, $\underline{C}H_2O$), 29.1 (q, $\underline{C}H_3$), 27.4 (q, $\underline{C}H_3$), 26.0 (t, $\underline{C}H_2$), 18.4 (s, $Si\underline{C}(CH_3)_3$), 14.5 (q, $\underline{C}H_2$), 13.7 (t, $\underline{C}H_3$), 9.5 (t, $\underline{C}H_2$), –5.3 ($\underline{C}H_3$) ppm.

LRMS (EI) *m/z* 419 (54%) $[M-C_4H_9]^{+\cdot}$, 291 (34%) $[M-C_{10}H_{22}OSi]^{+\cdot}$, 177 (74%) $[M-C_{18}H_{39}OSi]^{+\cdot}$.

HRMS (ES^+) For $C_{22}H_{48}NaOSiSn^{120}$ calculated 499.2392, found 499.2386 Da. (EI) For $C_{18}H_{39}OSiSn^{120}$ calculated 419.1792, found 419.1794 Da.

2.77 - (1*R*,2*S*)-2-Tritylcyclohexyl (*R*)-2-((*S*)-3-(((tert-butyldimethylsilyl)oxy)methyl)-1-hydroxybut-3-en-1-yl)-5-methyl-2-vinylhex-4-enoate



$C_{45}H_{60}O_4Si$
M.W. = 693.04 g/mol

To a stirred solution of malonate **2.51a** (284 mg, 0.53 mmol) in CH_2Cl_2 (6 mL) under Ar at –78 °C, was added DIBAL (1 M in hexanes, 1.33 mL, 1.33 mmol) dropwise over 30 min. After 6 h, Rochelle salt (5 mL) was added at –78 °C, and the suspension was warmed to rt, before extracting with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give the crude aldehyde.

In a separate flask, by adaptation of the procedure by Linclau *et al.*,[99] Mg (40 mg, 1.65 mg-atom) was suspended in Et_2O (4.5 mL) under Ar at rt, and dibromoethane (0.14 mL, 1.65 mmol) was added. After 30 min, the solvent was removed, and the residue was resuspended in CH_2Cl_2 (3 mL) under Ar, and cooled to –78 °C. To this was added the aforementioned crude aldehyde in CH_2Cl_2 (3.8 mL) dropwise over 30 min. After 30 min, allyltin reagent **2.76** (304 mg, 0.64 mmol) in CH_2Cl_2 (4.5 mL) was added dropwise over 30 min at –78 °C. After 1 h, the suspension was warmed to –25 °C, and stirred for a further 3 h. $NaHCO_3$ (6 mL) was then added, before extracting with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography twice (CH_2Cl_2:petrol, 2:5→CH_2Cl_2) gave the title compound (**2.77**) (98 mg, 0.14 mmol, 26%) as a viscous oil.

[α] –28.7 (c = 1.00).

FT-IR (neat) ν_{max} 2928 (m, C-H), 1718 (m, C=O), 1632 (m, C=C), 1596 (w, C=C), 1493 (m, C=C) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.01 (15H, m, C<u>H</u>$_{Ar}$), 5.56 (1H, dd, *J* = 17.9, 11.1 Hz, C<u>H</u>=CH$_2$), 5.19 – 5.13 (2H, m, CH=C<u>H</u>H, C=C<u>H</u>H), 5.01 – 4.94 (2H, m, CH=CH<u>H</u> C=C<u>H</u>), 4.89 (1H, s, C=CH<u>H</u>), 4.19 – 4.04 (3H, m, C<u>H</u>OC, C<u>H</u>$_2$OSi), 3.64 – 3.57 (2H, m, C<u>H</u>OH, PhCC<u>H</u>), 2.49 (1H, d, *J* = 5.0 Hz, CHO<u>H</u>), 2.24 (1H, dd, *J* = 15.6, 7.4 Hz, C<u>H</u>HCH=C), 2.16 (1H, m, PhCCHC<u>H</u>H), 2.07 – 1.96

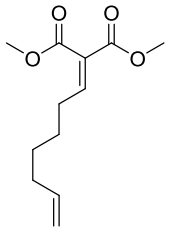
(2H, m, CH<u>H</u>CH=C, C<u>H</u>HCHOH), 1.92 – 1.83 (2H, m, CH<u>H</u>CHOH, OCHC<u>H</u>H), 1.72 (3H, s, CC<u>H</u>$_3$), 1.66 – 1.61 (5H, m, PhCCHCH$_2$C<u>H</u>H, OCHCH$_2$C<u>H</u>H, CC<u>H</u>$_3$), 1.51 – 1.39 (2H, m, PhCCHCH$_2$CH<u>H</u>, OCHCH<u>H</u>), 1.16 (1H, m, OCHCH$_2$CH<u>H</u>), 0.94 (9H, s, SiC(C<u>H</u>$_3$)$_3$), 0.84 (1H, m, PhCCHCH<u>H</u>), 0.10 (3H, s, SiC<u>H</u>$_3$), 0.10 (3H, s, SiC<u>H</u>$_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6 (s, <u>C</u>=O), 145.9 (s, <u>C</u>=CH$_2$), 136.1 (d, <u>C</u>H=CH$_2$), 132.8 (s, <u>C</u>=CH), 128.7 (d, <u>C</u>H$_{Ar}$), 127.8 (d, <u>C</u>H$_{Ar}$), 127.6 (d, <u>C</u>H$_{Ar}$), 126.5 (d, <u>C</u>H$_{Ar}$), 125.1 (s, <u>C</u>$_{Ar}$), 119.7 (d, C=<u>C</u>H), 116.4 (t, CH=<u>C</u>H$_2$), 111.8 (t, C=<u>C</u>H$_2$), 77.1 (d, <u>C</u>HOC), 73.6 (d, <u>C</u>HOH), 66.3 (t, <u>C</u>H$_2$O), 61.1 (s, PhC<u>C</u>H), 56.8 (s, <u>C</u>CHOH), 45.5 (d, PhC<u>C</u>H), 35.6 (t, <u>C</u>H$_2$CHOH), 32.6 (t, <u>C</u>H$_2$CHOC), 29.8 (t, <u>C</u>H$_2$CH=C), 28.5 (t, PhCH<u>C</u>H$_2$), 25.9 (q, SiC(<u>C</u>H$_3$)$_3$), 25.7 (t, <u>C</u>H$_2$CH$_2$CHCPh), 24.4 (t, <u>C</u>H$_2$CH$_2$COC), 18.4 (s, Si<u>C</u>(CH$_3$)$_3$), 18.1 (q, C<u>C</u>H$_3$), –5.4 (q, Si<u>C</u>H$_3$), –5.4 (q, Si<u>C</u>H$_3$) (C<u>C</u>H$_3$ covered by SiC(<u>C</u>H$_3$)$_3$) ppm.

LRMS (ES$^+$) *m/z* 1408 [2M+Na]$^+$, 715 [M+Na]$^+$.

HRMS (ES$^+$) For $C_{45}H_{60}O_4SiNa$ calculated 715.4153, found 715.4149 Da.

2.85 - Dimethyl 2-(hept-6-en-1-ylidene)malonate



$C_{12}H_{18}O_4$
M.W. = 226.27 g/mol

To a stirred suspension of $LiAlH_4$ (665 mg, 17.5 mmol) in Et_2O (50 mL) under Ar at 0 °C, was added 6-heptenoic acid (**2.84**) (2.00 g, 17.5 mmol) in Et_2O (12 mL) dropwise over 45 min. After 6 h at 0 °C, H_2O (1 mL) was added, followed by NaOH (15%, 1 mL), then H_2O (2 mL). The suspension was then filtered, washing with Et_2O (120 mL). The filtrate was washed with $NaHCO_3$ (50 mL), then dried ($MgSO_4$) and concentrated under reduced pressure, giving the crude alcohol (1.42 g).

In a separate flask, to a stirred solution of oxalyl chloride (2.10 mL, 24.8 mmol) in CH_2Cl_2 (27 mL) under Ar at –78 °C, was added DMSO (1.94 mL, 27.3 mmol) dropwise over 10 min. After 15 min at –78 °C, the aforementioned crude alcohol (1.42 g) in

CH_2Cl_2 (6 mL) was added dropwise over 10 min. After a further 15 min, Et_3N (10.4 mL, 74.4 mmol) was added dropwise over 15 min, and the suspension was stirred at –78 °C for 15 min, before warming to rt and stirring for a further 30 min. Et_2O (100 mL) was then added, and washed with HCl (2N, 2 x 35 mL), H_2O (35 mL) and brine (35 mL). The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (Et_2O:pentane, 1:4) was undertaken unsuccessfully, and so the crude aldehyde (800 mg) was taken forward without further purification.

Finally, to a stirred solution of crude heptenal (500 mg, 4.46 mmol) and dimethyl malonate (**2.05**) (0.57 mL, 4.91 mmol) in CH_2Cl_2 (5 mL) under Ar at 0 °C, was added piperidine (0.04 mL, 0.45 mmol) then AcOH (0.03 mL, 0.45 mmol). The solution was warmed to rt and stirred for 24 h before addition of EtOAc (40 mL). The organic phase was washed with H_2O (2 x 10 mL), before drying ($MgSO_4$) and concentrating under reduced pressure. Purification by column chromatography (EtOAc:petrol, 1:1) gave the title compound (**2.85**) (449 mg, 1.98 mmol, 18% over 3 steps) as a clear oil.

FT-IR (neat) ν_{max} 2928 (m, C-H), 1724 (s, C=O), 1642 (m, C=C), 1222 (s, C-O) cm^{-1}.

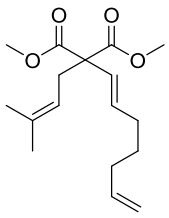
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (1H, t, *J* = 7.6 Hz, C=C<u>H</u>), 5.79 (1H, ddt, *J* = 17.0, 10.3, 6.6 Hz, CH_2=C<u>H</u>), 5.05 – 4.93 (2H, m, C<u>H$_2$</u>=CH), 3.84 (3H, s, OC<u>H$_3$</u>), 3.79 (3H, s, OC<u>H$_3$</u>), 2.32 (2H, q, *J* = 7.6 Hz, C=CHC<u>H$_2$</u>), 2.10 – 2.03 (2H, m, CH_2=CHC<u>H$_2$</u>), 1.56 – 1.39 (4H, m, $CHCH_2C$<u>H$_2$</u>, $CHCH_2C$<u>H$_2$</u>) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.9 (s, <u>C</u>=O), 164.4 (s, <u>C</u>=O), 150.3 (d, C=<u>C</u>H), 138.4 (d, CH_2=<u>C</u>H), 128.0 (s, <u>C</u>=CH), 114.7 (t, <u>C</u>H$_2$=CH), 52.2 (q, O<u>C</u>H$_3$), 33.3 (t, =CH<u>C</u>H$_2$), 29.6 (t, =CH<u>C</u>H$_2$), 28.3 (t, CH_2<u>C</u>H$_2$), 27.7 (t, CH_2<u>C</u>H$_2$) ppm.

LRMS (ES$^+$) *m/z* 290 $[M+CH_3CN+H]^+$, 249 $[M+Na]^+$.

HRMS (ES$^+$) For $C_{12}H_{18}O_4Na$ calculated 249.1097, found 249.1099 Da.

2.86 - (*E*)-Dimethyl 2-(hepta-1,6-dien-1-yl)-2-(3-methylbut-2-en-1-yl)malonate



$C_{17}H_{26}O_4$
M.W. = 294.39 g/mol

To a solution of LDA (1.77 M in THF, 0.30 mL, 2.53 mmol) under Ar at –78 °C, was added malonate **2.85** (300 mg, 1.33 mmol) in THF (6 mL) dropwise over 15 min. After 30 min, prenyl bromide (**2.02**) (0.19 mL, 1.46 mmol) was added dropwise at –78 °C, before the solution was allowed to warm to rt in the cardice bath, and stirred for 16 h. NH_4Cl (4 mL) was added, and extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:petrol, 1:10) gave the title compound (**2.86**) (222 mg, 0.75 mmol, 57%) as a clear oil.

FT-IR (neat) ν_{max} 2927 (m, C-H), 1736 (s, C=O), 1641 (w, C=C), 1232 (m, O-C) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (1H, dt, *J* = 16.2, 1.5 Hz, CCH=C<u>H</u>), 5.80 (1H, ddt, *J* = 17.0, 10.3, 6.6 Hz, CH_2=C<u>H</u>), 5.54 (1H, dt, *J* = 16.2, 6.8 Hz, CC<u>H</u>), 5.03 – 4.94 (3H, m, C<u>H</u>=C, C<u>H$_2$</u>=CH), 3.72 (6H, s, OC<u>H$_3$</u>), 2.76 (2H, d, *J* = 7.1 Hz, C<u>H$_2$</u>CH=C), 2.13 – 2.02 (4H, m, CH=CHC<u>H$_2$</u>, CH_2=CHC<u>H$_2$</u>), 1.68 (3H, s, CC<u>H$_3$</u>), 1.61 (3H, s, CC<u>H$_3$</u>), 1.48 (2H, apparent quin, *J* = 7.5 Hz, $CHCH_2$C<u>H$_2$</u>) ppm.

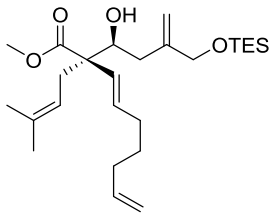
^{13}C NMR (101 MHz, $CDCl_3$) δ 171.2 (s, <u>C</u>=O), 138.6 (d, C<u>C</u>H), 135.2 (s, <u>C</u>=CH), 132.6 (d, CH_2=<u>C</u>H), 126.7 (d, CCH=<u>C</u>H), 117.9 (d, C=<u>C</u>H), 114.6 (t, <u>C</u>H$_2$=CH), 59.5 (s, <u>C</u>CO), 52.5 (q, O<u>C</u>H$_3$), 34.2 (t, =CH<u>C</u>H$_2$), 33.0 (t, =CH<u>C</u>H$_2$), 32.0 (t, =CH<u>C</u>H$_2$), 28.1 (t, $CHCH_2$<u>C</u>H$_2$), 25.9 (q, <u>C</u>CH$_3$), 17.9 (q, C<u>C</u>H$_3$) ppm.

LRMS (ES$^+$) *m/z* 317 $[M+Na]^+$, 295 $[M+H]^+$.

HRMS (ES$^+$) For $C_{17}H_{26}O_4Na$ calculated 317.1723, found 317.1724 Da.

Experimental

2.87 - (±)-Methyl (*R*,*E*)-2-((*S*)-1-hydroxy-3-(((triethylsilyl)oxy)methyl)but-3-en-1-yl)-2-(3-methylbut-2-en-1-yl)nona-3,8-dienoate



$C_{26}H_{46}O_4Si$
M.W. = 450.73 g/mol

To a stirred solution of malonate **2.86** (220 mg, 0.75 mmol) in CH_2Cl_2 (6 mL) under Ar at –78 °C, was added DIBAL (1 M in hexanes, 0.94 mL, 0.94 mmol) dropwise over 45 min. After 4 h, another portion of DIBAL (1 M in hexanes, 0.35 mL, 0.35 mmol) was added dropwise over 30 min. After 1h at –78 °C, Rochelle salt (4 mL) was added dropwise over 20 min, and the suspension was warmed to rt before extracting with CH_2Cl_2 (5 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give the crude aldehyde.

In a separate flask, by adaptation of the procedure by Linclau *et al.*,[99] Mg (47 mg, 1.92 mg-atom) was suspended in Et_2O (2 mL) under Ar, and dibromoethane (0.17 mL, 1.92 mmol) was added at rt. After 30 min, the solvent was removed, and the residue was resuspended in CH_2Cl_2 (1.4 mL) under Ar and cooled to –78 °C. To this was added the aforementioned crude aldehyde in CH_2Cl_2 (1.7 mL) dropwise over 30 min. After 30 min, allyltin reagent **2.66** (352 mg, 0.74 mmol) in CH_2Cl_2 (2 mL) was added dropwise over 30 min at –78 °C. The suspension was warmed to –30 °C, and stirred for 3.5 h. H_2O (4 mL) was then added, before extracting with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:petrol, 1:10) gave the title compound (**2.87**) (122 mg, 0.27 mmol, 36%) as a clear oil.

FT-IR (neat) ν_{max} 2914 (m, C-H), 1731 (m, C=O), 1647 (m, C=C), 1070 (s, O-C) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 – 5.71 (2H, m, C<u>H</u>=CHCH$_2$, C<u>H</u>=CH$_2$), 5.53 (1H, dt, *J* = 16.2, 6.8 Hz, CH=C<u>H</u>CH$_2$), 5.12 (1H, m, C=C<u>H</u>H), 5.06 – 4.92 (4H, m, C=CH<u>H</u>, CH=C<u>H</u>$_2$, C<u>H</u>=C), 4.06 (1H, d, *J* = 13.1 Hz, C<u>H</u>HO), 4.02 (1 H, d, *J* = 13.1 Hz, CH<u>H</u>O), 3.99 (1H, ddd, *J* = 10.6, 4.6, 2.0 Hz, C<u>H</u>OH), 3.70 (3H, s, OC<u>H</u>$_3$), 3.07 (1H, d, *J* = 4.6 Hz, O<u>H</u>), 2.54 – 2.42 (2H, m, C<u>H</u>$_2$CH=C), 2.29 (1H, d, *J* = 14.2 Hz, C<u>H</u>HCHO), 2.16 – 1.94 (5H, m, CH<u>H</u>CHO, CH$_2$=CHC<u>H</u>$_2$,

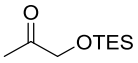
CH=CHC$\underline{H}_2$), 1.68 (3H, s, CC$\underline{H}_3$), 1.62 (3H, s, CC$\underline{H}_3$), 1.50 (2H, apparent quin, *J* = 7.5 Hz,$CH_2C\underline{H}_2$), 0.97 (9H, t, *J* = 8.1 Hz, $SiCH_2C\underline{H}_3$), 0.63 (6H, q, *J* = 8.2 Hz, Si$C\underline{H}_2$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.6 (s, $\underline{C}$=O), 145.9 (s, $\underline{C}$=CH_2), 138.7 (d, C$\underline{C}$H), 133.8 (s, $\underline{C}$=C$(CH_3)_2$), 132.0 (d, CH_2=$\underline{C}$H), 127.9 (d, CCH=$\underline{C}$H), 119.3 (d, C=$\underline{C}$H), 114.5 (t, CH=$\underline{C}H_2$), 112.6 (t, C=$\underline{C}H_2$), 74.7 (d, $\underline{C}$HO), 66.1 (t, $\underline{C}H_2O$), 56.9 (s, $\underline{C}$CO), 51.9 (q, O$\underline{C}H_3$), 36.0 (t, C$\underline{C}H_2$), 33.2 (t, CH=CH$\underline{C}H_2$), 32.5 (t, CH_2=CH$\underline{C}H_2$), 32.0 (t, C=CH$\underline{C}H_2$), 28.7 (t, $CHCH_2\underline{C}H_2$), 25.9 (q, C$\underline{C}H_3$), 17.9 (q, C$\underline{C}H_3$), 6.7 (q, $SiCH_2\underline{C}H_3$), 4.4 (t, Si$\underline{C}H_2$) ppm.

LRMS (ES$^+$) *m/z* 473 $[M+Na]^+$.

HRMS (ES$^+$) For $C_{26}H_{46}NaO_4Si$ calculated 473.3058 found 473.3054 Da.

2.93 - 1-((Triethylsilyl)oxy)propan-2-one



$C_9H_{20}O_2Si$
M.W. = 188.34 g/mol

Following a procedure by Hoppe *et al.*,[220] to a stirred solution of DMAP (990 mg, 8.10 mmol) and hydroxy acetone (**2.92**) (1.85 mL, 27.0 mmol) in CH_2Cl_2 (50 mL) under Ar at 0 °C, was added Et_3N (4.52 mL, 32.4 mmol). To the solution was added TESCl (4.98 mL, 29.7 mmol) dropwise over 30 min at 0 °C. The resulting suspension was stirred at rt for 2 h, before adding H_2O (30 mL) and extracting with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:petrol, 1:10) gave the title compound (**2.93**) (3.49 g, 18.5 mmol, 69%) as a clear oil.

FT-IR (neat) ν_{max} 2955 (m, C-H), 1737 (s, C=O), 1113 (s, O-C) cm^{-1}.

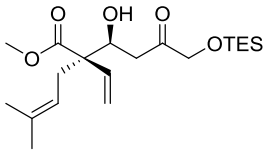
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16 (2H, s, $C\underline{H}_2O$), 2.18 (3H, s, $C\underline{H}_3$C=O), 0.98 (9H, t, *J* = 8.1 Hz, $CH_2C\underline{H}_3$), 0.65 (6H, t, *J* = 8.1 Hz, $C\underline{H}_2CH_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.1 (s, $\underline{C}$=O), 69.3 (t, $\underline{C}H_2O$), 25.9 (q, $\underline{C}H_3$C=O), 6.6 (q, $CH_2\underline{C}H_3$), 4.3 (t, $\underline{C}H_2CH_3$) ppm.

LRMS (EI) 159 (100%) $[M-C_2H_5]^{+\cdot}$, 131 (87%) $[M-C_4H_9]^{+\cdot}$.

HRMS (ES^+) For $C_9H_{20}NaO_2Si$ calculated 211.1125, found 211.1130 Da.

2.94 - (±)-Methyl (*R*)-2-((*S*)-1-hydroxy-3-oxo-4-((triethylsilyl)oxy)butyl)-5-methyl-2-vinylhex-4-enoate



$C_{20}H_{36}O_5Si$
M.W. = 384.58 g/mol

To a stirred solution of 2,6-lutidine (3.09 mL, 26.5 mmol) in toluene (45 mL) under Ar at 0 °C, was added TMSOTf (2.41 mL, 13.3 mmol) dropwise over 5 min. After 10 min, the solution was cooled to −35 °C, and ketone **2.93** (2.00 g, 10.6 mmol) in toluene (15 mL) was added dropwise over 40 min. The solution was stirred for 4 h maintaining the internal temperature between −20 and −40 °C, before addition of TMSOTf (1.20 mL, 6.65 mmol) dropwise over 5 min. The suspension was warmed to 0 °C and stirred for a further 2.5 h. $NaHCO_3$ (30 mL) was added, before extracting with Et_2O (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure, giving the crude silyl enol ether as a 1.8:1 mixture of regioisomers.

In a separate flask, by adaptation of the procedure by Linclau *et al.*,[99] Mg (273 mg, 11.2 mg-atom) was suspended in Et_2O (12 mL) under Ar, and dibromoethane (0.97 mL, 11.2 mmol) was added. After stirring for 1 h, the solvent was removed, and the residual solid was resuspended in CH_2Cl_2 (7.7 mL) under Ar, and cooled to −78 °C. To this was added aldehyde **2.19** (720 mg, 3.62 mmol) in CH_2Cl_2 (9.5 mL) dropwise over 1 h. After 30 min at −78 °C, the aforementioned crude silyl enol ether mix (1.94 g, ca. 3.63 mmol of required regioisomer) was added in CH_2Cl_2 (9.5 mL) dropwise over 1 h. After 30 min, the suspension was warmed to −14 °C and stirred for 18 h. Phosphate buffer (pH 7, 15 mL) was added, and then warmed to rt, before extracting with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:petrol, 1:5) gave the title compound (**2.94**) (714 mg, 1.86 mmol, 51%) as a clear oil.

FT-IR (neat) ν_{max} 3478 (br, O-H), 2914 (m, C-H), 1722 (s, C=O), 1637 (w, C=C), 1068 (s, O-C) cm^{-1}.

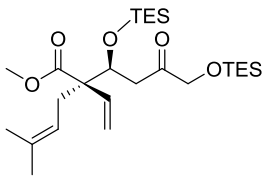
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.09 (1H, dd, *J* = 18.2, 11.1 Hz, C<u>H</u>=CH_2), 5.34 (1H, d, *J* = 11.1 Hz, CH=C<u>H</u>H_{cis}), 5.18 (1H, m, CH=CH<u>H</u>$_{trans}$), 5.03 (1H, finely coupled t, *J* = 7.1 Hz, C=C<u>H</u>), 4.45 (1H, ddd, *J* = 9.9, 5.1, 2.8 Hz, C<u>H</u>OH), 4.21 (1H, d, *J* = 17.7 Hz, C<u>H</u>HOSi), 4.16 (1H, d, *J* = 17.7 Hz, CH<u>H</u>OSi), 3.71 (3H, s, OC<u>H</u>$_3$), 3.19 (1H, d, *J* = 5.1 Hz, O<u>H</u>), 2.66 (1H, dd, *J* = 16.7, 10.1 Hz, C<u>H</u>$_2$CHOH), 2.57 (1H, dd, *J* = 16.7, 2.5 Hz, C<u>H</u>$_2$CHOH), 2.50 – 2.39 (2H, m, C<u>H</u>$_2$CH=C), 1.67 (3H, d, *J* = 1.0 Hz, CC<u>H</u>$_3$), 1.60 (3H, s, CC<u>H</u>$_3$), 0.96 (9H, t, *J* = 8.1 Hz, CH_2C<u>H</u>$_3$), 0.63 (6H, q, *J* = 8.1 Hz, C<u>H</u>$_2$$CH_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 210.4 (s, <u>C</u>=O), 174.6 (s, <u>C</u>=O), 135.6 (d, C<u>C</u>H=CH_2), 134.7 (s, <u>C</u>=CH), 118.3 (d, C=<u>C</u>H), 116.9 (t, CCH=<u>C</u>H$_2$), 71.2 (d, <u>C</u>HOH), 69.4 (t, <u>C</u>H$_2$OSi), 57.1 (s, <u>C</u>CH=CH_2), 52.0 (q, O<u>C</u>H$_3$), 40.6 (t, <u>C</u>H$_2$CHOH), 31.4 (t, <u>C</u>H$_2$CH=C), 25.9 (q, C<u>C</u>H$_3$), 17.8 (q, C<u>C</u>H$_3$), 6.6 (q, CH_2<u>C</u>H$_3$), 4.3 (t, <u>C</u>H$_2$$CH_3$) ppm.

LRMS (ES$^+$) *m/z* 448 [M+CH_3CN+Na]$^+$, 407 [M+Na]$^+$.

HRMS (ES$^+$) For $C_{20}H_{36}NaO_5Si$ calculated 407.2224, found 407.2220 Da.

2.95 - (±)-Methyl (*R*)-5-methyl-2-((*S*)-3,3,10,10-tetraethyl-7-oxo-4,9-dioxa-3,10-disiladodecan-5-yl)-2-vinylhex-4-enoate



$C_{26}H_{50}O_5Si_2$
M.W. = 498.85 g/mol

To a stirred solution of alcohol **2.94** (183 mg, 0.48 mmol) in CH_2Cl_2 (2 mL) under Ar at 0 °C was added Et_3N (0.13 mL, 0.96 mmol) then TESOTf (0.13 mL, 0.58 mmol) dropwise. The solution was stirred at rt for 2 h before adding H_2O (2 mL) and extracting with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:petrol, 1:10) gave the title compound (**2.95**) (195 mg, 0.39 mmol, 81%) as a clear oil.

FT-IR (neat) ν_{max} 2922 (m, C-H), 1743 (s, C=O), 1634 (w, C=C), 1223 (s, O-C) cm^{-1}.

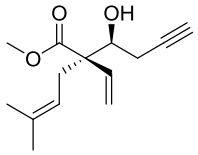
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.12 (1H, dd, *J* = 17.9, 11.3 Hz, C<u>H</u>=CH_2), 5.31 (1H, dd, *J* = 11.2, 0.9 Hz, CH=C<u>H</u>H), 5.11 (1H, dd, *J* = 18.1, 0.9 Hz, CH=CH<u>H</u>), 5.02 (1H, m, C=C<u>H</u>), 4.73 (1H, dd, *J* = 6.2, 4.4 Hz, C<u>H</u>O), 4.14 (2H, s, $C\underline{H_2}O$), 3.67 (3H, s, $OC\underline{H_3}$), 2.67 – 2.60 (2H, m, $C\underline{H_2}CH=C$), 2.45 (1H, m, C<u>H</u>HCHO), 2.16 (1H, m, CH<u>H</u>CHO), 1.66 (3H, s, $CC\underline{H_3}$), 1.60 (3H, s, $CC\underline{H_3}$), 1.01 – 0.88 (18H, s, $CH_2C\underline{H_3}$), 0.68 – 0.50 (12H, m, $SiC\underline{H_2}$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ 208.6 (s, <u>C</u>=O), 136.1 (d, <u>C</u>H=CH_2), 133.8 (s, <u>C</u>=CH), 119.1 (d, C=<u>C</u>H), 116.1 (t, CH=<u>C</u>H_2), 72.2 (d, <u>C</u>HO), 69.4 (t, $\underline{C}H_2O$), 58.9 (s, <u>C</u>CHO), 51.6 (q, $O\underline{C}H_3$), 43.0 (t, $\underline{C}H_2CHO$), 30.8 (t, $\underline{C}H_2CH=C$), 25.9 (q, $C\underline{C}H_3$), 17.9 (q, $C\underline{C}H_3$), 6.9 (q, $CH_2\underline{C}H_3$), 6.7 (q, $CH_2\underline{C}H_3$), 5.0 (t, $Si\underline{C}H_2$), 4.3 (t, $Si\underline{C}H_2$) ppm. Ester <u>C</u>=O missing,

LRMS (ES$^+$) *m/z* 521 $[M+Na]^+$.

HRMS (ES$^+$) For $C_{26}H_{50}NaO_5Si_2$ calculated 521.3089, found 521.3083 Da.

2.102 - (±)-Methyl (*R*)-2-((*S*)-1-hydroxybut-3-yn-1-yl)-5-methyl-2-vinylhex-4-enoate



$C_{14}H_{20}O_3$
M.W. = 236.31 g/mol

To a stirred solution of malonate **2.03** (361 mg, 1.60 mmol) in CH_2Cl_2 (13 mL) under Ar at –78 °C, was added DIBAL (1 M in hexanes, 3.20 mL, 3.20 mmol) dropwise over 30 min. After 5 h, Rochelle salt (5 mL) was added at –78 °C, and the suspension was warmed to rt, before extracting with CH_2Cl_2 (3 x 25 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give the crude aldehyde.

In a separate flask, by adaptation of the procedure by Linclau *et al.*,[99] to a suspension of Mg (120 mg, 4.94 mg-atom) in Et_2O (5 mL) under Ar, was added dibromoethane (0.43 mL, 4.94 mmol) at rt. After 30 min, the solvent was removed under reduced pressure, and the residue was resuspended in CH_2Cl_2 (3.5 mL) under Ar, and cooled to –78 °C. To this was added aforementioned crude aldehyde **2.19** in CH_2Cl_2 (4.3 mL) dropwise over 30 min. After 30 min, allenyltributyltin (0.57 mL, 1.92 mmol) in CH_2Cl_2

(5.1 mL) was added dropwise over 30 min at –78 °C. After 3 h, $NaHCO_3$ (5 mL) was then added, before extracting with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography twice (EtOAc:petrol, 1:10) gave the title compound **2.102** (165 mg, 0.70 mmol, 44%) as a white solid.

MP 56–58 °C (*solvent*: CH_2Cl_2).

FT-IR (neat) ν_{max} 3518 (br, O-H), 2919 (m, C-H), 2118 (w, alkyne C-C) 1727 (s, C=O), 1637 (w, alkene C=C), 1062 (s, O-C) cm^{-1}.

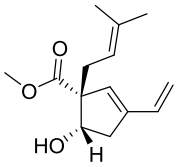
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.11 (1H, dd, *J* = 17.7, 11.1 Hz, C<u>H</u>=CH_2), 5.36 (1H, d, *J* = 11.1 Hz, CH=C<u>H</u>H_{cis}), 5.20 (1H, d, *J* = 17.7 Hz, CH=CH<u>H</u>$_{trans}$), 5.02 (1H, finely coupled t, *J* = 7.1 Hz, C=C<u>H</u>), 4.09 (1H, ddd, *J* = 9.1, 5.8, 3.3 Hz, C<u>H</u>OH), 3.72 (3H, s, OC<u>H</u>$_3$), 3.00 (1H, d, *J* = 6.1 Hz, O<u>H</u>), 2.51 (2H, d, *J* = 7.1 Hz, C<u>H</u>$_2$CH=C), 2.42 (1H, dt, *J* = 16.7, 3.0 Hz, C<u>H</u>HCHOH), 2.32 (1H, ddd, *J* = 16.7, 9.1, 2.5 Hz, CH<u>H</u>CHOH), 2.04 (1H, t, *J* = 2.5 Hz, CC<u>H</u>), 1.69 (3H, s, CC<u>H</u>$_3$), 1.62 (3H, s, CC<u>H</u>$_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.8 (s, <u>C</u>=O), 135.3 (d, <u>C</u>H=CH_2), 135.0 (s, <u>C</u>=CH), 118.2 (d, C=<u>C</u>H), 117.3 (t, CH=<u>C</u>H_2), 81.4 (s, CH_2<u>C</u>CH), 73.5 (d, <u>C</u>HOH), 70.2 (d, CH_2C<u>C</u>H), 56.9 (s, <u>C</u>CHOH), 52.2 (q, O<u>C</u>H_3), 31.7 (t, <u>C</u>H_2CH=C), 26.0 (q, C<u>C</u>H_3), 22.5 (t, <u>C</u>H_2CCH), 17.9 (q, C<u>C</u>H_3) ppm.

LRMS (ES^+) *m/z* 237 $[M+H]^+$.

HRMS (ES^+) For $C_{14}H_{20}O_3Na$ calculated 259.1305, found 259.1303 Da.

2.101 - (±)-Methyl (1*R*,5*S*)-5-hydroxy-1-(3-methylbut-2-en-1-yl)-3-vinylcyclopent-2-ene-1-carboxylate



$C_{14}H_{20}O_3$
M.W. = 236.31 g/mol

A stirred solution of alkyne **2.102** (236 mg, 1.00 mmol) and Grubbs' first generation catalyst (**1.139**) (82 mg, 0.10 mmol) was heated to 30 °C for 24 h, before removing the solvent under reduced pressure. Purification by column chromatography (EtOAc:hexane, 1:5) gave the title compound (**2.101**) (32 mg, 0.14 mmol, 14%) as a pale brown oil.

FT-IR (neat) ν_{max} 3433 (br, O-H), 2914 (m, C-H), 1716 (s, C=O), 1639 (w, C=C), 1226 (s, O-C), 1175 (s, O-C) cm^{-1}.

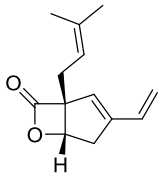
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.52 (1H, dd, *J* = 17.6, 10.4 Hz, C<u>H</u>=CH_2), 5.72 (1H, s, C<u>H</u>=CCH), 5.21 – 5.14 (2H, m, CH=C<u>H</u>$_2$), 5.08 (1H, m, C=C<u>H</u>CH_2), 4.30 (1H, td, *J* = 6.6, 3.7 Hz, C<u>H</u>OH), 3.72 (3H, s, OC<u>H</u>$_3$), 2.98 (1H, d, *J* = 6.7 Hz, O<u>H</u>), 2.80 (1H, m, C<u>H</u>HCHOH), 2.54 – 2.43 (2H, m, CH<u>H</u>CHOH, C<u>H</u>HCH=C), 2.34 (1H, dd, *J* = 14.2, 7.8 Hz, CH<u>H</u>CH=C), 1.70 (3H, s, CC<u>H</u>$_3$), 1.59 (3H, s, CC<u>H</u>$_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.7 (s, <u>C</u>=O), 142.0 (s, CH=<u>C</u>CH), 134.9 (s, <u>C</u>=$CHCH_2$), 133.1 (d, <u>C</u>H=CH_2), 130.4 (d, <u>C</u>H=CCH), 118.7 (d, C=<u>C</u>HCH_2), 116.2 (t, CH=<u>C</u>H_2), 64.5 (s, <u>C</u>C=O), 51.9 (q, O<u>C</u>H_3), 38.7 (t, <u>C</u>H_2CHOH), 35.1 (t, <u>C</u>H_2CH=C), 25.9 (q, C<u>C</u>H_3), 17.8 (q, C<u>C</u>H_3) ppm. <u>C</u>HOH covered by chloroform peaks.

LRMS (ES$^+$) *m/z* 237 $[M+H]^+$.

HRMS (ES$^+$) For $C_{14}H_{20}O_3Na$ calculated 259.1305, found 259.1306 Da.

2.104 - (±)- (1*R*,5*S*)-1-(3-Methylbut-2-en-1-yl)-3-vinyl-6-oxabicyclo[3.2.0]hept-2-en-7-one



$C_{13}H_{16}O_2$
M.W. = 204.27 g/mol

A stirred solution of alkyne **2.102** (236 mg, 1.00 mmol) and Grubbs' first generation catalyst (**1.139**) (82 mg, 0.10 mmol) was heated to 30 °C for 24 h, before removing the solvent under reduced pressure. Purification by column chromatography (EtOAc:hexane 1:5) gave impure cyclisation product **2.101** (74 mg, <0.31 mmol) as a pale brown oil.

In a separate flask, the aforementioned impure cyclisation product was taken into MeOH (6 mL) and H_2O (2 mL) at rt, and $LiOH \cdot H_2O$ (78 mg, 1.86 mmol) was added. After 24 h, the solvent was removed under reduced pressure, and the residue was diluted in H_2O (2 mL), and washed with EtOAc (3 mL). The aq. phase was acidified ~pH 2 with HCl (2 M), and extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure giving the crude hydroxyacid (22 mg).

The crude hydroxyacid was then taken into pyridine (2 mL) under Ar at 0 °C, and *p*-TsCl (23 mg, 0.12 mmol) was added. After 2 h at 0 °C, the solution was left to stand in a fridge overnight. Ice (~4 mL) was added, and extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:hexane, 1:3) gave the title compound (**2.104**) (18 mg, 0.09 mmol, 9% over three steps) as a clear oil.

FT-IR (neat) ν_{max} 2915 (w, C-H), 1817 (s, C=O), 1673 (w, C=C), 1635 (w, C=C), 1107 (m, C-O) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.54 (1H, dd, *J* = 17.3, 10.7 Hz, C<u>H</u>=CH_2), 5.63 (1H, s, C<u>H</u>=CCH), 5.28 – 5.21 (2H, 2 x d, *J* = 17.6 + 10.5 Hz, CH=C<u>H</u>H_{trans}, CH=CH<u>H</u>$_{cis}$), 5.13 (1H, finely coupled t, *J* = 7.2 Hz, C=C<u>H</u>CH_2), 4.82 (1H, d, *J* = 5.4 Hz, C<u>H</u>O), 2.91 (1H, d, *J* = 18.3 Hz, C<u>H</u>HCHO), 2.83 (1H, ddd, *J* = 18.3, 5.4, 1.7 Hz, CH<u>H</u>CHO), 2.64 (1H, dd, *J* = 15.0, 7.3 Hz, C<u>H</u>HCH=C),

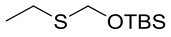
2.46 (1H, dd, *J* = 15.2, 7.3 Hz, CH<u>H</u>CH=C), 1.73 (3H, d, *J* = 0.7 Hz, CC<u>H</u>$_3$), 1.65 (3H, s, CC<u>H</u>$_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5 (s, <u>C</u>=O), 144.1 (s, <u>C</u>=CH), 136.0 (s, <u>C</u>=CH), 132.3 (d, <u>C</u>H=CH$_2$), 126.3 (d, <u>C</u>H=CCH), 117.7 (t, CH=<u>C</u>H$_2$), 117.3 (d, C=<u>C</u>HCH$_2$), 78.3 (d, <u>C</u>HO), 75.4 (s, <u>C</u>C=O), 35.8 (t, <u>C</u>H$_2$CHO), 27.8 (t, <u>C</u>H$_2$CH=C), 25.8 (q, C<u>C</u>H$_3$), 18.0 (q, C<u>C</u>H$_3$) ppm.

LRMS (ES^+) *m/z* 205 $[M+H]^+$.

HRMS (ES^+) For $C_{13}H_{16}O_2Na$ calculated 227.1043, found 227.1043 Da.

2.110 - *t*-Butyl((ethylthio)methoxy)dimethylsilane



$C_9H_{22}OSSi$
M.W. = 206.42 g/mol

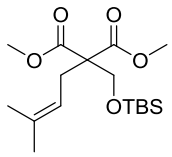
Following a procedure by Undheim *et al.*,[122] to a mixture of ethanethiol (**2.109**) (6.00 mL, 81.0 mmol) and paraformaldehyde (2.43 g, 81.0 mmol) was added NaOMe (4.6 M, 0.03 mL, 0.14 mmol). The mixture was warmed to 40 °C in a preheated bath and stirred for 30 min. After cooling to rt the residue (3.73 g, 40.5 mmol) was taken into CH_2Cl_2 (80 mL) under Ar at rt and TBSCl (6.72 g, 44.6 mmol) was added, followed by imidazole (5.51 g, 81 mmol) portionwise. The suspension was stirred at rt for 30 min before adding NH_4Cl (50 mL) and extracting with CH_2Cl_2 (4 x 80 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure, giving the title compound (**2.110**) (8.09 g, 39.2 mmol, 98%) as a clear oil. The analytical data acquired was in accordance with previously reported values.[122]

FT-IR (neat) ν_{max} 2929 (m, C-H), 1061 (s, O-C) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.82 (2H, s, C<u>H</u>$_2$O), 2.68 (2H, q, *J* = 7.3 Hz, CH$_3$C<u>H</u>$_2$S), 1.30 (3H, t, *J* = 7.3 Hz, C<u>H</u>$_3$CH$_2$S), 0.91 (9H, s C(C<u>H</u>$_3$)$_3$), 0.13 (6H, s, SiC<u>H</u>$_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 66.0 (t, <u>C</u>H$_2$O), 25.8 (q, C(<u>C</u>H$_3$)$_3$), 24.5 (t, CH$_3$<u>C</u>H$_2$S), 18.2 (s, Si<u>C</u>(CH$_3$), 14.9 (q, <u>C</u>H$_3$CH$_2$), –5.1 (q, Si<u>C</u>H$_3$) ppm.

2.111 - Dimethyl 2-(((tert-butyldimethylsilyl)oxy)methyl)-2-(3-methylbut-2-en-1-yl)malonate



$C_{17}H_{32}O_5Si$
M.W. = 344.52 g/mol

Following a procedure by Wang *et al.*,[221] to a stirred solution of thioether **2.110** (1.55 g, 7.50 mmol) in CH_2Cl_2 (15 mL) under Ar at 0 °C was added SO_2Cl_2 (0.61 mL, 7.50 mmol) in CH_2Cl_2 (15 mL) dropwise over 5 min. After 30 min at 0 °C, the solution was warmed to rt and stirred for a further 10 min. The solution was carefully concentrated under reduced pressure (~24 °C, +100 torr), before diluting in dry CH_2Cl_2 (10 mL) and concentrating in the same manner. This dilution and concentration was repeated 2 more times to give the crude chloro intermediate as a pale yellow oil.

In a separate flask, to a stirred suspension of NaH (220 mg, 5.49 mmol) in THF (20 mL) at 0 °C under Ar was added prenyl malonate **2.06** (1.00 g, 4.99 mmol) in THF (5 mL) dropwise. After 45 min at rt, the aforementioned crude chloride intermediate in THF (5 mL) was added dropwise, before stirring the resulting suspension at rt for 18 h. NH_4Cl (20 mL) was added and extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:petrol, 1:20) gave the title compound (**2.111**) (1.16 g, 3.37 mmol, 68%) as a clear oil.

FT-IR (neat) ν_{max} 2931 (m, C-H), 1736 (s, C=O), 1100 (s, O-C), 1061 (s, O-C) cm^{-1}.

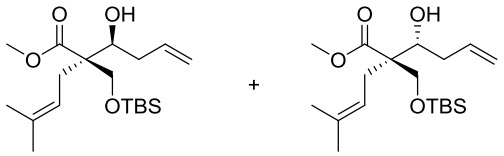
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.93 (1H, t, *J* = 7.6 Hz, C=C<u>H</u>), 3.95 (2H, s, C<u>H$_2$</u>O), 3.71 (6H, s, OC<u>H$_3$</u>), 2.74 (2H, d, *J* = 7.6 Hz, C<u>H$_2$</u>CH), 1.70 (3H, s, CC<u>H$_3$</u>), 1.63 (3H, s, CC<u>H$_3$</u>), 0.86 (9H, s, SiC(C<u>H$_3$</u>)$_3$), 0.02 (6H, s, SiC<u>H$_3$</u>) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4 (s, <u>C</u>=O), 136.1 (s, <u>C</u>=CH), 117.6 (d, C=<u>C</u>H), 62.7 (t, <u>C</u>H$_2$O), 59.8 (s, <u>C</u>C=O), 52.2 (q, O<u>C</u>H$_3$), 28.8 (t, <u>C</u>H$_2$CH), 26.0 (q, C<u>C</u>H$_3$), 25.6 (q, C(<u>C</u>H$_3$)$_3$), 18.0 (s, <u>C</u>(CH$_3$)$_3$), 17.9 (q, C<u>C</u>H$_3$), -5.7 (q, Si<u>C</u>H$_3$) ppm.

LRMS (ES$^+$) *m/z* 367 $[M+Na]^+$, 345 $[M+H]^+$.

HRMS (ES^+) For $C_{17}H_{32}O_5SiNa$ calculated 367.1911, found 367.1918 Da.

2.112a and 2.112b - (±)-Methyl (*R*)-2-(((tert-butyldimethylsilyl)oxy)methyl)-2-((*S*)-1-hydroxybut-3-en-1-yl)-5-methylhex-4-enoate and (±)-Methyl (*S*)-2-(((tert-butyldimethylsilyl)oxy)methyl)-2-((*S*)-1-hydroxybut-3-en-1-yl)-5-methylhex-4-enoate

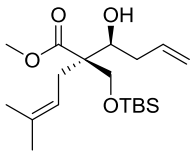


$C_{19}H_{36}O_4Si$
M.W. = 356.58 g/mol

To a stirred solution of diester **2.111** (1.00 g, 2.90 mmol) in CH_2Cl_2 (20 mL) under Ar at −78 °C was added DIBAL (1 M in hexanes, 5.80 mL, 5.80 mmol) dropwise over 45 min. After 4 h, Rochelle salt (10 mL) was carefully added at −78 °C before warming to rt and diluting in CH_2Cl_2 (100 mL) and Rochelle salt (125 mL). After stirring for 1 h the aq. phase was extracted with CH_2Cl_2 (3 x 150 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure, to give the crude mono-aldehyde (908 mg).

In a separate flask, by adaptation of the procedure by Linclau *et al.*,[99] to a stirred suspension of Mg (219 mg, 9.00 mg-atom) in Et_2O (6.4 mL) under Ar at rt was added 1,2-dibromoethane (0.78 mL, 9.00 mmol). After 30 min the solvent was removed under reduced pressure, and the residue was resuspended in CH_2Cl_2 (3.6 mL) under Ar and cooled to −78 °C. To this was added the aforementioned crude aldehyde in CH_2Cl_2 (5.4 mL) dropwise over 1h. After 30 min at −78 °C, allyltributylstannane (1.08 mL, 3.48 mmol) in CH_2Cl_2 (6.4 mL) was added dropwise over 1h. After 2 h at −78 °C $NaHCO_3$ (10 mL) was added and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure giving a crude dr of 3.8:1. Purification by column chromatography (EtOAc:petrol, 1:30→1:10 with a plug of K_2CO_3) gave the separated title compounds (**2.112a** and **2.112b**) (**a** 662 mg, 1.86 mmol, 65%. **b** 158 mg, 0.44 mmol, 15%) as a clear oils.

2.112a - (±)-Methyl (*R*)-2-(((tert-butyldimethylsilyl)oxy)methyl)-2-((*S*)-1-hydroxybut-3-en-1-yl)-5-methylhex-4-enoate.



$C_{19}H_{36}O_4Si$
M.W. = 356.56 g/mol

FT-IR (neat) ν_{max} 3502 (br, O-H), 2929 (m, C-H), 1734 (m, C=O), 1641 (w, C=C), 1093 (s, O-C), 1060 (s, O-C) cm^{-1}.

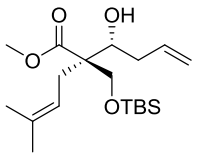
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.93 (1H, m, CH_2=C<u>H</u>), 5.15 – 5.06 (2H, m, C<u>H$_2$</u>CH), 4.99 (1H, t, *J* = 7.1 Hz, C=C<u>H</u>), 4.00 (1H, d, *J* = 10.2 Hz, C<u>H</u>HO), 3.94 (1H, apparent t, *J* = 9.1 Hz, C<u>H</u>OH), 3.77 (1H, d, *J* = 10.2 Hz, CH<u>H</u>O), 3.70 (3H, s, OC<u>H$_3$</u>), 3.23 (1H, d, *J* = 8.2 Hz, CHO<u>H</u>), 2.46 (1H, dd, *J* = 14.3, 7.0 Hz, C<u>H</u>HCH=C), 2.40 – 2.31 (2H, m, CH<u>H</u>CH=C, C<u>H</u>HCHOH), 2.20 (1H, m, CH<u>H</u>CHOH), 1.69 (3H, s, CC<u>H$_3$</u>), 1.62 (3H, s, CC<u>H$_3$</u>), 0.90 (9H, s, SiC(C<u>H$_3$</u>)$_3$), 0.09 (3H, br. s., SiC<u>H$_3$</u>), 0.08 (3H, br. s., SiC<u>H$_3$</u>) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.5 (s, <u>C</u>=O), 135.8 (d, <u>C</u>H=CH$_2$), 134.8 (s, <u>C</u>=CH), 118.7 (d, C=<u>C</u>H), 116.8 (t, CH=<u>C</u>H$_2$), 74.8 (d, <u>C</u>HOH), 63.9 (t, <u>C</u>H$_2$O), 55.4 (s, <u>C</u>CHOH), 51.6 (q, O<u>C</u>H$_3$), 37.3 (t, <u>C</u>H$_2$CHHOH), 29.6 (<u>C</u>H$_2$CH=C), 26.0 (q, C<u>C</u>H$_3$), 25.8 (s, SiC(<u>C</u>H$_3$)$_3$), 18.1 (s, Si<u>C</u>(CH$_3$)$_3$), 17.9 (q, C<u>C</u>H$_3$), -5.7 (q, Si<u>C</u>H$_3$), -5.8 (q, Si<u>C</u>H$_3$) ppm.

LRMS (ES^+) *m/z* 357 $[M+H]^+$.

HRMS (ES^+) For $C_{19}H_{36}O_4SiNa$ calculated 379.2275, found 379.2267 Da.

2.112b - (±)-Methyl (*R*)-2-(((tert-butyldimethylsilyl)oxy)methyl)-2-((*R*)-1-hydroxybut-3-en-1-yl)-5-methylhex-4-enoate.



$C_{19}H_{36}O_4Si$
M.W. = 356.58 g/mol

FT-IR (neat) ν_{max} 3502 (br, O-H), 2929 (m, C-H), 1731 (m, C=O), 1642 (w, C=C), 1094 (s, O-C), 1049 (s, O-C) cm^{-1}.

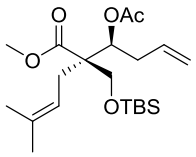
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91 (1H, m, C<u>H</u>=CH_2), 5.13 – 4.99 (3H, m, CH=C<u>H</u>$_2$, C=C<u>H</u>), 4.03 (1H, d, *J* = 10.4 Hz, C<u>H</u>HO), 3.92 (1H, m, C<u>H</u>OH), 3.86 (1H, d, *J* = 10.4 Hz, CH<u>H</u>O), 3.66 (3H, s, OC<u>H</u>$_3$), 3.33 (1H, d, *J* = 8.8 Hz, CHO<u>H</u>), 2.61 (1H, dd, *J* = 14.7, 8.1 Hz, C<u>H</u>HCH=C), 2.49 (1H, dd, *J* = 14.7, 7.0 Hz, CH<u>H</u>CH=C), 2.26 (2H, t, *J* = 6.5 Hz, C<u>H</u>$_2$CHOH), 1.70 (3H, s, CC<u>H</u>$_3$), 1.63 (3H, s, CC<u>H</u>$_3$), 0.90 (9H, s, SiC(C<u>H</u>$_3$)$_3$), 0.10 (3H, s, SiC<u>H</u>$_3$), 0.08 (3H, s, SiC<u>H</u>$_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.3 (s, <u>C</u>=O), 135.8 (d, <u>C</u>H=CH_2), 135.0 (s, <u>C</u>=CH), 118.6 (d, C=<u>C</u>H), 116.7 (t, CH=<u>C</u>H$_2$), 74.9 (d, <u>C</u>HOH), 63.6 (t, <u>C</u>H$_2$O), 54.4 (s, <u>C</u>CHOH), 51.6 (q, O<u>C</u>H$_3$), 38.5 (t, <u>C</u>H$_2$CHOH), 30.1 (t, <u>C</u>H$_2$CH=C), 26.0 (q, C<u>C</u>H$_3$), 25.8 (q, SiC(<u>C</u>H$_3$)$_3$), 18.0 (s, Si<u>C</u>(CH$_3$)$_3$), 17.9 (q, C<u>C</u>H$_3$), -5.8 (q, Si<u>C</u>H$_3$) ppm.

LRMS (ES^+) *m/z* 357 $[M+H]^+$.

HRMS (ES^+) For $C_{19}H_{36}O_4SiNa$ calculated 379.2275, found 379.2274 Da.

2.113 - (±)-Methyl (*R*)-2-((*S*)-1-acetoxybut-3-en-1-yl)-2-(((tert-butyldimethylsilyl)oxy) methyl)-5-methylhex-4-enoate.



$C_{21}H_{38}O_5Si$
M. W. = 398.61 g/mol

To a stirred solution of alcohol **2.112a** (522 mg, 1.31 mmol) and DMAP (48 mg, 0.39 mmol) in CH_2Cl_2 (11 mL) under Ar at 0 °C was added DIPEA (0.46 mL, 2.62 mL) then Ac_2O (0.19 mL, 1.97 mmol) dropwise. After 4 h at rt, NH_4Cl (10 mL) was added and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:hexane, 1:10) gave the title compound (**2.113**) (525 mg, 1.26 mmol, 96%) as a clear oil.

FT-IR (neat) ν_{max} 2929 (m, C-H), 1743 (s, C=O), 1643 (w, C=C), 1097 (s, O-C) cm^{-1}.

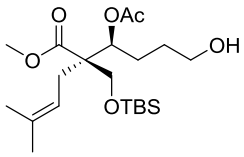
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 (1H, m, C<u>H</u>=CH_2), 5.38 (1H, dd, *J* = 10.2, 3.1 Hz, C<u>H</u>O), 5.06 – 4.98 (3H, m, CH=C<u>H</u>$_2$, C=C<u>H</u>), 3.83 (1H, d, *J* = 10.2 Hz, C<u>H</u>HO), 3.76 (1H, d, *J* = 10.2 Hz, CH<u>H</u>O), 3.66 (3H, s, OC<u>H</u>$_3$), 2.46 – 2.37 (4H, m, C<u>H</u>$_2$CH=CH_2, C<u>H</u>$_2$CH=C), 2.01 (3H, s, C<u>H</u>$_3$C=O), 1.69 (3H, d, *J* = 0.9 Hz, CC<u>H</u>$_3$), 1.62 (3H, s, CC<u>H</u>$_3$), 0.90 (9H, s, SiC(C<u>H</u>$_3$)$_3$), 0.06 (3H, s, SiC<u>H</u>$_3$), 0.04 (3H, s, SiC<u>H</u>$_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4 (s, <u>C</u>=O), 170.1 (s, <u>C</u>=O), 134.7 (d, <u>C</u>H=CH_2), 134.5 (s, <u>C</u>=CH), 118.9 (d, C=<u>C</u>H), 117.2 (t, CH=<u>C</u>H$_2$), 74.2 (d, <u>C</u>HO), 62.1 (t, <u>C</u>H$_2$O), 55.1 (s, <u>C</u>CHO), 51.5 (q, O<u>C</u>H$_3$), 35.6 (t, <u>C</u>H$_2$CHO), 28.6 (t, <u>C</u>H$_2$CH=C), 26.0 (q, C<u>C</u>H$_3$), 25.8 (q, SiC(<u>C</u>H$_3$)), 20.9 (q, <u>C</u>H$_3$C=O), 18.1 (s, Si<u>C</u>(CH$_3$)$_3$), 18.0 (q, C<u>C</u>H$_3$), –5.7 (q, Si<u>C</u>H$_3$), –5.8 (q, Si<u>C</u>H$_3$) ppm.

LRMS (ES$^+$) *m/z* 421 [M+Na]$^+$, 399 [M+H]$^+$.

HRMS (ES$^+$) For $C_{21}H_{38}O_5SiNa$ calculated 421.2381, found 421.2382 Da.

2.114 - (±)-Methyl (*R*)-2-((*S*)-1-acetoxy-4-hydroxybutyl)-2-(((tert-butyldimethylsilyl) oxy)methyl)-5-methylhex-4-enoate



$C_{21}H_{40}O_6Si$
M. W. = 416.63 g/mol

To a stirred solution of diene **2.113** (500 mg, 1.25 mmol) in THF (9 mL) under Ar at 0 °C was added 9-BBN dimer (381 mg, 1.56 mmol) in THF (5 mL) over 5 min. After 1.5 h at rt, the solution was cooled to 0 °C and NaOAc (2.05 g, 25.0 mmol) in H_2O (6.5 mL) was added dropwise, followed by H_2O_2 (30%, 3.12 mL, 27.5 mmol) dropwise. After 1 h at rt, the solvent was removed under reduced pressure and the aq. phase was extracted with EtOAc (4 x 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:hexane, 1:1) gave the title compound (**2.114**) (439 mg, 1.05 mmol, 84%) as a clear oil.

FT-IR (neat) ν_{max} 3433 (br, O-H), 2929 (m, C-H), 1741 (s, C=O), 1233 (s, O-C), 1095 (s, O-C) cm^{-1}.

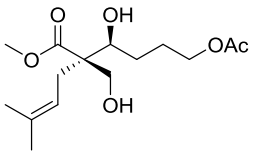
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.37 (1H, dd, *J* = 10.3, 2.5 Hz, C<u>H</u>O), 5.04 (1H, finely coupled t, *J* = 7.3 Hz, C=C<u>H</u>), 3.80 (1H, d, *J* = 10.2 Hz, C<u>H</u>HOSi), 3.75 (1H, d, *J* = 10.2 Hz, CH<u>H</u>OSi), 3.69 – 3.62 (5H, m, OC<u>H</u>$_3$, C<u>H</u>$_2$OH), 2.41 (2H, d, *J* = 7.3 Hz, C<u>H</u>$_2$CH=C), 2.06 (3H, s, CC<u>H</u>$_3$), 1.77 – 1.64 (5H, m, CC<u>H</u>$_3$, C<u>H</u>$_2$CHO), 1.62 (3H, s, CC<u>H</u>$_3$), 1.57 – 1.50 (2H, m, C<u>H</u>$_2$CH$_2$OH), 0.89 (9H, s, SiC(C<u>H</u>$_3$)$_3$), 0.05 (3H, s, SiC<u>H</u>$_3$), 0.03 (3H, s, SiC<u>H</u>$_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6 (s, <u>C</u>=O), 170.5 (s, <u>C</u>=O), 134.4 (s, <u>C</u>=CH), 119.0 (d, C=<u>C</u>H), 74.8 (d, <u>C</u>HO), 62.4 (t, <u>C</u>H$_2$OH), 62.2 (t, <u>C</u>H$_2$OSi), 55.4 (s, <u>C</u>CHO), 51.6 (q, O<u>C</u>H$_3$), 29.4 (t, <u>C</u>H$_2$CH$_2$OH), 28.5 (t, <u>C</u>H$_2$CH=C), 27.0 (t, <u>C</u>H$_2$CHO), 26.1 (q, C<u>C</u>H$_3$), 25.8 (q, SiC(<u>C</u>H$_3$)$_3$), 21.0 (q, <u>C</u>H$_3$C=O), 18.1 (s, Si<u>C</u>(CH$_3$)$_3$), 18.0 (q, C<u>C</u>H$_3$), –5.7 (q, Si<u>C</u>H$_3$), –5.8 (q, Si<u>C</u>H$_3$) ppm.

LRMS (ES$^+$) *m/z* 417 [M+H]$^+$.

HRMS (ES$^+$) For $C_{21}H_{40}O_6SiNa$ calculated 439.2486, found 439.2490 Da.

2.116 - (±)-Methyl (*R*)-2-((*S*)-1-acetoxy-4-hydroxybutyl)-2-(hydroxymethyl)-5-methyl hex-4-enoate



$C_{15}H_{26}O_6$
M. W. = 302.37 g/mol

To a stirred solution of alcohol **2.114** (410 mg, 0.98 mmol) in THF (10 mL) under Ar at 0 °C was added TBAF (1 M in THF, 1.96 mL, 1.96 mmol) dropwise. After stirring at rt for 18 h, the solution was cooled to 0 °C and TBAF (1 M in THF, 0.98 mL, 0.98 mmol) was added dropwise, before warming to rt and stirring for a further 2.5 h. NH_4Cl (10 mL) was added and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:hexane, 1:1) gave the title compound (**2.116**) (148 mg, 0.49 mmol, 50%) as a clear oil.

FT-IR (neat) ν_{max} 3439 (br, O-H), 2951 (w, C-H), 1722 (s, C=O), 1230 (s, O-C), 1033 (s, O-C) cm^{-1}.

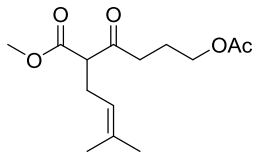
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.91 (1H, finely coupled t, *J* = 7.6 Hz, C=C<u>H</u>), 4.13 (2H, td, *J* = 6.5, 3.2 Hz, $CH_2C\underline{H}_2O$), 4.02 – 3.90 (2H, m, $C\underline{H}_2OH$), 3.80 – 3.74 (4H, m, $OC\underline{H}_3$, C<u>H</u>OH), 3.20 (1H, d, *J* = 8.3 Hz, CHO<u>H</u>), 3.06 (1H, t, *J* = 6.0 Hz, CH_2OH), 2.18 (1H, dd, *J* = 14.6, 7.5 Hz, C<u>H</u>HCH=C), 2.13 – 1.97 (5H, m, CH<u>H</u>CH=C, $C\underline{H}_3C$=O, C<u>H</u>HCH_2OH), 1.74 (1H, m, CH<u>H</u>CH_2OH), 1.68 (3H, s, $CC\underline{H}_3$), 1.63 – 1.50 (5H, m, $CC\underline{H}_3$, $C\underline{H}_2$CHOH) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.0 (s, <u>C</u>=O), 171.1 (s, <u>C</u>=O), 135.4 (s, <u>C</u>=CH), 117.5 (d, C=<u>C</u>H), 75.7 (d, <u>C</u>HOH), 65.1 (t, $\underline{C}H_2OH$), 64.3 (t, $CH_2\underline{C}H_2O$), 55.5 (s, <u>C</u>CHO), 52.1 (q, $O\underline{C}H_3$), 30.7 (t, $\underline{C}H_2CH$=C), 28.0 (t, $\underline{C}H_2$CHOH), 25.9 (q, $C\underline{C}H_3$), 25.8 (t, $\underline{C}H_2CH_2O$), 21.0 (q, $\underline{C}H_3C$=O), 17.8 (q, $C\underline{C}H_3$) ppm.

LRMS (ES$^+$) *m/z* 303 [M+H]$^+$.

HRMS (ES$^+$) For $C_{15}H_{26}O_6Na$ calculated 325.1622, found 325.1620 Da.

2.117 - (±)-Methyl 2-(4-acetoxybutanoyl)-5-methylhex-4-enoate



$C_{14}H_{22}O_5$
M.W. = 270.32 g/mol

To a stirred solution of alcohol **2.116** (120 mg, 0.40 mmol) in CH_2Cl_2 (7 mL) under Ar at rt was added DMP (445 mg, 1.05 mmol) in 3 portions. The suspension was stirred at rt for 24 h before addition of DMP (85 mg, 0.20 mmol) and CH_2Cl_2 (3 mL). After a further 3.5 h the suspension was filtered through a pad of silica, washing with CH_2Cl_2 then EtOAc, and concentrated under reduced pressure to give the title compound (**2.117**) (102 mg, 0.38 mmol, 95%) as a clear oil.

FT-IR (neat) ν_{max} 2956 (w, C-H), 1736 (s, C=O), 1715 (s, C=O), 1233 (s, O-C) cm^{-1}.

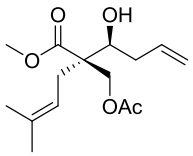
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.01 (1H, finely coupled t, *J* = 7.3 Hz, C=C<u>H</u>), 4.06 (2H, t, *J* = 6.5 Hz, C<u>H</u>$_2$O), 3.73 (3H, s, OC<u>H</u>$_3$), 3.48 (1H, t, *J* = 7.5 Hz, C<u>H</u>C=O), 2.70 – 2.50 (4H, m, C<u>H</u>$_2$CH, C<u>H</u>$_2$CO), 2.05 (3H, s, C<u>H</u>$_3$CO), 1.92 (2H, quin, *J* = 6.7 Hz, C<u>H</u>$_2$CH$_2$O), 1.68 (3H, d, *J* = 0.9 Hz, CC<u>H</u>$_3$), 1.63 (3H, s, C<u>C</u>H$_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 204.1 (s, CH$_2$<u>C</u>=O), 171.0 (s, <u>C</u>=O), 169.9 (s, <u>C</u>=O), 135.0 (s, <u>C</u>=CH), 119.6 (d, C=<u>C</u>H), 63.4 (t, <u>C</u>H$_2$O), 58.9 (d, <u>C</u>HCO), 52.4 (q, O<u>C</u>H$_3$), 38.5 (t, <u>C</u>H$_2$CO), 27.1 (t, <u>C</u>H$_2$CH), 25.7 (q, C<u>C</u>H$_3$), 22.5 (t, <u>C</u>H$_2$CH$_2$O), 20.9 (q, <u>C</u>H$_2$CO), 17.7 (q, C<u>C</u>H$_3$) ppm.

LRMS (ES$^+$) *m/z* 293 [M+H]$^+$.

HRMS (ES$^+$) For $C_{14}H_{22}O_5Na$ calculated 293.1359, found 293.1358 Da.

2.119 - (±)-Methyl (*R*)-2-(acetoxymethyl)-2-((*S*)-1-hydroxybut-3-en-1-yl)-5-methylhex-4-enoate



$C_{15}H_{24}O_5$
M.W. = 284.35 g/mol

By adaptation of the procedure by DiLauro *et al.*,[125] to a solution of TBAF (1 M in THF, 1.80 mL, 1.80 mmol) under Ar at rt was added pH 7 phosphate buffer solution (0.18 mL) which was sonicated for 3 min.

In a separate flask, to a stirred solution of acetate **2.113** (50 mg, 0.13 mmol) in THF (1.3 mL) under Ar at 0 ˚C was added the aforementioned buffered TBAF solution (0.14 mL, 0.13 mmol). After 36 h at rt, NH_4Cl (2 mL) was added, and extracted with EtOAc (3 x 4 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:hexane, 1:2) gave the title compound (**2.119**) (18 mg, 0.06 mmol, 46%) as a clear oil.

FT-IR (neat) ν_{max} 3521 (br, O-H), 2917 (w, C-H), 1731 (s, C=O), 1642 (w, C=C), 1223 (s, O-C) cm^{-1}.

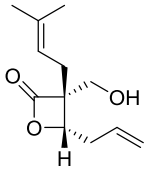
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 (1H, m, C<u>H</u>=CH_2), 5.15 (1H, m, CH=C<u>H</u>H), 5.11 (1H, m, CH=CH<u>H</u>), 5.02 (1H, m, C=C<u>H</u>), 4.31 (2H, s, C<u>H</u>$_2$O), 3.87 (1H, ddd, *J* = 10.1, 7.6, 2.5 Hz, C<u>H</u>OH), 3.73 (3H, s, OC<u>H</u>$_3$), 2.58 – 2.51 (2H, m, O<u>H</u>, C<u>H</u>HCH=C), 2.49 – 2.35 (2H, m, CH<u>H</u>CH=C, C<u>H</u>HCHOH), 2.12 (1H, m, CH<u>H</u>CHOH), 2.07 (3H, s, C<u>H</u>$_3$C=O), 1.70 (3H, s, CC<u>H</u>$_3$), 1.61 (3H, s, CC<u>H</u>$_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1 (s, <u>C</u>=O), 170.5 (s, <u>C</u>=O), 135.7 (s, <u>C</u>=CH), 135.1 (d, <u>C</u>H=CH_2), 117.9 (d, C=<u>C</u>H), 117.7 (t, CH=<u>C</u>H$_2$), 73.0 (d, <u>C</u>HOH), 63.6 (t, <u>C</u>H$_2$O), 53.9 (s, <u>C</u>CHOH), 52.0 (q, O<u>C</u>H$_3$), 37.3 (t, <u>C</u>H$_2$CHOH), 29.9 (t, <u>C</u>H$_2$CH=C), 26.0 (q, C<u>C</u>H$_3$), 20.9 (q, <u>C</u>H$_3$C=O), 17.8 (q, C<u>C</u>H$_3$) ppm.

LRMS (ES$^+$) *m/z* 285 $[M+H]^+$.

HRMS (ES$^+$) For $C_{15}H_{24}O_5Na$ calculated 307.1516, found 307.1519 Da.

2.122a - (±)- (3*R*,4*S*)-4-Allyl-3-(hydroxymethyl)-3-(3-methylbut-2-en-1-yl)oxetan-2-one



$C_{12}H_{18}O_3$
M.W. = 210.27 g/mol

To a stirred solution of ester **2.112a** (400 mg, 1.12 mmol) in MeOH (8.4 mL) and H_2O (2.1 mL) at rt was added $LiOH \cdot H_2O$ (282 mg, 6.72 mmol). After 24 h another portion of $LiOH \cdot H_2O$ (188 mmol, 4.48 mmol) was added. The solution was heated to 50 °C and stirred for 4 h before cooling to rt and removing the solvent under reduced pressure. The residue was acidified to ~pH 2 with citric acid (1 M) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure, giving the crude hydroxyacid (273 mg).

In a separate flask, the aforementioned crude hydroxyacid was taken into pyridine (15 mL) under Ar and cooled to 0 °C before adding *p*-TsCl (280 mg, 1.47 mmol). The solution was stirred at 0 °C for 1 h then left to stand in a fridge overnight. Ice (~10 mL) was added, and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with $NaHCO_3$ (15 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:hexane, 1:2) gave the title compound (**2.122a**) (163 mg, 0.78 mmol, 70%) as a clear oil.

FT-IR (neat) ν_{max} 3477 (br, O-H), 2916 (w, C-H), 1802 (s, C=O), 1642 (w, C=C), 1129 (m, O-C), 1038 (m, O-C) cm^{-1}.

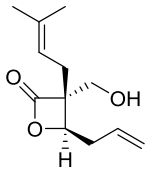
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (1H, m, C<u>H</u>=CH_2), 5.27 – 5.12 (3H, m, C=C<u>H</u>, CH=C<u>H</u>$_2$), 4.43 (1H, dd, *J* = 8.1, 6.4 Hz, C<u>H</u>O), 3.92 (2H, d, *J* = 5.1 Hz, C<u>H</u>$_2$OH), 2.85 – 2.66 (2H, m, C<u>H</u>$_2$CH=CH_2), 2.49 (2H, d, *J* = 7.7 Hz, C<u>H</u>$_2$CH=C), 1.77 – 1.72 (4H, m, CC<u>H</u>$_3$, O<u>H</u>), 1.66 (3H, s, CC<u>H</u>$_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3 (s, <u>C</u>=O), 137.1 (s, <u>C</u>=CH), 132.3 (d, <u>C</u>H=CH_2), 118.5 (t, CH=<u>C</u>H$_2$), 116.7 (d, C=<u>C</u>H), 79.1 (d, <u>C</u>HO), 63.6 (s, <u>C</u>CO), 60.8 (t, <u>C</u>H$_2$OH), 34.0 (t, <u>C</u>H$_2$CH=CH_2), 29.6 (t, <u>C</u>H$_2$CH=C), 25.9 (q, C<u>C</u>H$_3$), 18.0 (q, C<u>C</u>H$_3$) ppm.

LRMS (ES$^+$) *m/z* 211 $[M+H]^+$.

HRMS (ES$^+$) For $C_{12}H_{18}O_3Na$ calculated 233.1148, found 233.1153 Da.

2.122b - (±)- (3*S*,4*S*)-4-Allyl-3-(hydroxymethyl)-3-(3-methylbut-2-en-1-yl)oxetan-2-one



$C_{12}H_{18}O_3$
M.W. = 210.27 g/mol

To a stirred solution of ester **2.112b** (73 mg, 0.20 mmol) in MeOH (1.6 mL) and H_2O (0.4 mL) at rt was added $LiOH \cdot H_2O$ (50 mg, 1.19 mmol). The solution was stirred at rt for 18 h before removing the solvent under reduced pressure. The residue was diluted with H_2O (1 mL), acidified to ~pH 2 with HCl (2 N) and extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure, providing the crude hydroxyacid.

In a separate flask, the aforementioned crude hydroxyacid was taken into pyridine (4.2 mL) under Ar and cooled to 0 °C before adding *p*-TsCl (42 mg, 0.22 mmol). The solution was stirred at 0 °C for 1 h then left to stand in a fridge for 36 h. Ice (~5 mL) was added, and extracted with EtOAc (3 x 8 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:hexane, 1:2) gave the title compound (**2.122b**) (22 mg, 0.10 mmol, 50%) as a clear oil.

FT-IR (neat) ν_{max} 3467 (br, O-H), 2917 (w, C-H), 1802 (s, C=O), 1643 (w, C=C), 1076 (m, O-C), 1044 (m, O-C) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (1H, ddt, *J* = 17.1, 10.4, 6.5 Hz, C<u>H</u>=CH$_2$), 5.25 – 5.14 (3H, m, CH=C<u>H</u>$_2$,C=C<u>H</u>), 4.72 (1H, dd, *J* = 8.9, 5.2 Hz, C<u>H</u>O), 3.93 (1H, dd, *J* = 11.4, 5.3 Hz, C<u>H</u>HO), 3.72 (1H, dd, *J* = 11.4, 5.4 Hz, CH<u>H</u>O), 2.65 (1H, m, C<u>H</u>HCHO), 2.59 – 2.49 (2H, m, CH<u>H</u>CHO, C<u>H</u>HCH=C), 2.42 (1H, dd, *J* = 15.2, 7.7 Hz, CH<u>H</u>CH=C), 1.88 (1H, t, *J* = 5.6 Hz, O<u>H</u>), 1.74 (3H, d, *J* = 0.7 Hz, CC<u>H</u>$_3$), 1.64 (3H, s, CC<u>H</u>$_3$) ppm.

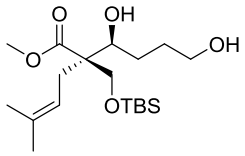
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6 (s, <u>C</u>=O), 136.0 (s, <u>C</u>=CH), 132.1 (d, <u>C</u>H=CH$_2$), 118.5 (t, CH=<u>C</u>H$_2$), 117.1 (d, C=<u>C</u>H), 77.4 (d, <u>C</u>HO), 63.4 (s, <u>C</u>CH$_2$O), 62.5 (t,

$\underline{C}H_2O$), 34.3 (t, $\underline{C}H_2CH=CH_2$), 25.9 (q, $C\underline{C}H_3$), 25.2 (t, $\underline{C}H_2CH=C$), 17.9 (q, $C\underline{C}H_3$) ppm.

LRMS (ES$^+$) *m/z* 211 $[M+H]^+$.

HRMS (ES$^+$) For $C_{12}H_{18}O_3Na$ calculated 233.1148, found 233.1148 Da.

2.125 - (±)-Methyl (*R*)-2-(((tert-butyldimethylsilyl)oxy)methyl)-2-((*S*)-1,4-dihydroxy butyl)-5-methylhex-4-enoate



$C_{19}H_{38}O_5Si$
M.W. = 374.59 g/mol

To a stirred solution of alcohol **2.112a** (301 mg, 0.84 mmol) in THF (12 mL) under Ar at 0 °C was added 9-BBN dimer (256 mg, 1.05 mmol) in THF (10 mL) over 5 min. After 3 h at rt, the solution was cooled to 0 °C and NaOAc (1.38 g, 16.8 mmol) in H_2O (4 mL) was added dropwise, followed by H_2O_2 (30%, 2.10 mL, 18.5 mmol) dropwise. After 2 h at rt, the solvent was removed under reduced pressure, and the aq. phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:hexane, 1:1) gave the title compound (**2.125**) (316 mg, 0.84 mmol, 100%) as a clear oil.

FT-IR (neat) ν_{max} 3390 (br, O-H), 2929 (m, C-H), 1727 (m, C=O), 1252 (m, O-C), 1073 (s, O-C) cm^{-1}.

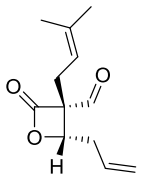
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.96 (1H, finely coupled t, *J* = 7.8 Hz, C=C$\underline{H}$), 4.02 (1H, d, *J* = 10.2 Hz, C$\underline{H}$HOSi), 3.90 (1H, apparent d, *J* = 10.6 Hz, C$\underline{H}$OH), 3.76 (1H, d, *J* = 10.2 Hz, CH$\underline{H}$OSi), 3.73 – 3.64 (5H, m, O$C\underline{H}_3$, $C\underline{H}_2OH$), 2.40 (1H, dd, *J* = 14.6, 7.1 Hz, C$\underline{H}$HCH=C), 2.27 (1H, dd, *J* = 14.6, 7.8 Hz, CH$\underline{H}$CH=C), 1.87 – 1.72 (3H, m, $C\underline{H}_2$CHOH, C$\underline{H}HCH_2OH$), 1.68 (3H, s, $CC\underline{H}_3$), 1.60 (3H, s, $CC\underline{H}_3$), 1.44 (1H, m, CH$\underline{H}CH_2OH$) 0.89 (9H, s, $SiC(C\underline{H}_3)_3$), 0.09 (3H, s, $SiC\underline{H}_3$), 0.08 (3H, s, $SiC\underline{H}_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.5 (s, C=O), 134.8 (s, C=CH), 118.5 (d, C=CH), 75.8 (d, CHOH), 64.5 (t, CH_2OSi), 62.9 (t, CH_2OH), 55.5 (s, CCHOH), 51.7 (q, OCH_3), 30.4 (t, $CH_2CH=C$), 30.0 (t, CH_2CHOH), 29.6 (t, CH_2CH_2OH), 26.0 (q, CCH_3), 25.7 (q, $SiC(CH_3)_3$), 18.0 (s, $SiC(CH_3)_3$), 17.9 (q, CCH_3), −5.8 (q, $SiCH_3$), −5.8 (q, $SiCH_3$) ppm.

LRMS (ES^+) *m/z* 375 $[M+H]^+$.

HRMS (ES^+) For $C_{19}H_{38}O_5SiNa$ calculated 397.2381, found 397.2381 Da.

2.130 - (±)- (2*S*,3*S*)-2-Allyl-3-(3-methylbut-2-en-1-yl)-4-oxooxetane-3-carbaldehyde



$C_{12}H_{16}O_3$
M.W. = 208.26 g/mol

To a stirred solution of DMSO (26 µL, 0.36 mmol) in CH_2Cl_2 (1.5 mL) under Ar at −78 °C was added oxalyl chloride (11 µL, 0.20 mmol) dropwise. The solution was stirred at −78 °C for 10 min before addition of alcohol **2.122a** (38 mg, 0.18 mmol) in CH_2Cl_2 (1.5 mL) dropwise. After a further 15 min at −78 °C Et_3N (0.11 mL, 0.81 mmol) was added, and the solution was then allowed to warm to rt, before stirring for 30 min. NH_4Cl (2 mL) was then added before diluting with CH_2Cl_2 (10 mL) and washing with NH_4Cl (3 x 5 mL), citric acid (1 M, 5 mL) and H_2O (5 mL). The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure, to give the title compound (**2.130**) (35 mg, 0.17 mmol, 94%) as a pale orange oil.

FT-IR (neat) ν_{max} 2921 (w, C-H), 1825 (s, C=O), 1719 (m, C=O), 1643 (w, C=C) cm^{-1}.

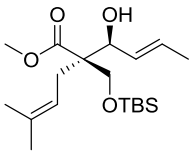
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (1 H, s, O=CH), 5.74 (1 H, ddt, *J* = 17.1, 10.4, 6.7 Hz, $CH=CH_2$), 5.25 – 5.11 (3 H, m, $CH=CH_2$, C=CH), 4.50 (1 H, t, *J* = 7.2 Hz, CHO), 2.73 (2 H, d, *J* = 7.8 Hz, $CH_2CH=C$), 2.69 – 2.64 (2 H, m, $CH_2CH=CH_2$), 1.76 (3 H, s, CCH_3), 1.67 (3 H, s, CCH_3) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 194.1 (d, O=CH), 166.4 (s, C=O), 138.6 (s, C=CH), 130.6 (d, CH=CH_2), 119.8 (t, CH=CH_2), 114.9 (d, C=CH), 77.9 (d, CHO), 72.0 (s, CC=O), 34.9 (t, CH_2CH=CH_2), 28.6 (t, CH_2CH=C), 25.9 (q, CCH_3), 18.1 (q, CCH_3) ppm.

LRMS (ES^+) *m/z* 480 $[2M+CH_3CN+Na]^+$, 263 $[M+MeOH+Na]^+$, 165 $[M-CO_2+H]^+$.

HRMS (ES^+) For $C_{13}H_{20}O_4Na$ calculated 263.1254, found 263.1251 Da.

2.133 - (±)-Methyl (2*R*,3*S*,*E*)-2-(((*t*-butyldimethylsilyl)oxy)methyl)-3-hydroxy-2-(3-methylbut-2-en-1-yl)hex-4-enoate



$C_{19}H_{36}O_4Si$
M.W. = 356.58 g/mol

To a stirred solution of alkene **2.112a** (37 mg, 0.10 mmol) and butyl vinyl ether (0.06 mL, 0.50 mmol) in CH_2Cl_2 (1 mL) under Ar at rt was added Grubbs' second generation catalyst (**1.140**) (8.0 mg, 0.01 mmol). The solution was heated to reflux for 16 h, before removing the solvent under reduced pressure. Purification by column chromatography (EtOAc:hexane, 1:10) gave the title compound (**2.133**) (29 mg, 0.08 mmol, 80%) as a clear oil.

FT-IR (neat) ν_{max} 3491 (br, O-H), 2929 (m, C-H), 1733 (m, C=O), 1089 (s, O-C), 1054 (s, O-C) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.73 (1 H, m, CH_3CH=CH), 5.52 (1 H, ddq, *J* = 15.2, 7.7, 1.5 Hz, CH_3CH=CH), 4.96 (1 H, finely coupled t, *J* = 7.5 Hz, C=CH), 4.32 (1 H, t, *J* = 8.3 Hz, CHOH), 3.97 (1 H, d, *J* = 10.0 Hz, CHHO), 3.74 – 3.69 (4 H, m, CHHO, OCH_3), 3.66 (1 H, d, *J* = 8.9 Hz, OH), 2.36 (1 H, dd, *J* = 14.3, 7.3 Hz, C=CHCHH), 2.21 (1 H, dd, *J* = 14.7, 7.8 Hz, C=CHCHH), 1.73 (3 H, dd, *J* = 6.5, 1.2 Hz, CH_3CH=CH), 1.68 (3 H, s, CCH_3), 1.58 (3 H, s, CCH_3), 0.90 (9 H, s, $SiC(CH_3)_3$), 0.08 (6 H, Sm, $SiCH_3$) ppm.

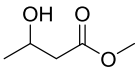
^{13}C NMR (101 MHz, $CDCl_3$) δ 174.3 (s, C=O), 134.7 (s, C=CH), 129.6 (d, CH_3CH=CH), 129.2 (d, CH_3CCH=CH), 118.4 (d, CH_3C=CH), 76.8 (d, CHOH), 64.2 (t,

$\underline{C}H_2O$), 55.4 (s, $\underline{C}CHO$), 51.6 (q, $O\underline{C}H_3$), 30.4 (t, $C{=}CH\underline{C}H_2$), 26.0 (q, $C\underline{C}H_3$), 25.8 (q, $SiC(\underline{C}H_3)_3$), 18.1 (s, $Si\underline{C}(CH_3)_3$), 17.9 (q, $\underline{C}H_3CH$), 17.8 (q, $C\underline{C}H_3$), –5.7 (q, $Si\underline{C}H_3$), –5.9 (q, $Si\underline{C}H_3$) ppm.

LRMS (ES^+) *m/z* 379 $[M+Na]^+$, 339 $[M-H_2O+H]^+$.

HRMS (ES^+) For $C_{19}H_{36}O_4SiNa$ calculated 379.2275, found 379.2271 Da.

(±)-4.01 - (±)-Methyl 3-hydroxybutanoate



$C_5H_{10}O_3$
M.W. = 118.13 g/mol

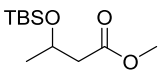
Following a procedure by Samama *et al.*,[222] to a stirred solution of methyl acetoacetate (**3.99**) (4.65 mL, 43.1 mmol) in MeOH (100 mL), under Ar at 0 °C was added $NaBH_4$ (545 mg, 14.4 mmol) in three portions. After 1 h, brine (20 mL) was added before extracting with Et_2O (3 x 40 mL). The combined organic phases were dried ($MgSO_4$) and concentrated by distillation, to give the title compound ((±)-**4.01**) (1.77 g, 15.0 mmol, 35%) as a pale yellow oil. The analytical data acquired was in accordance with previously reported values.[222]

FT-IR (neat) ν_{max} 3411 (bs, O-H), 2972 (w, C-H), 1723 (s, C=O), 1172 (s, O-H) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (1H, m, $C\underline{H}OH$), 3.72 (3H, s, $OC\underline{H}_3$), 2.94 (1H, d, *J* = 3.5 Hz, $O\underline{H}$), 2.51 (1H, dd, *J* = 16.7, 3.5 Hz, $C\underline{H}H$), 2.43 (1H, dd, *J* = 16.7, 8.6 Hz, $CH\underline{H}$), 1.24 (3H, d, *J* = 6.6 Hz, $CHC\underline{H}_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3 (s, $\underline{C}{=}O$), 64.2 (d, $\underline{C}HO$), 51.7 (q, $O\underline{C}H_3$), 42.5 (t, $\underline{C}H_2$), 22.4 (q, $CH\underline{C}H_3$) ppm.

(±)-4.02 - (±)-Methyl 3-((*t*-butyldimethylsilyl)oxy)butanoate



$C_{11}H_{24}O_3Si$
M.W. = 232.39 g/mol

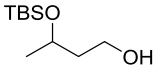
To a stirred solution of alcohol (±)-**4.01** (1.61 g, 13.6 mmol), imidazole (973 mg, 14.3 mmol) and DMAP (830 mg, 6.79 mmol) in DMF (30 mL) under Ar at 0 °C was added TBSCl (2.22 g, 14.3 mmol) in DMF (10 mL) dropwise over 10 min. The solution was warmed to rt, and stirred for 24 h, before diluting with H_2O (300 mL), and extracting with Et_2O (3 x 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:petrol, 1:5) gave the title compound ((±)-**4.02**) (2.16 g, 9.29 mmol, 68%) as a clear oil. The analytical data acquired was in accordance with previously reported values.[223]

FT-IR (neat) ν_{max} 2931 (m, C-H), 1741 (m, C=O), 1082 (s, O-C) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.29 (1H, m, C<u>H</u>O), 3.67 (3H, s, OC<u>H</u>$_3$), 2.49 (1H, dd, *J* = 14.7, 7.6 Hz, C<u>H</u>H), 2.38 (1H, dd, *J* = 14.7, 5.1 Hz, CH<u>H</u>), 1.20 (3H, d, *J* = 6.1 Hz, C<u>H</u>$_3$CH), 0.87 (9H, s, C(C<u>H</u>$_3$)$_3$), 0.07 (3H, s, SiC<u>H</u>$_3$), 0.05 (3H, s, SiC<u>H</u>$_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1 (s, <u>C</u>=O), 65.8 (d, <u>C</u>HO), 51.4 (q, O<u>C</u>H$_3$), 44.7 (t, <u>C</u>H$_2$), 25.7 (q, C(<u>C</u>H$_3$)$_3$), 23.9 (q, CH<u>C</u>H$_3$), 17.9 (s, <u>C</u>(CH$_3$)$_3$), -4.5 (q, Si<u>C</u>H$_3$), -5.1 (q, Si<u>C</u>H$_3$) ppm.

(±)-4.03 - (±)-3-((*t*-Butyldimethylsilyl)oxy)butan-1-ol



$C_{10}H_{24}O_2Si$
M.W. = 204.38 g/mol

By adaptation of a procedure by Urch *et al.*,[224] to a stirred solution of ester (±)-**4.02** (1.96 g, 8.43 mmol) in CH_2Cl_2 (40 mL) under Ar at 0 °C was added DIBAL (1 M in cyclohexane, 21.1 mL, 21.1 mmol) dropwise over 20 min. The solution was warmed to rt, and stirred for 4 h. Rochelle salt (20 mL) was carefully added, before stirring for 30 min and extracting with CH_2Cl_2 (3 x 40 mL). The combined organic extracts were dried

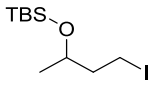
($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (Et_2O) gave the title compound ((±)-**4.03**) (920 mg, 4.50 mmol, 53%) as a clear oil. The analytical data acquired was in accordance with previously reported values.[224]

FT-IR (neat) ν_{max} 3352 (bs, O-H), 2923 (m, C-H), 1026 (s, O-H) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (1H, apparent quind, *J* = 6.4, 4.0 Hz, C<u>H</u>O), 3.85 (1H, m, C<u>H</u>HOH), 3.73 (1H, m, CH<u>H</u>OH), 2.50 (1H, t, *J* = 5.3 Hz, O<u>H</u>), 1.80 (1H, m, CHC<u>H</u>H), 1.64 (1H, m, CHCH<u>H</u>), 1.21 (3H, d, *J* = 6.6 Hz, C<u>H</u>$_3$CH), 0.91 (9H, s, C(C<u>H</u>$_3$)$_3$), 0.10 (3H, s, SiC<u>H</u>$_3$), 0.10 (3H, s, SiC<u>H</u>$_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 68.4 (d, <u>C</u>HO), 60.5 (t, <u>C</u>H$_2$O), 40.5 (t, CH<u>C</u>H$_2$), 25.8 (q, C(<u>C</u>H$_3$)$_3$), 23.4 (q, CH<u>C</u>H$_3$), 17.9 (s, <u>C</u>(CH$_3$)$_3$) –4.4 (q, Si<u>C</u>H$_3$), –5.0 (q, Si<u>C</u>H$_3$) ppm.

(±)-4.04 - (±)-*t*-Butyl((4-iodobutan-2-yl)oxy)dimethylsilane



$C_{10}H_{23}IOSi$
M.W. = 314.28 g/mol

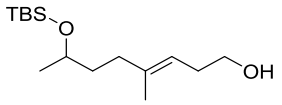
To a stirred solution of alcohol (±)-**4.03** (814 mg, 3.98 mmol) in CH_2Cl_2 (18 mL) under Ar at rt was added imidazole (813 mg, 11.9 mmol), PPh_3 (2.09 g, 7.96 mmol) then I_2 (2.02 g, 7.96 mmol). The suspension was stirred for 3.5 h, before diluting with CH_2Cl_2 (30 mL), and washing with $Na_2S_2O_4$ (sat. aq., 18 mL), $NaHCO_3$ (sat. aq., 18 mL) and brine (18 mL). The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure. Purification by crystallisation of impurities from CH_2Cl_2 with pentane, followed by trituration of the product with pentane, gave the title compound ((±)-**4.04**) (956 mg, 3.04 mmol, 76%) as a clear oil. The analytical data acquired was in accordance with previously reported values.[225]

FT-IR (neat) ν_{max} 2928 (m, C-H), 1062 (s, O-C) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (1 H, m, C<u>H</u>O), 3.29 – 3.18 (2 H, m, C<u>H</u>$_2$I), 2.00 – 1.85 (2 H, m, CHC<u>H</u>$_2$), 1.16 (3 H, d, *J* = 6.1 Hz, CH$_2$C<u>H</u>$_3$), 0.90 (9 H, s, C(C<u>H</u>$_3$)$_3$), 0.11 (3 H, s, SiC<u>H</u>$_3$), 0.09 (3 H, s, SIC<u>H</u>$_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 68.3 (d, $\underline{C}HO$), 43.3 (t, $\underline{C}H_2CH$), 25.9 (q, $C(\underline{C}H_3)_3$), 23.4 (q, $\underline{C}H_3CH$), 18.0 (s, $\underline{C}(CH_3)_3$), 3.5 (t, $\underline{C}H_2I$), –4.2 (q, $Si\underline{C}H_3$), –4.6 (q, $Si\underline{C}H_3$) ppm.

(±)-4.05 - (±)-(*E*)-7-((*t*-Butyldimethylsilyl)oxy)-4-methyloct-3-en-1-ol



$C_{15}H_{32}O_2Si$
M.W. = 272.50 g/mol

To a stirred solution of 2,3-dihydrofuran (0.04 mL, 0.53 mmol) in THF (0.5 mL) under Ar at 0 °C was added *t*-BuLi (1.58 M in pentane, 0.37 mL, 0.58 mmol) dropwise. The solution was stirred at 0 °C for 45 min, before cooling to –45 °C and adding HMPA (0.08 mL, 0.48 mmol), then iodo compound (±)-**4.04** (150 mg, 0.48 mmol) in THF (0.5 mL) dropwise over 5 min. The solution was allowed to warm to rt in a cardice bath, and stirred overnight. The solution was poured over NH_4Cl (1 mL), and extracted with Et_2O (3 x 4mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give the crude alkylated furan.

In a separate flask, $NiCl_2(PPh_3)_2$ (**3.103**) (33 mg, 0.05 mmol) was taken into benzene (1.5 mL) under Ar at rt and MeMgCl (**3.101**) (2.5 M in THF, 0.64 mL, 1.59 mmol) was added dropwise. After 20 min, the aforementioned crude alkylated furan in THF (0.75 mL) was added dropwise at rt, before heating to reflux for 4 h. Et_2O (7 mL) and NH_4Cl (4 mL) were added at rt, and stirred until no black colour persisted, before extracting with Et_2O (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:petrol, 1:5) gave the title compound ((±)-**4.05**) (42 mg, 0.15 mmol, 32%) as a clear oil.

FT-IR (neat) ν_{max} 3340 (br, O-H), 2929 (m, C-H), 1040 (m, O-C) cm^{-1}.

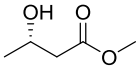
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.14 (1 H, m, C=C$\underline{H}$), 3.77 (1 H, sxt, *J* = 6.1 Hz, C$\underline{H}$O), 3.63 (2 H, t, *J* = 6.6 Hz, $C\underline{H}_2OH$), 2.31 (1 H, d, *J* = 6.6 Hz, C$\underline{H}$HCH_2OH), 2.27 (1 H, d, *J* = 6.6 Hz, CH$\underline{H}$CH_2OH), 2.10 (1 H, m, C$\underline{H}$HC=CH), 1.98 (1 H, m, CH$\underline{H}$C=CH), 1.65 (3 H, s, $C\underline{H}_3$C=CH), 1.55 – 1.47 (2 H, m, $C\underline{H}_2$CHO), 1.14 (3 H, d, *J* = 6.1 Hz, $C\underline{H}_3$CHO), 0.90 (9 H, s, $C(C\underline{H}_3)_3$), 0.05 (6 H, s, $SiC\underline{H}_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.0 (s, C=CH), 119.5 (d, C=CH), 68.4 (d, CHO), 62.5 (t, CH_2OH), 38.2 (t, CH_2CHO), 36.1 (t, $CH_2C=CH$), 31.5 (t, CH_2CH_2OH), 25.9 (q, $C(CH_3)_3$), 23.8 (q, CH_3CHO), 18.1 (s, SiC), 16.3 (q, $CH_3C=CH$), –4.4 (q, $SiCH_3$), –4.7 (q, $SiCH_3$) ppm.

LRMS (ES^+) *m/z* 273 $[M+H]^+$.

HRMS (ES^+) For $C_{15}H_{32}NaO_2Si$ calculated 295.2069, found 295.2068 Da.

(+)-4.01 - Methyl (*S*)-3-hydroxybutanoate



$C_5H_{10}O_3$
M.W. = 118.13 g/mol

Following a procedure by Takaya *et al.*,[201] to a solution of methyl acetoacetate (**3.99**) (10.0 g, 86.1 mmol) in MeOH (10 mL) was added Ru[I(*S*-BINAP)-*p*-cymene]I (77 mg, 0.068 mmol). The solution was place under 100 bar of pressure of H_2 for 6 days, before concentrating under reduced pressure. Purification by distillation gave the title compound ((+)-**4.01**) (9.02 g, 76.4 mmol, 89%) as a clear oil. The ee of this product was established to be 98.6% by chiral GC analysis of acylated alcohol **(+)-4.10**. The analytical data acquired was in accordance with previously reported values.[201]

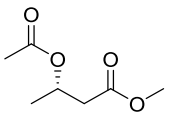
[α] 49.3 (c = 1.00).

FT-IR (neat) ν_{max} 3413 (br, O-H), 2972 (m, C-H), 1724 (s, C=O), 1171 (s, O-C) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.20 (1H, m, CHOH), 3.72 (3H, s, OCH_3), 2.94 (1H, d, *J* = 4.1 Hz, OH), 2.51 (1H, dd, *J* = 16.7, 3.5 Hz, CHH), 2.43 (1H, dd, *J* = 16.7, 8.6 Hz, CHH), 1.23 (3H, d, *J* = 6.1 Hz, $CHCH_3$)) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3 (s, C=O), 64.2 (d, CHO), 51.7 (q, OCH_3), 42.5 (t, CH_2), 22.4 (q, $CHCH_3$) ppm.

(+)-4.10 - Methyl (*S*)-3-acetoxybutanoate



$C_7H_{12}O_4$
M.W. = 160.17 g/mol

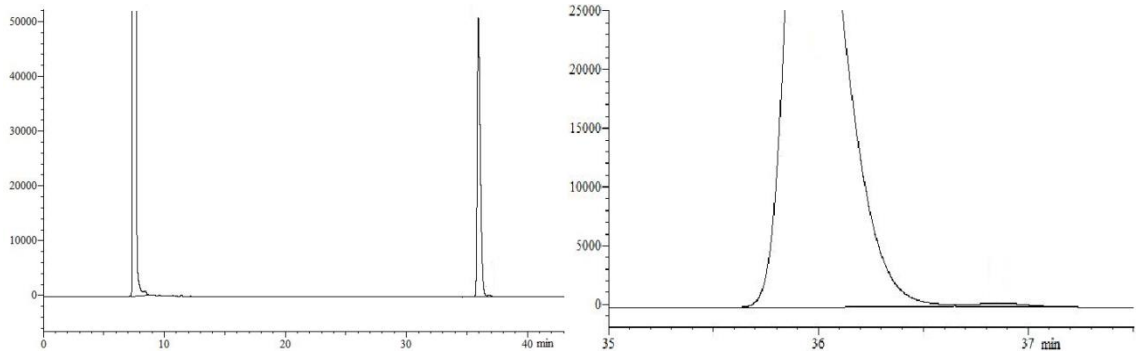
To a stirred solution of DMAP (54 mg, 0.44 mmol), alcohol (+)-**4.01** (171 mg, 1.45 mmol) and Et_3N (0.40 mL, 2.90 mmol) in CH_2Cl_2 (4 mL) under Ar at 0 °C was added AcCl (0.12 mL, 1.74 mmol) dropwise. The solution was warmed to rt and stirred for 2 hr. H_2O (2 mL) was added and extracted with CH_2Cl_2 (3 x 4 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:petrol, 1:5) gave the title compound ((+)-**4.10**) (93 mg, 0.58 mmol, 40%) as a clear oil at 98.6% ee by GC (Column WCOT fused silica (50 m x 0.25 mm x 0.25 µm) coated with CP-cyclodextrin B. Detector temperature 300 °C. He carrier gas (60 kPa).Oven temperature 100 °C.). The analytical data acquired was in accordance with previously reported values.[226]

[α] 5.3 (c = 0.63).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.27 (1 H, m, C<u>H</u>O), 3.69 (3 H, s, OC<u>H</u>$_3$), 2.65 (1 H, dd, *J* = 15.5, 7.3 Hz, C<u>H</u>H), 2.51 (1 H, dd, *J* = 15.5, 5.8 Hz, CH<u>H</u>), 2.02 (3 H, s, C<u>H</u>$_3$CO), 1.30 (3 H, d, *J* = 6.6 Hz, C<u>H</u>$_3$CH) ppm.

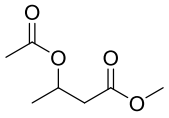
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7 (s, <u>C</u>=O), 170.2 (s, <u>C</u>=O), 67.3 (d, <u>C</u>HO), 51.7 (q, O<u>C</u>H$_3$), 40.6 (t, <u>C</u>H$_2$), 21.2 (q, <u>C</u>H$_3$CH), 19.9 (q, <u>C</u>H$_3$CO) ppm.

LRMS (ES$^+$) *m/z* 224 $[M+CH_3CN+Na]^+$.



Peak#	Ret.Time	Area	Height
1	7.376	133685717	13609528
2	35.945	900476	50913
3	36.857	6276	314
Total		134592469	13660755

(±)-4.10 - (±)-Methyl 3-acetoxybutanoate



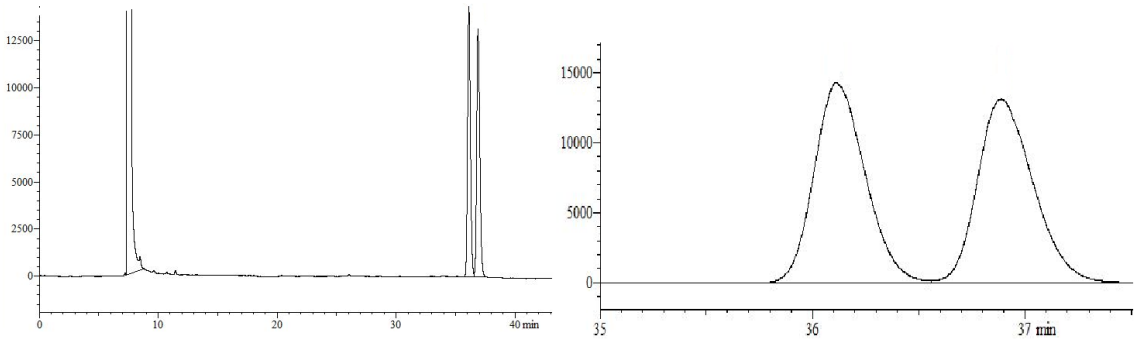
$C_7H_{12}O_4$
M.W. = 160.16 g/mol

To a stirred solution of DMAP (76 mg, 0.62 mmol), alcohol (±)-**4.01** (242 mg, 2.05 mmol) and Et_3N (0.57 mL, 4.10 mmol) in CH_2Cl_2 (5 mL) under Ar at 0 °C was added AcCl (0.17 mL, 2.46 mmol) dropwise. The solution was slowly warmed to rt and stirred for 16 hr. H_2O (2 mL) was added and extracted with CH_2Cl_2 (3 x 4 mL). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:petrol, 1:5) gave the title compound ((±)-**4.10**) (227 mg, 1.42 mmol, 69%) as a clear oil. Enantiomers were separated by GC (Column WCOT fused silica (50 m x 0.25 mm x 0.25 μm) coated with CP-cyclodextrin B. Detector temperature 300 °C. He carrier gas (60 kPa). Oven temperature 100 °C.). The analytical data acquired was in accordance with previously reported values.[226]

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.27 (1 H, m, C<u>H</u>), 3.69 (3 H, s, OC<u>H</u>$_3$), 2.65 (1 H, dd, *J* = 15.4, 8.1 Hz, CH<u>H</u>), 2.50 (1 H, dd, *J* = 15.4, 5.9 Hz, CH<u>H</u>), 2.03 (3 H, s, C<u>H</u>$_3$CO), 1.30 (3 H, d, *J* = 6.6 Hz, C<u>H</u>$_3$CH) ppm.

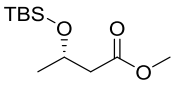
^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7 (s, <u>C</u>=O), 170.2 (s, <u>C</u>=O), 67.2 (d, <u>C</u>HO), 51.7 (q, O<u>C</u>H$_3$), 40.6 (t, <u>C</u>H$_2$), 21.2 (q, <u>C</u>H$_3$CH), 19.9 (q, <u>C</u>H$_3$C=O) ppm.

LRMS (ES$^+$) *m/z* 224 [M+CH_3CN+Na]$^+$.



Peak#	Ret.Time	Area	Height
1	7.394	133716494	13572313
2	36.111	239891	14375
3	36.890	240391	13168
Total		134196776	13599856

(+)-4.02 - Methyl (*S*)-3-((*t*-butyldimethylsilyl)oxy)butanoate



$C_{11}H_{24}O_3Si$
M.W. = 232.39 g/mol

To a stirred solution of alcohol (+)-**4.01** (6.80 g, 57.6 mmol) and imidazole (9.80 g, 144 mmol) in DMF (14 mL) under Ar at rt was added TBSCl portion over 15 min. The suspension was stirred at rt for 18 h, before pouring over brine (50%, 200 mL), and extracting with Et_2O (5 x 70 mL). The combined organic extracts were washed with HCl (1N, 3 x 50 mL), $NaHCO_3$ (50 mL) and brine (35 mL) before drying ($MgSO_4$) and concentrating under reduced pressure. Purification by column chromatography (EtOAc:petrol, 1:5) gave the title compound ((+)-**4.02**) (12.8 g, 55.1 mmol, 96%) as a clear oil. The analytical data acquired was in accordance with previously reported values.[223]

[α] 32.6 (c = 0.67).

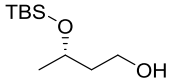
FT-IR (neat) ν_{max} 2931 (m, C-H), 1741 (s, C=O), 1082 (s, O-C) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.29 (1H, m, C<u>H</u>O), 3.67 (3H, s, OC<u>H</u>$_3$), 2.49 (1H, dd, *J* = 14.7, 7.6 Hz, C<u>H</u>H), 2.39 (1H, dd, *J* = 14.7, 5.1 Hz, CH<u>H</u>), 1.20 (3H, d, *J* =

6.1 Hz, CHC$\underline{H}_3$), 0.87 (9H, s, C(C$\underline{H}_3$)$_3$), 0.07 (3H, s, SiC$\underline{H}_3$), 0.05 (3H, s, SiC$\underline{H}_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1 ($\underline{C}$=O), 65.8 ($\underline{C}$HO), 51.4 (O$\underline{C}H_3$), 44.7 ($\underline{C}H_2$), 25.7 (SiC($\underline{C}H_3$)$_3$), 23.9 ($\underline{C}H_3$CH), 17.9 (Si$\underline{C}$(CH$_3$)$_3$), –4.5 (Si$\underline{C}H_3$), –5.1 (Si$\underline{C}H_3$) ppm.

(+)-4.03 - (*S*)-3-((*t*-Butyldimethylsilyl)oxy)butan-1-ol



$C_{10}H_{24}O_2Si$
M.W. = 204.38 g/mol

To a stirred solution of ester (+)-**4.02** (12.5 g, 53.8 mmol) in CH_2Cl_2 (200 mL) under Ar at 0 °C was added DIBAL (1 M in hexanes, 135 mL, 135 mmol) dropwise over 2 h. The solution was warmed to rt, and stirred for 2 h. The reaction was then cooled to 0 °C before slowly adding Rochelle salt (80 mL) and then diluting with Rochelle salt (200 mL) and CH_2Cl_2 (100 mL). The solution was stirred at rt for 16 h, before extracting with CH_2Cl_2 (3 x 300 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:petrol, 1:5) gave the title compound ((+)-**4.03**) (8.30 g, 40.6 mmol, 75%) as a clear oil. The analytical data acquired was in accordance with previously reported values.[227]

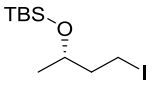
[α] 30.9 (c = 1.00).

FT-IR (neat) ν_{max} 3347 (br, O-H), 2930 (m, C-H), 1026 (s, O-C) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (1 H, aparent quind, *J* = 6.4, 4.0 Hz, C$\underline{H}$O), 3.85 (1 H, m, C$\underline{H}$HOH), 3.73 (1 H, m, CH$\underline{H}$OH), 2.53 (1 H, t, *J* = 5.3 Hz, O$\underline{H}$), 1.79 (1 H, m, CHC$\underline{H}$H), 1.65 (1 H, m, CHCH$\underline{H}$), 1.21 (3 H, d, *J* = 6.2 Hz, C$\underline{H}_3$CH), 0.90 (9 H, s, SiC(C$\underline{H}_3$)$_3$), 0.10 (3 H, s, SiC$\underline{H}_3$), 0.10 (3 H, s, SiC$\underline{H}_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 68.4 (d, $\underline{C}$HO), 60.5 (t, $\underline{C}H_2$OH), 40.5 (t, CH$\underline{C}H_2$), 25.8 (q, SiC($\underline{C}H_3$)$_3$), 23.4 (q, $\underline{C}H_3$CH), 17.9 (s, Si$\underline{C}$(CH$_3$)$_3$), –4.4 (q, Si$\underline{C}H_3$), –5.0 (q, Si$\underline{C}H_3$) ppm.

(+)-4.04 - (*S*)-*t*-Butyl((4-iodobutan-2-yl)oxy)dimethylsilane



$C_{10}H_{23}IOSi$
M.W. = 314.28 g/mol

Following a procedure by Yang *et al*.,[227] to a stirred solution of alcohol (+)-**4.03** (2.00 g, 9.79 mmol) in CH_2Cl_2 under Ar at rt was added imidazole (2.00 g, 29.4 mmol), PPh_3 (5.14 g, 19.6 mmol), then I_2 (4.97 g, 19.6 mmol) portionwise. The suspension was stirred at rt for 3.5 h, before diluting in CH_2Cl_2 (70 mL) and washing with $N_2S_2O_4$ (2 x 45 mL), $NaHCO_3$ (45 mL) and brine (45 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by crystallisation from CH_2Cl_2 with pentane, followed by trituration with pentane, gave the title compound ((+)-**4.04**) (3.01 g, 9.58 mmol, 98%) as a clear oil. The analytical data acquired was in accordance with previously reported values.[227]

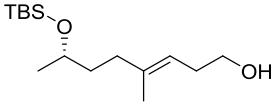
[α] 46.75 (c = 0.53).

FT-IR (neat) ν_{max} 2929 (m, C-H), 1060 (s, O-C) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (1 H, m, C<u>H</u>), 3.29 – 3.16 (2 H, m, C<u>H$_2$</u>I), 2.01 – 1.85 (2 H, m, CHC<u>H$_2$</u>), 1.16 (3 H, d, *J* = 6.0 Hz, C<u>H$_3$</u>CH), 0.90 (9 H, s, SiC(C<u>H$_3$</u>)$_3$), 0.10 (3 H, s, SiC<u>H$_3$</u>), 0.09 (3 H, s, SiC<u>H$_3$</u>) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 68.3 (d, <u>C</u>HO), 43.3 (t, CH<u>C</u>H$_2$), 25.9 (q, SiC(<u>C</u>H$_3$)$_3$), 23.5 (q, <u>C</u>H$_3$CH), 18.0 (s, Si<u>C</u>(CH$_3$)$_3$), 3.6 (t, <u>C</u>H$_2$I), –4.2 (q, Si<u>C</u>H$_3$), –4.6 (q, Si<u>C</u>H$_3$) ppm.

(+)-4.05 - (*S*,*E*)-7-((*t*-Butyldimethylsilyl)oxy)-4-methyloct-3-en-1-ol



$C_{15}H_{32}O_2Si$
M. W. = 272.50 g/mol

To a stirred solution of 2,3-dihydrofuran (1.81 mL, 24.0 mmol) in THF (12 mL) under Ar at –78 °C was added *t*-BuLi (1.5 M in pentane, 17.5 mL) dropwise over 30 min. The solution was warmed to 0 °C, and stirred for 45 min before cooling to –45 °C. HMPA

(3.79 mL, 21.8 mmol) was added dropwise over 20 min, followed by iodide (+)-**4.04** (6.82 g, 21.8 mmol) dropwise over 20 min, washing the flask with THF (3 mL). The solution was slowly warmed to rt and stirred for 16 h before carefully syringing over NH_4Cl (50 mL) and extracting with Et_2O (3 x 60 mL), The extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give the crude alkylated furan.

In a separate flask, $Ni(PPh_3)_2Cl_2$ (**3.103**) (307 mg, 1.09 mmol) was dissolved in benzene (66 mL) under Ar at rt and MeMgCl (**3.101**) (3 M in THF, 21.8 mL, 65.4 mmol) was added dropwise over 20 min. After 20 min the aforementioned crude alkylated furan in benzene (34 mL) was added dropwise over 20 min, and the black solution was heated to 90 °C for 6.5 h. The solution was cooled to rt, and poured over NH_4Cl (140 mL) and Et_2O (70 mL) and stirred until no black colour persisted. The aq. phase was then extracted with Et_2O (3 x 170 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:petrol, 1:10) gave the title compound ((+)-**4.05**) (4.58 g, 16.8 mmol, 77%) as a pale yellow oil.

[α] 9.3 (c = 1.20).

FT-IR (neat) ν_{max} 3329 (br, O-H), 2929 (m, C-H), 1040 (m, O-C) cm^{-1}.

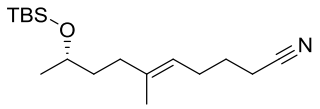
^{1}HNMR ^{1}H NMR (400 MHz, $CDCl_3$) δ .515 (1 H, m, C=C<u>H</u>), 3.78 (1 H, sxt, *J* = 6.0 Hz, C<u>H</u>O), 3.63 (2 H, t, *J* = 6.6 Hz, C<u>H$_2$</u>OH), 2.29 (2 H, q, *J* = 6.6 Hz, C<u>H$_2$</u>CH$_2$OH), 2.15 – 1.92 (2 H, m, C<u>H$_2$</u>C=CH), 1.65 (3 H, s, C<u>H$_3$</u>C), 1.61 – 1.44 (2 H, m, C<u>H$_2$</u>CHO), 1.36 (1 H, br s, O<u>H</u>), 1.14 (3 H, d, *J* = 6.0 Hz, C<u>H$_3$</u>CH), 0.90 (9 H, s, C(C<u>H$_3$</u>)$_3$), 0.06 (6 H, s, SiC<u>H$_3$</u>) ppm.

^{13}CNMR ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.1 (s, <u>C</u>=CH), 119.5 (d, C=<u>C</u>H), 68.4 (d, <u>C</u>HO), 62.5 (t, <u>C</u>H$_2$OH), 38.2 (t, <u>C</u>H$_2$CHO), 36.1 (t, <u>C</u>H$_2$C=CH), 31.5 (t, <u>C</u>H$_2$CH$_2$OH), 25.9 (q, SiC(<u>C</u>H$_3$)$_3$), 23.8 (q, <u>C</u>H$_3$CH), 18.1 (s, Si<u>C</u>(CH$_3$)$_3$), 16.3 (q, <u>C</u>H$_3$C=CH), –4.3 (q, Si<u>C</u>H$_3$), –4.7 (q, Si<u>C</u>H$_3$) ppm.

LRMS (ES$^+$) *m/z* 273 $[M+H]^+$.

HRMS (ES$^+$) For $C_{15}H_{32}NaO_2Si$ calculated 295.2069, found 295.2065 Da.

4.11 - (*S*,*E*)-9-((*t*-Butyldimethylsilyl)oxy)-6-methyldec-5-enenitrile



$C_{17}H_{33}NOSi$
M.W. = 295.54 g/mol

To a stirred solution of alcohol (+)-**4.05** (1.00 g, 3.67 mmol) and PPh_3 (1.25 g, 4.77 mmol) in CH_2Cl_2 (18 mL) under Ar at 0 °C was added NBS (8.49 g, 4.77 mmol) portionwise. The solution was stirred at rt for 3 h, before diluting in CH_2Cl_2 (20 mL) and washing with $Na_2S_2O_3$ (20 mL), H_2O (20 mL) and brine (20 mL). The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure. Precipitation of impurities from minimal CH_2Cl_2 with pentane, followed by trituration with pentane gave the crude bromide (1.22 g).

In a separate flask, DIPA (1.02 mL, 7.26 mmol) was taken into THF (9 mL) under Ar and cooled to –78 °C. *n*-BuLi (2.36 M in hexanes, 2.92 mL, 6.90 mmol) was added dropwise over 10 min, and the solution was warmed to rt and stirred for 20 min, before cooling back to –78 °C. CH_3CN (0.38 mL, 7.26 mmol) was added dropwise and stirred for 30 min. The aforementioned crude bromide was then added in THF (10 mL) dropwise over 10 min, and the suspension was slowly warmed to rt and stirred for 6 h. NH_4Cl (20 mL) was added, and extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:petrol, 1:20) gave the title compound (**4.11**) (523 mg, 1.77 mmol, 48%) as a clear oil.

[α] 7.7 (c = 1.45).

FT-IR (neat) ν_{max} 2929 (m, C-H), 2247 (w, nitrile C-N), 1039 (m, O-C) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.07 (1 H, m, C=C<u>H</u>), 3.77 (1 H, sxt, *J* = 6.1 Hz, C<u>H</u>O), 2.33 (2 H, t, *J* = 7.1 Hz, C<u>H</u>$_2$CN), 2.16 (2 H, q, *J* = 7.1 Hz, C=CHC<u>H</u>$_2$), 2.08 (1 H, m, C<u>H</u>HC=CH), 1.96 (1 H, m, CH<u>H</u>C=CH), 1.71 (2 H, quin, *J* = 7.1 Hz, C<u>H</u>$_2$CH$_2$CN), 1.63 (3 H, s, CC<u>H</u>$_3$), 1.57 – 1.42 (2 H, m, C<u>H</u>$_2$CHO), 1.14 (3 H, d, *J* = 6.1 Hz, CHC<u>H</u>$_3$), 0.90 (9 H, s, SiC(C<u>H</u>$_3$)$_3$), 0.06 (6 H, s, SiC<u>H</u>$_3$) ppm.

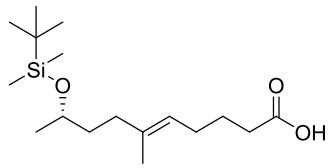
^{13}C NMR (101 MHz, $CDCl_3$) δ 138.0 (s, <u>C</u>=CH), 121.4 (d, C=<u>C</u>H), 119.8 (s, CH$_2$<u>C</u>N), 68.4 (d, <u>C</u>HO), 38.2 (t, <u>C</u>H$_2$CHO), 35.9 (t, <u>C</u>H$_2$C=CH), 26.7 (t, C=CH<u>C</u>H$_2$),

25.9 (q, SiC($\underline{C}H_3$)$_3$, 25.5 (t, $\underline{C}H_2CH_2CN$), 23.8 (q, $\underline{C}H_3CH$), 18.1 (s, Si$\underline{C}$), 16.4 (t, $\underline{C}H_2CN$), 16.2 (q, $\underline{C}H_3C{=}CH$), –4.3 (q, Si$\underline{C}H_3$), –4.7 (q, Si$\underline{C}H_3$) ppm.

LRMS (EI) *m/z* 238 (73%) $[M–C_4H_9]^{+\cdot}$, 164 (23%) $[M–C_6H_{15}OSi]^{+\cdot}$.

HRMS (ES^+) For $C_{17}H_{33}NNaOSi$ calculated 318.2229, found 318.2219 Da.

4.12 - (*E*)-9-((*t*-butyldimethylsilyl)oxy)-6-methyldec-5-enoic acid



$C_{17}H_{34}O_3Si$
M.W. = 314.54 g/mol

To a stirred solution of nitrile **4.11** (523 mg, 1.77 mmol) in CH_2Cl_2 (27 mL) under Ar at –78 °C was added DIBAL (1 M in cyclohexane, 2.12 mL, 2.12 mmol) dropwise over 45 min. After 3 h at –78 °C, Rochelle salt (10 mL) was carefully added before diluting in Rochelle salt (50 mL) and CH_2Cl_2 (50 mL). After stirring for 1 h at rt, the aq. phase was extracted with EtOAc (4 x 70 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure, giving the crude aldehyde (533 mg).

In a separate flask, the aforementioned crude aldehyde was taken into *t*-BuOH (13.5 mL), and 2-methyl-2-butene (2 M in THF, 13.5 mL, 27.0 mmol) was added before cooling to 0 °C. NaH_2PO_4 (317 mg, 2.64 mmol) was added, followed by $NaClO_2$ (299 mg, 2.64 mmol). The solution was stirred at 0 °C for 4 h before adding NH_4Cl (10 mL), and extracting with EtOAc (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:petrol, 2:5) gave the title compound (**4.12**) (424 mg, 1.35 mmol, 76%) as a clear oil.

[α] 7.3 (c = 0.94).

FT-IR (neat) ν_{max} 2929 (m, C-H), 1708 (s, C=O), 1135 (m, O-C) cm^{-1}.

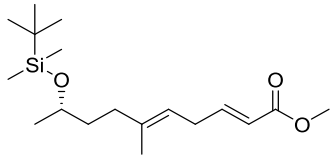
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.11 (1 H, m, C=C<u>H</u>), 3.77 (1 H, sxt, *J* = 6.1 Hz, C<u>H</u>O), 2.36 (2 H, t, *J* = 7.5 Hz, C<u>H$_2$</u>CO), 2.10 – 1.91 (4 H, m, C<u>H$_2$</u>C=CH, C=CHC<u>H$_2$</u>), 1.69 (2 H, quin, *J* = 7.4 Hz, C<u>H$_2$</u>CH$_2$C=O), 1.60 (3 H, s, C<u>H$_3$</u>C=CH), 1.56 – 1.44 (2 H, m, C<u>H$_2$</u>CHO), 1.14 (3 H, d, *J* = 6.1 Hz, C<u>H$_3$</u>CH), 0.90 (9 H, s, SiC(C<u>H$_3$</u>)$_3$), 0.06 (6 H, s, SiC<u>H$_3$</u>) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.6 (<u>C</u>=CH), 122.8 (C=<u>C</u>H), 68.5 (<u>C</u>HO), 38.2 (<u>C</u>H$_2$CHO), 35.9 (<u>C</u>H$_2$C=CH), 33.1 (<u>C</u>H$_2$CO), 27.2 (C=CH<u>C</u>H$_2$), 25.9 ((SiC(<u>C</u>H$_3$)$_3$), 24.8 (<u>C</u>H$_2$CH$_2$CO), 23.7 (<u>C</u>H$_3$CH), 18.2 (Si<u>C</u>(CH$_3$)$_3$), 16.1 (<u>C</u>H$_3$C=CH), –4.4 (Si<u>C</u>H$_3$), –4.7 (Si<u>C</u>H$_3$) ppm. Carbonyl carbon not present.

LRMS (ES$^-$) *m/z* 313 [M–H]$^-$.

HRMS (ES$^-$) For $C_{17}H_{33}O_3Si$ calculated 313.2204, found 313.2202 Da.

4.13 - Methyl (2*E*,5*E*)-9-((*t*-butyldimethylsilyl)oxy)-6-methyldeca-2,5-dienoate



$C_{18}H_{34}O_3Si$
M.W. = 326.55 g/mol

To a stirred solution of alcohol (+)-**4.05** (200 mg, 0.74 mmol) in CH_2Cl_2 (12 mL) under Ar at rt was added DMP (378 mg, 0.89 mmol). The suspension was stirred at rt for 2.5 h before adding $NaHCO_3$ (5 mL) and extracting with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give the crude aldehyde.

In a separate flask, NaH (38.4 mg, 0.96 mmol) was suspended in THF (5 mL) under Ar at 0 °C and trimethyl phosphonoacetate (0.16 mL, 0.96 mmol) in THF (5 mL) was added dropwise. The suspension was stirred at 0 °C for 30 min before addition of the aforementioned crude aldehyde in THF (3 mL) dropwise. The suspension was warmed to rt and stirred for 16 h. NH_4Cl (7 mL) was added, and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:hexane, 1:40) gave the title compound (**4.13**) (148 mg, 0.45 mmol, 61%) as a clear oil.

[α] 9.0 (c = 1.00).

FT-IR (neat) ν_{max} 2930 (m, C-H), 1723 (m, C=O), 1647 (w, alkene C=C), 1135 (m, O-C) cm^{-1}.

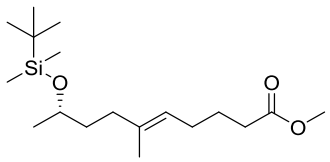
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (1 H, dt, *J* = 15.6, 6.3 Hz, C<u>H</u>=CHC=O), 5.82 (1 H, dt, *J* = 15.7, 1.7 Hz, CHC=O), 5.16 (1 H, m, C=C<u>H</u>), 3.81 – 3.71 (4 H, m, OC<u>H</u>$_3$, C<u>H</u>O), 2.90 (2 H, t, *J* = 6.5 Hz, CHC<u>H</u>$_2$CH), 2.11 (1 H, m, C<u>H</u>HCH$_2$CHO), 1.98 (1 H, m, CH<u>H</u>CH$_2$CHO), 1.61 (3 H, s, C<u>H</u>$_3$C), 1.59 – 1.44 (2 H, m, C<u>H</u>$_2$CHO), 1.14 (3 H, d, *J* = 6.1 Hz, C<u>H</u>$_3$CHO), 0.90 (9 H, s, SiC(C<u>H</u>$_3$)$_3$), 0.06 (6 H, s, SiC<u>H</u>$_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.2 (s, <u>C</u>=O), 148.0 (d, <u>C</u>H=CHCO), 138.8 (s, <u>C</u>=CH), 120.6 (d, <u>C</u>HCO), 118.5 (d, C=<u>C</u>H), 68.4 (d, <u>C</u>HO), 51.4 (q, O<u>C</u>H$_3$), 38.1 (t, <u>C</u>H$_2$CHO), 35.9 (t, <u>C</u>H$_2$CH$_2$CHO), 30.7 (t, C=CH<u>C</u>H$_2$), 25.9 (q, SiC(<u>C</u>H$_3$)$_3$), 23.8 (q, <u>C</u>H$_3$CO), 18.1 (s, Si<u>C</u>(CH$_3$)$_3$), 16.2 (q, <u>C</u>H$_3$C), –4.3 (q, Si<u>C</u>H$_3$), –4.7 (q, Si<u>C</u>H$_3$) ppm.

LRMS (EI) *m/z* 269 (100%) $[M-C_4H_9]^{+\cdot}$.

HRMS (ES^+) For $C_{18}H_{34}NaO_3Si$ calculated 349.2175, found 349.2169 Da.

4.14 - Methyl (*S*,*E*)-9-((*t*-butyldimethylsilyl)oxy)-6-methyldec-5-enoate



$C_{18}H_{36}O_3Si$
M.W. = 328.57 g/mol

To a stirred solution of ester **4.13** (603 mg, 1.85 mmol) in MeOH (10 mL) and THF (2.5 mL) under Ar at 0 °C was added $NiCl_2.6H_2O$ (226 mg, 0.95 mmol) then $NaBH_4$ (288 mg, 7.60 mmol) portionwise. The black solution was stirred at 0 °C for 2.5 h, before addition of NH_4Cl (1 mL). MeOH was removed under reduced pressure, and the resultant mixture was filtered through a pad of silica (EtOAc 100%), before concentrating under reduced pressure. Purification by column chromatography (EtOAc:hexane, 1:10) gave the title compound (**4.14**) (600 mg, 1.83 mmol, 99%) as a clear oil.

[α] 7.1 (c = 1.15).

FT-IR (neat) ν_{max} 2930 (m, C-H), 1741 (s, C=O), 1135 (m, O-C) cm^{-1}.

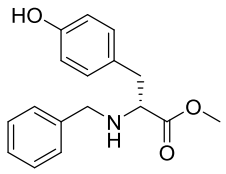
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.11 (1 H, t, *J* = 7.0 Hz, C=C<u>H</u>), 3.77 (1 H, m, C<u>H</u>O), 3.67 (3 H, s, OC<u>H</u>$_3$), 2.31 (2 H, t, *J* = 7.4 Hz, C<u>H</u>$_2$CO), 2.10 – 1.99 (3 H, m, C=CHC<u>H</u>$_2$, C<u>H</u>HCH$_2$CHO), 1.95 (1 H, m, CH<u>H</u>CH$_2$CHO), 1.72 – 1.64 (2 H, m, C<u>H</u>$_2$CH$_2$CO), 1.59 (3 H, s, C<u>H</u>$_3$C), 1.52 – 1.40 (2 H, m, C<u>H</u>$_2$CHO), 1.13 (3 H, d, *J* = 5.8 Hz, C<u>H</u>$_3$CHO), 0.90 (9 H, s, SiC(C<u>H</u>$_3$)$_3$), 0.05 (6 H, s, SiC<u>H</u>$_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.2 (s, <u>C</u>=O), 136.4 (s, <u>C</u>=CH), 123.0 (d, C=<u>C</u>H), 68.4 (d, <u>C</u>HO), 51.4 (q, O<u>C</u>H$_3$), 38.2 (t, <u>C</u>H$_2$CHO), 36.0 (t, <u>C</u>H$_2$CH$_2$CHO), 33.5 (t, <u>C</u>H$_2$C=O), 27.2 (t, C=CH<u>C</u>H$_2$), 25.9 (q, C(<u>C</u>H$_3$)$_3$), 25.0 (t, <u>C</u>H$_2$CH$_2$CO), 23.8 (q, <u>C</u>H$_3$CHO), 18.2 (s, Si<u>C</u>(CH$_3$)$_3$), 16.1 (q, <u>C</u>H$_3$C), –4.4 (q, Si<u>C</u>H$_3$), –4.7 (q, Si<u>C</u>H$_3$) ppm.

LRMS (EI) *m/z* 271 (31%) $[M-C_4H_9]^{+\cdot}$.

HRMS (ES^+) For $C_{18}H_{36}NaO_3Si$ calculated 351.2331, found 351.2330 Da.

4.15 - Methyl (*R*)-2-(benzylamino)-3-(4-hydroxyphenyl)propanoate



$C_{17}H_{19}NO_3$
M.W. = 285.34 g/mol

To a stirred solution of (D)-tyrosine (**3.118**) (3.55 g, 19.6 mmol) in MeOH (24 mL) under Ar at 0 °C, was added $SOCl_2$ (1.42 mL, 19.6 mmol) dropwise over 20 min. The suspension was heated to reflux for 16 h, before removing the solvent under reduced pressure, giving the crude methylated ester (4.50 g, 19.4 mmol).

In a separate flask, by adaptation of the procedure by Konopelski *et al.*,[205] to a suspension of the aforementioned crude methylated ester (3.95 g, 17.1 mmol) in THF (95 mL) at rt, was added benzaldehyde (1.91 mL, 18.8 mmol), AcOH (0.98 mL) then $NaBH(OAc)_3$ (9.51 g, 42.6 mmol). After 16 h EtOAc (200 mL) was added before filtering

and washing with EtOAc (3 x 70 mL). The filtrate was concentrated under reduced pressure, before taking into EtOAc (200 mL) and washing with $NaHCO_3$ (100 mL). The combined organics were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:petrol, 1:1) gave the title compound (**4.15**) (3.73 g, 13.1 mmol, 76%) as a thick clear oil.

[α] –19.6 (c = 0.83, MeOH).

FT-IR (neat) ν_{max} 3013 (br, O-H), 2951 (w, C-H), 1745 (m, C=O), 1514 (m, C=C) cm^{-1}.

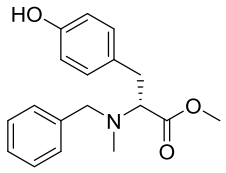
^{1}H NMR (400 MHz, DMSO-d_6) δ 9.17 (1 H, s, OH), 7.30 – 7.17 (5 H, m, CH_{Ar}), 6.93 (2 H, d, *J* = 8.6 Hz, CHCHCOH), 6.64 (2 H, d, *J* = 8.6 Hz, CHCOH), 3.72 (1 H, d, *J* = 13.6 Hz, NCHH), 3.60 – 3.51 (4 H, m, CH_3, NCHH), 3.35 (1 H, m, $CHCH_2$), 2.76 (2 H, dd, *J* = 6.8, 2.8 Hz, $CHCH_2$), 2.35 (1 H, br. s., NH) ppm.

^{13}C NMR (101 MHz, DMSO-d_6) δ 174.4 (s, C=O), 155.8 (s, OC_{Ar}), 140.1 (s, C_{Ar}), 130.0 (d, CH_{Ar}), 128.0 (d, CH_{Ar}), 127.8 (d, CH_{Ar}), 127.6 (s, C_{Ar}), 126.6 (d, CH_{Ar}), 114.9 (d, CH_{Ar}), 62.1 (d, $CHCH_2$), 51.2 (q, OCH_3), 50.8 (t, NCH_2), 38.0 (t, $CHCH_2$) ppm.

LRMS (ES^+) *m/z* 593 $[2M+Na]^+$, 349 $[M+CH_3CN+Na]^+$, 286 $[M+H]^+$.

HRMS (ES^+) For $C_{17}H_{20}NO_3$ calculated 286.1438, found 286.1436 Da.

3.86 - Methyl (*R*)-2-(benzyl(methyl)amino)-3-(4-hydroxyphenyl)propanoate



$C_{18}H_{21}NO_3$
M.W. = 299.36 g/mol

By adaptation of the procedure by Konopelski *et al.*,[205] to a stirred solution of the tyrosine derivative **4.15** (3.71 g, 13.0 mmol) in THF (75 mL) at rt, was added formaldehyde (37% aq. sol., 1.16 mL, 14.3 mmol) AcOH (0.74 mL, 13.0 mmol) then $NaBH(OAc)_3$ (6.88 g, 32.5 mmol). After 16 h, the solvent was removed under reduced

pressure. The residue was taken into EtOAc (200 mL) and washed with $NaHCO_3$ (100 mL). The organics were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:petrol, 1:1) gave the title compound (**3.86**) (3.63 g, 12.1 mmol, 93%) as a clear oil. The analytical data acquired was in accordance with previously reported values.[205]

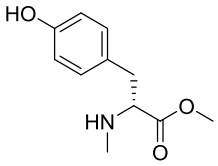
[α] 68.0 (c = 0.57, MeOH).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.17 (5H, m, C$\underline{H}_{Ar}$), 7.00 (2H, d, *J* = 8.4 Hz, C$\underline{H}$CHCOH), 6.70 (2H, d, *J* = 8.4 Hz, C$\underline{H}$COH), 5.66 (1H, br. s, O$\underline{H}$), 3.78 (1H, d, *J* = 13.6 Hz, NC$\underline{H}$H), 3.65 (3H, s, OC$\underline{H}_3$), 3.59 (1H, d, *J* = 13.6 Hz, NCH$\underline{H}$), 3.54 (1H, dd, *J* = 8.4, 6.9 Hz, C$\underline{H}$CH$_2$), 3.03 (1H, dd, *J* =13.7, 8.4 Hz, CHC$\underline{H}$H), 2.90 (1H, dd, *J* = 13.7, 6.9 Hz, CHCH$\underline{H}$), 2.30 (3H, s, NC$\underline{H}_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7 (s, $\underline{C}$=O), 154.3 (s, O$\underline{C}_{Ar}$), 138.9 (s, $\underline{C}_{Ar}$), 130.3 (d, $\underline{C}H_{Ar}$), 130.1 (s, $\underline{C}_{Ar}$), 128.7 (d, $\underline{C}H_{Ar}$), 128.2 (d, $\underline{C}H_{Ar}$), 127.0 (d, $\underline{C}H_{Ar}$), 115.2 (d, $\underline{C}H_{Ar}$), 67.7 (d, $\underline{C}$HCH$_2$), 58.8 (t, N$\underline{C}$H$_2$), 51.1 (q, O$\underline{C}$H$_3$), 38.0 (q, N$\underline{C}$H$_3$), 34.9 (t, CH$\underline{C}$H$_2$) ppm.

LRMS (ES$^+$) *m/z* 300 [M+H]$^+$.

4.16 - Methyl (*R*)-3-(4-hydroxyphenyl)-2-(methylamino)propanoate



$C_{11}H_{15}NO_3$
M.W. = 209.24 g/mol

By adaptation of the procedure by Konopelski *et al.*,[205] to a mixture of tyrosine derivative **3.86** (3.58 g, 12.0 mmol) and Pd/C (5%, 730 mg) under Ar at rt, was added MeOH (150 mL). The atmosphere was evacuated under reduced pressure and replaced with H_2 three times, before stirring at rt for 4 h. The suspension was then filtered through celite and concentrated, giving the title compound (**4.16**) (2.45 g, 11.7 mmol, 98%) as a white solid. The analytical data acquired was in accordance with previously reported values.[205]

MP 104–106 °C (*solvent*: MeOH).

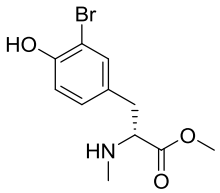
[α] –25.7 (c = 0.63, MeOH).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (2H, d, *J* = 8.6 Hz, C<u>H</u>CHCOH), 6.67 (2H, d, *J* = 8.6 Hz, C<u>H</u>COH), 4.02 (1 H, br. s, N<u>H</u>), 3.70 (3H, s, OC<u>H$_3$</u>), 3.46 (1H, t, *J* = 6.7 Hz, C<u>H</u>CH$_2$), 2.94 (1H, dd, *J* = 13.7, 6.4 Hz, CHC<u>H</u>H), 2.89 (1H, dd, *J* = 13.7, 6.7 Hz, CHCH<u>H</u>), 2.39 (3H, s, NC<u>H$_3$</u>) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.6 (s, <u>C</u>=O), 155.0 (s, O<u>C$_{Ar}$</u>), 130.2 (d, <u>C</u>H$_{Ar}$), 128.2 (s, <u>C$_{Ar}$</u>), 115.6 (d, <u>C</u>H$_{Ar}$), 64.6 (d, <u>C</u>HCH$_2$), 51.8 (q, O<u>C</u>H$_3$), 38.4 (t, CH<u>C</u>H$_2$), 34.5 (q, N<u>C</u>H$_3$) ppm.

LRMS (ES$^+$) *m/z* 210 $[M+H]^+$.

3.117 - Methyl (*R*)-3-(3-bromo-4-hydroxyphenyl)-2-(methylamino)propanoate



$C_{11}H_{14}BrNO_3$
M.W. = 288.14 g/mol

Following a procedure by Ye *et al.*,[199] to a stirred solution of tyrosine derivative **4.16** (1.17 g, 5.59 mmol) in MeCN (120 mL) under Ar at rt was added PTSA.H$_2$O (1.28 g, 6.71 mmol). After 5 min NBS (995 mg, 5.59 mmol) was added, before stirring at rt for 24 h. $NaHCO_3$ (564 mg, 6.71 mmol) in H_2O (30 mL) was added, before removing the solvent under reduced pressure, and extracting with EtOAc (3 x 60 mL). Organics were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc) gave the title compound (**3.117**) (1.10 g, 3.82 mmol, 68%) as a clear oil. The analytical data acquired was in accordance with previously reported values.[199]

[α] –16.6 (c = 1.34, MeOH).

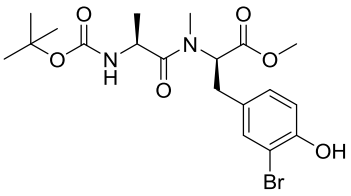
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (1 H, s, C<u>H</u>CBr), 6.98 (1 H, dd, *J* = 8.1, 2.0 Hz, C<u>H</u>CHCOH), 6.81 (1 H, d, *J* = 8.1 Hz, C<u>H</u>COH), 3.77 – 3.66 (4 H, m, N<u>H</u>,

$OC\underline{H}_3$), 3.42 (1 H, t, *J* = 6.6 Hz, $NC\underline{H}$), 2.86 (2 H, tt, *J* = 14.3, 6.9 Hz, $C\underline{H}_2$), 2.38 (3 H, s, $NC\underline{H}_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.5 (s, $\underline{C}$=O), 151.5 (s, $\underline{C}OH$), 132.6 (d, $\underline{C}H_{Ar}$), 130.3 (s, $\underline{C}_{Ar}$), 129.7 (d, $\underline{C}H_{Ar}$), 116.3 (d, $\underline{C}H_{Ar}$), 110.2 (s, $\underline{C}Br$), 64.4 (d, $N\underline{C}H$), 51.8 (q, $O\underline{C}H_3$), 38.1 (t, $\underline{C}H_2$), 34.5 (q, $N\underline{C}H_3$) ppm.

LRMS (ES$^+$) *m/z* 290 [M^{81Br}+Na]$^+$, 288 [M^{79Br}+H]$^+$.

3.95 - Methyl (*R*)-3-(3-bromo-4-hydroxyphenyl)-2-((*S*)-2-((*t*-butoxycarbonyl)amino)-*N*-methylpropanamido)propanoate



$C_{19}H_{27}BrN_2O_6$
M.W. = 459.34 g/mol

Following a procedure by Ye *et al*.,[199] to a stirred solution of Boc-ala-OH (1.16 g, 6.11 mmol) and amine **3.117** (1.60 g, 5.55 mmol) in THF (53 mL) under Ar at 0 °C was added DEPBT (**4.17**) (1.99 g, 6.66 mmol) in one portion. NMM (1.22 mL, 11.1 mmol) was then added dropwise over 10 min. The solution was allowed to slowly warm to rt and stirred for 24 h. H_2O (40 mL) was then added, and extracted with EtOAc (3 x 50 mL). The extracts were washed with $NaHCO_3$ (50 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:hexane, 4:1) gave the title compound (**3.95**) (2.11 g, 4.59 mmol, 83%) as a white foam. The analytical data acquired was in accordance with previously reported values.[199]

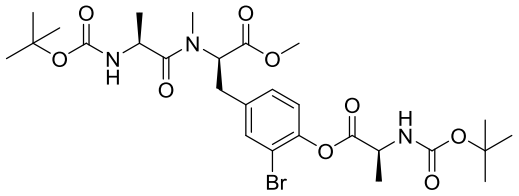
[α] 40.0 (c = 1.0, MeOH).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (1 H, s, $C\underline{H}CBr$), 7.03 (1 H, m, $C\underline{H}CHCOH$), 6.91 (1 H, d, *J* = 8.3 Hz, $C\underline{H}COH$), 5.82 (1 H, br s, $O\underline{H}$), 5.43 (1 H, d, *J* = 7.8 Hz, $N\underline{H}$), 5.24 (1 H, dd, *J* = 11.2, 5.0 Hz, $C\underline{H}CH_2$), 4.54 (1 H, m, $C\underline{H}CH_3$), 3.75 (3 H, s, $OC\underline{H}_3$), 3.31 (1 H, dd, *J* = 14.9, 5.1 Hz, $CHC\underline{H}H$), 2.95 (1 H, dd, *J* = 14.6, 11.6 Hz, $CHCH\underline{H}$), 2.88 (3 H, s, $NC\underline{H}_3$), 1.43 (9 H, s, $C(C\underline{H}_3)_3$), 0.97 (3 H, d, *J* = 6.7 Hz, $CHC\underline{H}_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8 (s, C=O), 170.6 (s, NC=O), 155.1 (s, NHC=O), 151.3 (s, COH), 132.1 (d, CH_{Ar}), 130.1 (s, C_{Ar}), 129.5 (d, CH_{Ar}), 116.1 (d, CH_{Ar}), 110.0 (s, CBr), 79.6 (s, $C(CH_3)_3$), 58.1 (d, $CHCH_2$), 52.5 (q, OCH_3), 46.5 (d, $CHCH_3$), 33.5 (t, $CHCH_2$), 32.5 (q, NCH_3), 28.3 (q, $C(CH_3)_3$), 18.5 (q, $CHCH_3$) ppm.

LRMS (ES$^+$) *m/z* 461 $[M^{Br81}+H]^+$, 459 $[M^{79Br}+H]^+$.

4.22 - Methyl (*R*)-3-(3-bromo-4-(((*t*-butoxycarbonyl)-L-alanyl)oxy)phenyl)-2-((*S*)-2-((*t*-butoxycarbonyl)amino)-*N*-methylpropanamido)propanoate



$C_{27}H_{40}BrN_3O_9$
M.W. = 630.53 g/mol

To a stirred solution of Boc-ala-OH (100 mg, 0.53 mmol), amine **3.117** (100 mg, 0.35 mmol) and PyBOP (276 mg, 0.53 mmol) in CH_2Cl_2 (4 mL) under Ar at 0 °C was added DIPEA (0.18 mL, 1.06 mmol) dropwise. The solution was allowed to slowly warm to rt and stirred for 24 h. NH_4Cl (3 mL) was added, and extracted with CH_2Cl_2 (3 x 5 mL). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:petrol, 1:1) gave the title compound (**4.22**) (74 mg, 0.12 mmol, 45%) as a white foam.

[α] 11.8 (c = 1.35).

FT-IR (neat) ν_{max} 3337 (s, N-H), 2978 (w, C-H), 1701 (s, C=O), 1489 (m, C=C), 1162 (s, O-C) cm^{-1}.

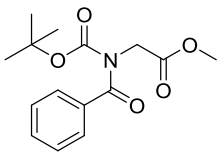
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (1 H, s, CHCBr), 7.16 (1 H, m, CHCHCOC), 7.06 (1 H, d, *J* = 8.3 Hz, CHCOC), 5.40 (1 H, d, *J* = 8.1 Hz, NH), 5.29 (1 H, dd, *J* = 11.1, 5.1 Hz, $CHCH_2$), 5.10 (1 H, d, *J* = 6.6 Hz, NH), 4.62 – 4.47 (2 H, m, $CHCH_3$, $CHCH_3$), 3.74 (3 H, s, OCH_3), 3.38 (1 H, dd, *J* = 14.7, 5.1 Hz, CHCHH), 3.01 (1 H, dd, *J* = 14.7, 11.4 Hz, CHCHH), 2.88 (3 H, s, NCH_3), 1.60 (3 H, d, *J* = 7.3 Hz, $CHCH_3$), 1.46 (9 H, s, $C(CH_3)_3$), 1.42 (9 H, s, $C(CH_3)_3$), 0.97 (3 H, d, *J* = 6.7 Hz, $CHCH_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ173.8 (s, C=O), 170.9 (s, C=O), 170.4 (s, C=O), 155.0 (s, C=O), 146.7 (s, CHCO), 136.5 (s, C_{Ar}), 133.4 (d, CH_{Ar}), 129.0 (d, CH_{Ar}), 123.6 (d, CH_{Ar}), 115.7 (s, CBr), 80.1 (s, $C(CH_3)_3$), 79.5 (s, $C(CH_3)_3$), 57.8 (d, $CHCH_2$), 52.5 (q, OCH_3), 49.4 (d, $CHCH_3$), 46.5 (d, $CHCH_3$), 33.8 (t, CH_2), 32.5 (q, NCH_3), 28.3 (q, $CH(CH_3)_3$), 28.3 (q, $CH(CH_3)_3$), 18.5 (q, $CHCH_3$), 18.5 (q, $CHCH_3$) ppm.

LRMS (ES$^+$) *m/z* 654 [M(Br^{81})+Na]$^+$, 652 [M(Br^{79})+Na]$^+$, 632 [M(Br^{81})+H]$^+$, 630 [M(Br^{79})+H]$^+$.

HRMS (ES$^+$) For $C_{27}H_{40}Br^{79}N_3NaO_9$ calculated 652.1846, found 652.1842 Da.

4.23 - Methyl *N*-benzoyl-*N*-(*t*-butoxycarbonyl)glycinate



$C_{15}H_{19}NO_5$
M.W. = 293.32 g/mol

Following a procedure by Somfai *et al.*,[207] to a stirred solution of HCl.gly-OMe (**3.119**) (3.00 g, 23.9 mmol) in Et_2O (10 mL) at 0 °C was added K_2CO_3 (19 mL) and BzCl (4.2 mL, 36.1 mmol). The suspension was stirred at 0 °C for 3 h, before diluting in H_2O (10 mL) and extracting with Et_2O (3 x 40 mL). The combined organic extracts were washed with $NaHCO_3$ (40 mL), H_2O (40 mL) and brine (40 mL), then dried ($MgSO_4$) and concentrated under reduced pressure, giving the crude benzoylated product (5.12 g).

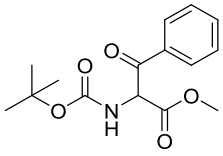
In a separate flask, the aforementioned benzoylated product (1 g) was taken into CH_3CN (5 mL) under Ar at rt, and Boc_2O (1.70 g, 7.77 mmol) followed by DMAP (506 mg, 4.14 mmol) was added. The solution was stirred at rt for 5 h before the solvent was removed under reduced pressure. The residue was taken into EtOAc (50 mL) and washed with H_2O (50 mL) and NH_4Cl (50 mL). The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:petrol, 1:5) gave the title compound (**4.23**) (953 mg, 3.25 mmol, 70%) as a clear oil. The analytical data acquired was in accordance with previously reported values.[207]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.61 (2 H, m, C$\underline{H}_{Ar}$), 7.50 (1 H, m, C$\underline{H}_{Ar}$), 7.44 – 7.39 (2 H, m, C$\underline{H}_{Ar}$), 4.56 (2 H, s, C$\underline{H}_2$), 3.80 (3 H, s, OC$\underline{H}_3$), 1.17 (9 H, s, C(C$\underline{H}_3$)$_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9 (s, $\underline{C}$=O), 169.5 (s, $\underline{C}$=O), 152.7 (s, C=O), 137.1 (s, $\underline{C}_{Ar}$), 131.2 (d, $\underline{C}H_{Ar}$), 128.0 (d, $\underline{C}H_{Ar}$), 127.7 (d, $\underline{C}H_{Ar}$), 83.7 (s, $\underline{C}(CH_3)_3$), 52.3 (q, O$\underline{C}H_3$), 46.3 (t, $\underline{C}H_2$), 27.3 (q, C($\underline{C}H_3$)$_3$) ppm.

LRMS (ES$^+$) *m/z* 609 $[2M+Na]^+$, 316 $[M+Na]^+$, 194 $[M-C_5H_9O_2+2H]^+$.

3.96 - (±)-Methyl 2-((*t*-butoxycarbonyl)amino)-3-oxo-3-phenylpropanoate



$C_{15}H_{19}NO_5$
M.W. = 293.32 g/mol

Following a procedure by Somfai *et al.*,[207] To a stirred solution of DIPA (1.33 mL, 9.51 mmol) and DMPU (0.01 mL, 0.10 mmol) in THF (10 mL) under Ar at –78 °C, was added *n*-BuLi (2.36 M in hexanes, 4.03 mL, 9.51 mmol) dropwise over 10 min. The solution was warmed to 0 °C and stirred for 20 min, before cooling to –78 °C. Benzoyl amine **4.23** (929 mg, 3.17 mmol) in THF (20 mL) was added over 20 min before stirring at –78 °C for 1.5 h. NH_4Cl (20 mL) was added, and extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:petrol, 2:5) gave the title compound (**3.96**) (740 mg, 2.52 mmol, 79%) as a white solid. The analytical data acquired was in accordance with previously reported values.[207]

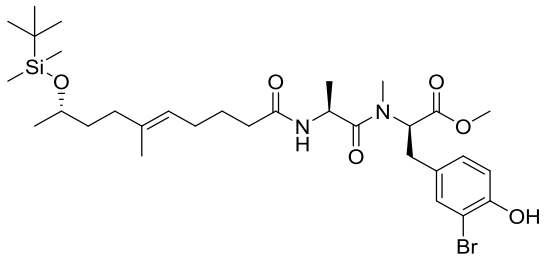
MP 95–97 °C (*solvent*: EtOAc/*n*-hexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (2 H, d, *J* = 7.3 Hz, C$\underline{H}_{Ar}$), 7.64 (1 H, m, C$\underline{H}_{Ar}$), 7.55 – 7.48 (2 H, m, C$\underline{H}_{Ar}$), 5.98 (1 H, d, *J* = 8.2 Hz, C$\underline{H}$), 5.90 (1 H, m, N$\underline{H}$), 3.72 (3 H, s, OC$\underline{H}_3$), 1.46 (9 H, s, C(C$\underline{H}_3$)$_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 191.8 (s, $\underline{C}$=O), 167.6 (s, $\underline{C}$=O), 155.0 (s, $\underline{C}$=O), 134.3 (d, $\underline{C}H_{Ar}$), 134.2 (s, $\underline{C}_{Ar}$), 129.5 (d, $\underline{C}H_{Ar}$), 128.8 (d, $\underline{C}H_{Ar}$), 80.7 (s, $\underline{C}(CH_3)_3$), 59.1 (d, $\underline{C}$HC=O), 53.1 (q, O$\underline{C}H_3$), 28.2 (q, C($\underline{C}H_3$)$_3$) ppm.

LRMS (ES$^+$) *m/z* 316 [M+H]$^+$, 238 [M–C_4H_9+2H]$^+$, 194 [M–$C_5H_9O_2$+2H]$^+$.

4.25 - Methyl (5*S*,15*S*,18*R*,*E*)-18-(3-bromo-4-hydroxybenzyl)-2,2,3,3,5,8,15,17-octamethyl-13,16-dioxo-4-oxa-14,17-diaza-3-silanonadec-8-en-19-oate



$C_{31}H_{51}BrN_2O_6Si$
M.W. = 655.75 g/mol

To a stirred solution of ester **4.14** (150 mg, 0.46 mmol) in MeOH (1.5 mL) and H_2O (1.5 mL) at rt was added LiOH·H_2O (116 mg, 2.76 mmol). After 16 h at rt, the solvent was removed under reduced pressure, and the residue was cooled to 0 °C and acidified to ~pH 2 with HCl (2 M) before extracting with EtOAc (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give the crude acid **4.12**.

In a separate flask, to a stirred solution of peptide **3.95** (800 mg, 1.74 mmol) in CH_2Cl_2 (44 mL) under Ar at 0 °C was added TFA (11.2 mL) dropwise over 10 min. After 3 h at rt, the solvent was removed under reduced pressure, and the excess TFA was azeotroped with toluene (4 x 20 mL) to give the crude deprotected amine **4.24**.

Finally, the aforementioned crude acid (**4.12**) and amine (**4.24**) (260 mg, ~0.55 mmol) were taken into CH_2Cl_2 (12 mL) under Ar at 0 °C, and NMM (0.30 mL, 2.76 mmol) was added dropwise. To this was added T3P (**4.28**) (0.33 mL, 0.55 mmol) dropwise. After 16 h at rt, H_2O (7 mL) was added and extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:petrol, 2:1) gave the title compound (**4.25**) (100 mg, 0.15 mmol, 33%) as a white foam.

[α] 27.3 (c = 1.00).

FT-IR (neat) ν_{max} 3626 (w, N-H), 3278 (br, O-H), 2930 (m, C-H), 1743 (m, C=O), 1630 (s, C=O), 1080 (m, O-C) cm^{-1}.

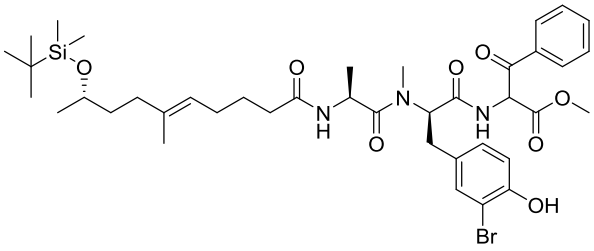
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (1 H, m, C<u>H</u>CBr), 7.03 (1 H, dd, *J* = 8.3, 2.1 Hz, C<u>H</u>CHCOH), 6.92 (1 H, d, *J* = 8.3 Hz, C<u>H</u>COH), 6.47 (1 H, d, *J* = 7.5 Hz, N<u>H</u>), 6.15 (1 H, br. s., O<u>H</u>), 5.30 (1 H, dd, *J* = 11.4, 5.1 Hz, NC<u>H</u>), 5.09 (1 H, td, *J* = 7.2, 1.0 Hz, C=C<u>H</u>), 4.82 (1 H, quin, *J* = 7.0 Hz, NHC<u>H</u>), 3.78 – 3.72 (4 H, m, OC<u>H$_3$</u>, C<u>H</u>O), 3.33 (1 H, dd, *J* = 14.9, 5.1 Hz, NCHC<u>H</u>H), 2.97 – 2.89 (4 H, m, NCHCH<u>H</u>, NC<u>H$_3$</u>), 2.21 – 2.14 (2 H, m, C<u>H$_2$</u>C=O), 2.11 – 1.88 (4 H, m, C=CHC<u>H$_2$</u>, C<u>H$_2$</u>CH$_2$CHO), 1.70 – 1.62 (2 H, m, C<u>H$_2$</u>CH$_2$C=O), 1.57 (3 H, s, C<u>H$_3$</u>C=CH), 1.55 – 1.40 (2 H, m, C<u>H$_2$</u>CHO), 1.13 (3 H, d, *J* = 6.1 Hz, C<u>H$_3$</u>CHO), 0.97 (3 H, d, *J* = 6.7 Hz, NHCHC<u>H$_3$</u>), 0.89 (9H, s, SiC(C<u>H$_3$</u>)$_3$), 0.05 (7 H, s. SiC<u>H$_3$</u>) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6 (s, <u>C</u>=O), 172.3 (s, <u>C</u>=O), 170.5 (s, <u>C</u>=O), 151.5 (s, <u>C</u>OH), 136.3 (s, <u>C</u>=CH), 132.1 (d, <u>C</u>H$_{Ar}$), 129.9 (s, <u>C</u>$_{Ar}$), 129.4 (d, <u>C</u>H$_{Ar}$), 123.1 (d, C=<u>C</u>H), 116.2 (d, <u>C</u>H$_{Ar}$), 110.0 (s, <u>C</u>Br), 68.5 (d, <u>C</u>HO), 58.0 (d, N<u>C</u>H), 52.5 (q, O<u>C</u>H$_3$), 45.3 (d, NH<u>C</u>H), 38.2 (t, <u>C</u>H$_2$CHO), 36.1 (t, <u>C</u>H$_2$C=O), 36.0 (t, C=CH<u>C</u>H$_2$), 33.5 (t, NHCH<u>C</u>H$_2$), 32.4 (q, N<u>C</u>H$_3$), 27.4 (t, <u>C</u>H$_2$CH$_2$CHO), 25.9 (q, SiC(<u>C</u>H$_3$)$_3$), 25.7 (t, <u>C</u>H$_2$CH$_2$C=O), 23.8 (q, <u>C</u>H$_3$CHO), 18.3 (q, NHCH<u>C</u>H$_3$), 18.1 (s, Si<u>C</u>(CH$_3$)$_3$), 16.1 (q, <u>C</u>H$_3$C=CH), –4.4 (q, Si<u>C</u>H$_3$), –4.7 (q, Si<u>C</u>H$_3$) ppm.

LRMS (ES$^+$) *m/z* 657 [M^{Br81}+H]$^+$, 655 [M^{Br79}+H]$^+$.

HRMS (ES$^+$) For $C_{31}H_{52}Br^{81}N_2O_6Si$ calculated 657.2752, found 657.2757 Da.

4.29 - Methyl (5*S*,15*S*,18*R*,*E*)-21-benzoyl-18-(3-bromo-4-hydroxybenzyl)-2,2,3,3,5,8,15,17-octamethyl-13,16,19-trioxo-4-oxa-14,17,20-triaza-3-siladocos-8-en-22-oate



$C_{40}H_{58}BrN_3O_8Si$
M.W. = 816.91 g/mol

To a stirred solution of peptide **4.25** (71 mg, 0.11 mmol) in MeOH (1 mL), THF (1 mL) and H_2O (1 mL) at rt was added $LiOH \cdot H_2O$ (26 mg, 1.1 mmol). After 18 h, the solvents were removed under reduced pressure. The residue was diluted in H_2O (2 mL), acidified

to ~pH 2 with HCl_2 (2M), and extracted with EtOAc (3 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to give the crude acid.

In a separate flask, to a stirred solution of β-ketoester **4.96** (363 mg, 1.24 mmol) in CH_2Cl_2 (33 mL) under Ar at 0 °C was added TFA (8 ml) dropwise. After 3 h at rt, the solvent was removed under reduced pressure. The TFA was azeotroped with toluene (4 x 20 mL) to give the crude deprotected amine.

Finally, the aforementioned crude acid and amine (163 mg, ~0.53 mmol) were taken into CH_2Cl_2 (5 mL) under Ar at 0 °C, and NMM (0.12 mL, 1.06 mmol) was added. T3P (**4.28**) (0.13 mL, 0.21 mmol) was then added dropwise, followed by NMM (0.12 ml, 1.06 mmol). After 5 h at rt, H_2O (5 mL) was added and extracted with CH_2Cl_2 (3 x 8 mL). The combined organic extracts were washed with citric acid (1 M, 2 x 15 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography twice (EtOAc:hexane, 2:1) gave the title compound (**4.29**) (45 mg, 0.055 mmol, 50%) as a white foam.

[α] 27.3 (c = 1.00).

FT-IR (neat) ν_{max} 3625 (w, N-H), 3293 (br, O-H), 2929 (m, C-H), 1748 (m, C=O), 1630 (s, C=O) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 – 8.02 (2 H, m, C$\underline{H}_{Ar}$), 7.63 (1 H, m, C$\underline{H}_{Ar}$), 7.54 – 7.44 (3 H, m, C$\underline{H}_{Ar}$, N$\underline{H}$CHC), 7.28 (1 H, m, C$\underline{H}_{Ar}$), 7.03 (1 H, dt, *J* = 8.3, 2.0 Hz, C$\underline{H}_{Ar}$), 6.89 (1 H, dd, *J* = 8.3, 6.8 Hz, C$\underline{H}_{Ar}$), 6.46 (1 H, m, N$\underline{H}$CHCH$_3$), 6.38 (1 H, br. s, O$\underline{H}$), 6.15 + 6.12 (1 H, 2 x d, *J* = 7.5 + 7.6 Hz, NHC$\underline{H}$C), 5.51 (1 H, m, NC$\underline{H}$), 5.09 (1 H, t, *J* = 7.0 Hz, C=C$\underline{H}$), 4.82 + 4.74 (1 H, 2 x q, *J* = 6.9 Hz, NHC$\underline{H}$CH$_3$), 3.79 – 3.69 (4 H, m, OC$\underline{H}_3$, C$\underline{H}$O), 3.28 (1 H, m, NCHC$\underline{H}$H), 3.00 + 2.85 (3 H, 2 x s, NC$\underline{H}_3$), 2.92 (1 H, m, NCHCH$\underline{H}$), 2.23 – 2.14 (2 H, m, C$\underline{H}_2$C=O), 2.08 – 1.83 (4 H, m, C=CHC$\underline{H}_2$, C$\underline{H}_2$CH$_2$CHO), 1.69 – 1.59 (2 H, m, C$\underline{H}_2$CH$_2$C=O), 1.57 (3 H, s, C$\underline{H}_3$C=CH), 1.50 – 1.33 (2 H, m, C$\underline{H}_2$CHO), 1.14 – 1.09 (3 H, m, C$\underline{H}_3$CHO), 1.02 + 0.99 (3 H, 2 x d, *J* = 6.9 + 6.7 Hz, NHCHC$\underline{H}_3$), 0.89 (9 H, s, SiC(C$\underline{H}_3$)$_3$), 0.04 (6 H, s, SiC$\underline{H}_3$) ppm.

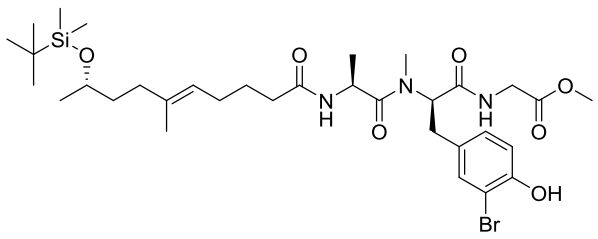
^{13}C NMR (101 MHz, $CDCl_3$) δ 191.0 + 190.6 (C=O), 174.5 + 174.4 (C=O), 172.7 + 172.6 (C=O), 169.4 + 169.2 (C=O), 167.0 + 166.6 (C=O), 151.5 + 151.4 (COH), 136.2 + 136.2 (C=CH), 134.5 + 134.4 (C$\underline{H}_{Ar}$), 134.1 + 133.9 (C$_{Ar}$),

132.3 ($\underline{C}H_{Ar}$), 129.9 + 129.8 ($\underline{C}_{Ar}$), 129.6 + 129.5 ($\underline{C}H_{Ar}$), 129.4 + 129.3 ($\underline{C}H_{Ar}$), 128.8 + 128.8 ($\underline{C}H_{Ar}$), 123.1 (C=$\underline{C}$H), 116.2 ($\underline{C}H_{Ar}$), 109.9 ($\underline{C}$Br), 67.0 + 68.5 ($\underline{C}$HO), 58.4 + 57.8 (NH$\underline{C}$HC), 57.0 (N$\underline{C}$HCH$_2$), 53.3 + 53.2 (O$\underline{C}$H$_3$), 45.5 (NH$\underline{C}$HCH$_3$), 38.2 ($\underline{C}$H$_2$CHO), 36.0 ($\underline{C}$H$_2$C=O), 35.9 (C=CH$\underline{C}$H$_2$), 32.3 (NCH$\underline{C}$H$_2$), 31.0 + 31.0 (N$\underline{C}$H$_3$), 27.4 ($\underline{C}$H$_2$CH$_2$CHO), 25.9 (SiC($\underline{C}$H$_3$)$_3$), 25.6 + 25.6 ($\underline{C}$H$_2$CH$_2$C=O), 23.8 + 23.8 ($\underline{C}$H$_3$CHO), 18.1 (Si$\underline{C}$(CH$_3$)$_3$), 17.9 + 17.8 (NHCH$\underline{C}$H$_3$), 16.1 ($\underline{C}$H$_3$C=CH), –4.4 (Si$\underline{C}$H$_3$), –4.7 (Si$\underline{C}$H$_3$) ppm.

LRMS (ES$^+$) *m/z* 840 [M^{Br81}+Na]$^+$, 838 [M^{Br79}+Na]$^+$, 818 [M^{Br81}+H]$^+$, 816 [M^{Br79}+H]$^+$.

HRMS (ES$^+$) For $C_{40}H_{58}Br^{79}N_3NaO_8Si$ calculated 838.3074, found 838.3087 Da.

4.31 - Methyl ((*R*)-3-(3-bromo-4-hydroxyphenyl)-2-((*S*)-2-((*S*,*E*)-9-((*t*-butyldimethylsilyl)oxy)-6-methyldec-5-enamido)-N-methylpropanamido)propanoyl)glycinate



$C_{33}H_{54}BrN_3O_7Si$
M.W. = 712.80 g/mol

To a stirred solution of peptide **4.29** (44 mg, 0.054 mmol) in THF (2 mL) under Ar at 0 °C was added TBAF (1 M in THF, 65 µL, 0.065 mmol) dropwise. After 24 h at rt, the solution was cooled to 0 °C and TBAF (1 M in THF, 16µL, 0.016 mmol) was added. After a further 16 h at rt, H_2O (2 mL) was added and extracted with CH_2Cl_2 (3 x 4 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:hexane, 2:1) gave the title compound (**4.31**) (30 mg, 0.042 mmol, 78%) as a white foam.

[α] 15.4 (c = 0.73).

FT-IR (neat) ν_{max} 3626 (w, N-H), 3306 (br, O-H), 2930 (m, C-H), 1639 (s, C=O) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (1 H, s, C$\underline{H}_{Ar}$), 7.05 (1 H, dd, *J* = 8.3, 1.8 Hz, C$\underline{H}_{Ar}$), 6.94 (1 H, m, N$\underline{H}$CH$_2$), 6.89 (1 H, d, *J* = 8.3 Hz, C$\underline{H}_{Ar}$), 6.36 (1 H, br. s., O$\underline{H}$), 6.26 (1 H, m, N$\underline{H}$CH), 5.55 (1 H, dd, *J* = 10.8, 5.7 Hz, NC$\underline{H}$), 5.09 (1 H, t, *J* =

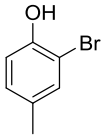
6.9 Hz, C=CH), 4.66 (1 H, quin, *J* = 6.7 Hz, NHCH), 4.18 (1 H, dd, *J* = 17.8, 6.5 Hz, NHCHH), 3.84 (1 H, dd, *J* = 17.9, 5.1 Hz, NHCHH), 3.79 – 3.70 (4 H, m, OCH_3, CHO), 3.37 (1 H, dd, *J* = 15.2, 5.6 Hz, NCHCHH), 3.00 (3 H, s, NCH_3), 2.89 (1 H, dd, *J* = 15.2, 10.9 Hz, NCHCHH), 2.22 – 2.14 (2 H, m, CH_2CH_2CO) 2.09 (1 H, m, CCHH), 2.03 – 1.97 (2 H, m, $C=CHCH_2$), 1.92 (1 H, m, CCHH), 1.77 – 1.62 (2 H, m, CH_2CH_2CO), 1.57 (3 H, s, $CH_3C=CH$), 1.52 – 1.37 (2 H, m, CH_3CHCH_2), 1.14 – 1.09 (3 H, m, CH_3CHO), 0.99 (3 H, d, *J* = 6.8 Hz, $NHCHCH_3$), 0.89 (9 H, s, $SiC(CH_3)_3$), 0.05 (6 H, s, $SiCH_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.6 (s, C=O), 173.5 (s, C=O), 170.1 (s, C=O), 169.8 (s, C=O), 151.3 (s, COH), 136.3 (s, C=CH), 132.2 (d, CH_{Ar}), 130.3 (s, C_{Ar}), 129.3 (d, CH_{Ar}), 123.0 (d, C=CH), 116.1 (d, CH_{Ar}), 109.8 (s, CBr), 68.5 (d, CHO), 56.9 (d, NCH), 52.3 (q, OCH_3), 45.6 (d, NHCH), 41.1 (t, $NHCH_2$), 38.2 (t, CH_3CHCH_2), 36.0 (t, CCH_2), 35.7 (t, CH_2CH_2CO), 32.2 (t, $NCHCH_2$), 30.9 (q, NCH_3), 27.3 (t, $C=CHCH_2$), 25.9 (q, $SiC(CH_3)_3$), 25.6 (t, CH_2CH_2CO), 23.8 (q, CH_3CHO), 18.1 (s, $SiC(CH_3)_3$), 16.9 (q, $NHCHCH_3$), 16.1 (q, $CH_3C=CH$), –4.4 (q, $SiCH_3$), –4.7 (q, $SiCH_3$) ppm.

LRMS (ES$^+$) *m/z* 736 [M^{Br81}+Na]$^+$, 734 [M^{Br79}+Na]$^+$, 714 [M^{Br81}+H]$^+$, 712 [M^{Br79}+H]$^+$.

HRMS (ES$^+$) For $C_{33}H_{54}Br^{79}N_3NaO_7Si$ calculated 734.2812, found 734.2803 Da.

4.43 - 2-Bromo-4-methylphenol



C_7H_7BrO
M.W. = 187.04 g/mol

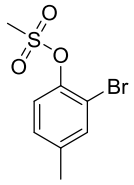
By adaptation of the procedure by Natarajan *et al.*,[228] to a stirred solution of *p*-cresol (**4.42**) (3.00 g, 27.7 mmol) in CH_2Cl_2 (100 mL) under Ar at 0 °C was added Br_2 (1.49 mL, 29.1 mmol) dropwise. The solution was stirred at rt for 1 h, before removing the solvent under reduced pressure to give the title compound (**4.43**) (5.17 g, 27.6 mmol, 100%) as an orange oil. The analytical data acquired was in accordance with previously reported values.[229]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (1 H, d, *J* = 1.5 Hz, C<u>H</u>CBr), 7.02 (1 H, dd, *J* = 8.3, 1.5 Hz, C<u>H</u>CCH_3), 6.92 (1 H, d, *J* = 8.2 Hz, C<u>H</u>COH), 5.33 (1 H, s, O<u>H</u>), 2.28 (3 H, s, C<u>H</u>$_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.0 (<u>C</u>OH), 132.1 (<u>C</u>H), 131.4 (<u>C</u>CH_3), 129.8 (<u>C</u>H), 115.7 (<u>C</u>H), 109.8 (<u>C</u>Br), 20.2 (<u>C</u>H_3) ppm.

LRMS (EI) *m/z* 188 (69%) $[M^{Br81}]^{+\cdot}$, 186 (76%) $[M^{Br79}]^{+\cdot}$, 107 (100%) $[M-Br]^{+\cdot}$.

4.44 - 2-Bromo-4-methylphenyl methanesulfonate



$C_8H_9BrO_3S$
M.W. = 265.12 g/mol

To a stirred solution of phenol **4.43** (500 mg, 2.67 mmol) in CH_2Cl_2 (20 mL) under Ar at 0 °C was added DIPEA (0.70 mL, 4.01 mmol) then MsCl (0.23 mL, 2.95 mmol) dropwise. After 30 min at 0 °C for 30 min NH_4Cl (10 mL) was added extracted with CH_2Cl_2 (3 x 15 mL). Combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:hexane, 3:10) gave the title compound (**4.44**) (582 mg, 2.20 mmol, 82%) as a white solid.

MP 41–43 °C (*solvent*: CH_2Cl_2).

FT-IR (neat) ν_{max} 3028 (m, C-H), 1326 (S=O) cm^{-1}.

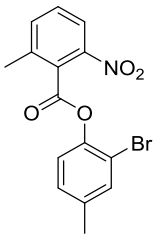
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (1 H, d, *J* = 1.5 Hz, C<u>H</u>CBr), 7.34 (1 H, d, *J* = 8.3 Hz, C<u>H</u>CO), 7.16 (1 H, dd, *J* = 8.3, 1.5 Hz, C<u>H</u>CCH_3), 3.25 (3 H, s, SC<u>H</u>$_3$), 2.36 (3 H, s, CC<u>H</u>$_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.3 (s, <u>C</u>O), 138.9 (s, <u>C</u>CH_3), 134.2 (d, (<u>C</u>H_{Ar}), 129.5 (d, <u>C</u>H_{Ar}), 123.9 (d, <u>C</u>H_{Ar}), 115.3 (s, <u>C</u>Br), 38.7 (q, S<u>C</u>H_3), 20.6 (q, C<u>C</u>H_3) ppm.

LRMS (EI) *m/z* 266 (69%) $[M^{Br81}]^{+\cdot}$, 264 (56%) $[M^{Br79}]^{+\cdot}$, 187 (85%) $[M^{Br81}-CH_3SO_2]^{+\cdot}$, 185 (100%) $[M^{Br79}-CH_3SO_2]^{+\cdot}$.

HRMS (APPI$^+$) For $C_8H_9Br^{79}O_3S$ calculated 263.9456, found 263.9448 Da.

4.47 - 2-Bromo-4-methylphenyl 2-methyl-6-nitrobenzoate



$C_{15}H_{12}BrNO_4$
M.W. = 350.17 g/mol

To a stirred solution of MNBA (103 mg, 0.30 mmol) and phenol **4.43** (50 mg, 0.27 mmol) in CH_2Cl_2 (5 mL) under Ar at rt was added DMAP (99 mg, 0.81 mmol). After 30 min, $NaHCO_3$ (2 mL) was added and washed with citric acid (1 M, 2 mL), H_2O (2 mL) and brine (2 mL). The organic solvent was dried ($MgSO_4$) and concentrated under reduced pressure to give the title compound (**4.47**) (90 mg, 0.26 mmol, 96%) as a white solid.

MP 91–93 °C (*solvent*: CH_2Cl_2/*n*-hexane).

FT-IR (neat) ν_{max} 1763 (m, C=O), 1534 (s, NO_2), 1044 (m, O-C) cm^{-1}.

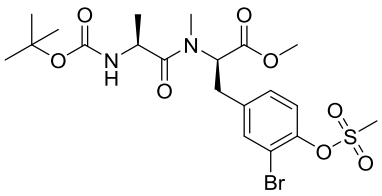
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (1 H, d, *J* = 8.1 Hz, C<u>H</u>CNO$_2$), 7.64 (1 H, d, *J* = 7.8 Hz, C<u>H</u>CHCHCN), 7.56 (1 H, dd, *J* = 8.1, 7.8 Hz, C<u>H</u>CHCNO$_2$), 7.47 (1 H, d, *J* = 1.2 Hz, C<u>H</u>CBr), 7.43 (1 H, d, *J* = 8.3 Hz, C<u>H</u>CO), 7.23 (1 H, dd, *J* = 8.3, 1.2 Hz, C<u>H</u>CHCO), 2.68 (3 H, s, C<u>H</u>$_3$CC), 2.38 (3 H, s, C<u>H</u>$_3$CCH) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.2 (s, <u>C</u>=O), 146.4 (s, <u>C</u>NO$_2$), 145.3 (s, <u>C</u>O), 138.5 (s, <u>C</u>CH$_3$), 138.0 (s, <u>C</u>CH$_3$), 136.4 (d, <u>C</u>HCHCHCN), 133.7 (d, <u>C</u>HCBr), 130.3 (d, <u>C</u>HCHCNO$_2$), 129.4 (d, <u>C</u>HCHCO), 128.3 (s, <u>C</u>C=O), 123.1 (d, <u>C</u>HCO), 122.0 (d, <u>C</u>HCNO$_2$), 115.0 (s, <u>C</u>Br), 20.6 (q, <u>C</u>H$_3$CCH), 19.8 (q, <u>C</u>H$_3$CC) ppm.

LRMS (EI) *m/z* 164 (100%) [M–C_7H_6OBr]$^{+\cdot}$.

HRMS (APPI$^+$) For $C_{15}H_{16}Br^{79}N_2O_4$ calculated 367.0288, found 367.0292 Da.

4.49 - Methyl (*R*)-3-(3-bromo-4-((methylsulfonyl)oxy)phenyl)-2-((*S*)-2-((*t*-butoxy-carbonyl)amino)-N-methylpropanamido)propanoate



$C_{20}H_{29}BrN_2O_8S$
M.W. = 537.42 g/mol

To a stirred solution of peptide **3.95** (246 mg, 0.54 mmol) in CH_2Cl_2 (12 mL) under Ar at 0 °C was added DIPEA (0.56 mL, 3.24 mmol) then MsCl (0.13 mL, 1.62 mmol) dropwise. After 3 h at rt, NH_4Cl (5 mL) was added and extracted with CH_2Cl_2 (3 x 7 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:hexane, 2:1) gave the title compound (**4.49**) (268 mg, 0.50 mmol, 93%) as a white foam.

[α] 37.8 (c = 1.00).

FT-IR (neat) ν_{max} 3627 (w, N-H), 2978 (m, C-H), 1739 (m, C=O), 1703 (s, C=O), 1648 (s, C=O) cm^{-1}.

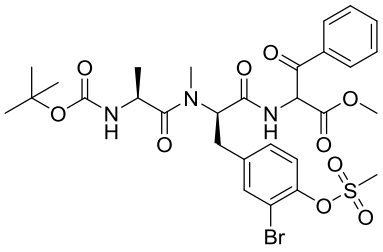
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (1 H, d, *J* = 2.1 Hz, C<u>H</u>CBr), 7.36 (1 H, d, *J* = 8.4 Hz, CHC<u>H</u>CO), 7.20 (1 H, dd, *J* = 8.4, 2.1 Hz, C<u>H</u>CHCO), 5.37 (1 H, d, *J* = 8.0 Hz, N<u>H</u>), 5.26 (1 H, dd, *J* = 10.9, 5.2 Hz, NC<u>H</u>), 4.52 (1 H, apparent quin, *J* = 7.1 Hz, NHC<u>H</u>), 3.75 (3 H, s, OC<u>H$_3$</u>), 3.39 (1 H, dd, *J* = 14.7, 5.1 Hz, CHC<u>H</u>H), 3.24 (3 H, s, SC<u>H$_3$</u>), 3.03 (1 H, dd, *J* = 14.7, 11.1 Hz, CHCH<u>H</u>), 2.89 (3 H, s, NC<u>H$_3$</u>), 1.43 (9 H, s, C(C<u>H$_3$</u>)$_3$), 0.97 (3 H, d, *J* = 6.9 Hz, CHC<u>H$_3$</u>) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8 (<u>C</u>=O), 170.2 (<u>C</u>=O), 155.0 (<u>C</u>=O), 145.3 (<u>C</u>O), 137.8 (<u>C</u>CH$_2$), 134.0 (<u>C</u>HCBr), 129.4 (<u>C</u>HCHCO), 124.2 (<u>C</u>HCO), 115.8 (<u>C</u>Br), 79.6 (<u>C</u>(CH$_3$)$_3$), 57.9 (N<u>C</u>H), 52.6 (O<u>C</u>H$_3$), 46.5 (NH<u>C</u>H), 38.9 (S<u>C</u>H$_3$), 33.8 (CH<u>C</u>H$_2$), 32.6 (N<u>C</u>H$_3$), 28.3 (C(<u>C</u>H$_3$)$_3$), 18.4 (CH<u>C</u>H$_3$) ppm.

LRMS (ES$^+$) *m/z* 561 $[M^{Br81}+Na]^+$, 559 $[M^{Br79}+Na]^+$, 539 $[M^{Br81}+H]^+$, 537 $[M^{Br79}+H]^+$.

HRMS (ES$^+$) For $C_{20}H_{29}Br^{79}N_2NaO_8S$ calculated 559.0726, found 559.0720 Da.

4.50 - (6*S*,9*R*)-12-Benzoyl-9-(3-bromo-4-((methylsulfonyl)oxy)benzyl)-2,2,6,8-tetramethyl-4,7,10-trioxo-3-oxa-5,8,11-triazatridecan-13-oic acid



$C_{29}H_{36}BrN_3O_{10}S$
M.W. = 698.58 g/mol

To a stirred solution of peptide **4.49** (100 mg, 0.19 mmol) in THF (1.4 mL) and MeOH (1.4 mL) at 0 ˚C was added $LiOH \cdot H_2O$ (11 mg, 0.26 mmol) in H_2O (0.7 mL) dropwise. After 1 h at 0 ˚C, the solution was warmed to rt and stirred for a further 2 h. The solvent was removed under reduced pressure and the residue was diluted in H_2O (1 mL) and washed with EtOAc (1 mL). The aq. phase was then acidified to ~pH 2 with HCl (2 N) and extracted with EtOAc (3 x 5mL). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give the crude acid as a clear oil

In a separate flask, to a stirred solution β-ketoester **3.96** (85 mg, 0.29 mmol) in CH_2Cl_2 (6.6 mL) at 0 ˚C under Ar was added TFA (1.9 mL) dropwise. The solution was stirred at rt for 2 h, before the solvent was removed under reduced pressure. The excess TFA was azeotroped with toluene (4 x 2.5 mL) to give the crude deprotected amine as an off white solid.

Finally, the aforementioned crude amine, acid and DIPEA (0.20 mL, 1.14 mmol) were taken into THF (4 mL) under Ar and cooled to 0 ˚C. To this was added T3P (**4.28**) (0.19 mL, 0.32 mmol) dropwise. The solution was stirred at rt for 36 h, before addition of H_2O (4 mL) and extracting with CH_2Cl_2 (3 x 8 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Purification by column chromatography (EtOAc:hexane, 2:1) gave the title compound (**4.50**) (102 mg, 0.15 mmol, 79%) as a white foam.

[α] 25.1 (c = 0.81).

FT-IR (neat) ν_{max} 3323 (w, N-H), 2926 (m, C-H), 1675 (s, C=O) cm^{-1}.

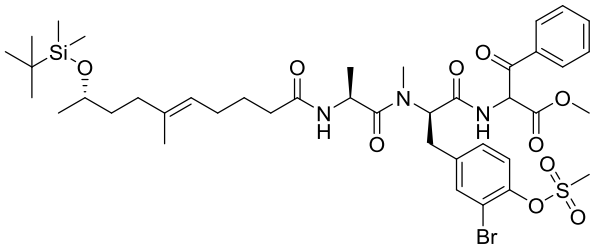
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 – 8.01 (2 H, m, C$\underline{H}_{Ar}$), 7.63 (1 H, m, C$\underline{H}_{Ar}$), 7.55 – 7.45 (4 H, m, C$\underline{H}_{Ar,.}$ N$\underline{H}$CHC), 7.35 (1 H, m, C$\underline{H}_{Ar}$), 7.21 (1 H, m, C$\underline{H}_{Ar}$), 6.17 + 6.11 (1 H, 2 x d, *J* = 7.2 Hz, NHC$\underline{H}$C), 5.59 (1 H, apparent t, *J* = 8.0 Hz, NC$\underline{H}$), 5.34 (1 H, m, N$\underline{H}$CHCH$_3$), 4.53 + 4.41 (1 H, 2 x quin, *J* = 7.1 + *J* = 7.0 Hz, NHC$\underline{H}$CH$_3$), 3.72 (3 H, s, OC$\underline{H}_3$), 3.38 (1 H, m, NCHC$\underline{H}$H), 3.28 – 3.19 (3 H, m, SC$\underline{H}_3$), 3.01 + 2.82 (3 H, 2 x s, NC$\underline{H}_3$), 2.95 (1 H, m, NHCHCH$\underline{H}$), 1.42 + 1.40 (9 H, 2 x s, C(C$\underline{H}_3$)$_3$), 1.02 + 0.98 (3 H, 2 x d, *J* = 6.9 Hz, CHC$\underline{H}_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 190.8 + 190.4 (C=O), 174.7 + 174.6 (C=O), 169.2 + 167.0 (C=O), 166.9 + 166.6 (C=O), 155.3 (C=O), 145.2 (C$_{Ar}$), 137.8 (C$_{Ar}$), 134.5 + 134.3 (C$\underline{H}_{Ar}$), 134.1 + 134.0 (C$\underline{H}_{Ar}$), 129.5 + 129.4 (C$\underline{H}_{Ar}$), 129.3 (C$\underline{H}_{Ar}$), 128.8 + 128.7 (C$\underline{H}_{Ar}$), 124.1 (C$\underline{H}_{Ar}$), 115.7 (C$_{Ar}$), 79.8 (C(CH$_3$)$_3$), 58.4 + 57.8 (NHCHC), 56.6 (NCH), 53.3 + 53.2 (OCH$_3$),, 46.6 (NHCHCH$_3$), 38.8 (SCH$_3$), 32.8 (CHCH$_2$), 30.9 + 30.8 (NCH$_3$), 28.3 (C(CH$_3$)$_3$), 17.8 (CHCH$_3$) ppm.

LRMS (ES$^+$) *m/z* 700 [M^{Br81}+H]$^+$, 698 [M^{Br79}+H]$^+$.

HRMS (ES$^+$) For $C_{29}H_{37}Br^{79}N_3NaO_{10}S$ calculated 698.1378, found 698.1380 Da.

4.51 - (5*S*,15*S*,18*R*,*E*)-21-Benzoyl-18-(3-bromo-4-((methylsulfonyl)oxy)benzyl)-2,2,3,3, 5,8,15,17-octamethyl-13,16,19-trioxo-4-oxa-14,17,20-triaza-3-siladocos-8-en-22-oic acid



$C_{41}H_{60}BrN_3O_{10}SSi$
M. W. = 894.99 g/mol

To a stirred solution of peptide **4.50** (74 mg, 0.11 mmol) in CH_2Cl_2 (2.5 mL) at 0 °C under Ar was added TFA (0.5 mL) dropwise. After 3 h at rt, the solvent was removed under reduced pressure, and the excess TFA was azeotroped with toluene (4 x 2.5 mL) to give the crude deprotected amine as an off white solid.

Experimental

In a separate flask, the aforementioned crude amine, acid **4.12** (33 mg, 0.11 mmol) and DIPEA (0.11 mL, 0.64 mmol) were taken into THF (2.1 mL) under Ar, and cooled to 0 °C. To this was added T3P (**4.28**) (83 µL, 0.14 mmol) dropwise, before stirring at rt for 18 h. H_2O (3 mL) was added and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic extracts were washed with citric acid (1 M, 6 mL) and H_2O (6 mL) before drying ($MgSO_4$) and concentrating under reduced pressure. Purification by column chromatography (EtOAc:hexane, 5:3) gave the title compound (**4.51**) (38 mg, 0.042 mmol, 39%) as a clear oil.

[α] 22.4 (c = 1.00).

FT-IR (neat) ν_{max} 2932 (w, C-H), 1737 (s, C=O), 1647 (w, alkene C=C) cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 – 8.02 (2 H, m, C$\underline{H}_{Ar}$), 7.65 (1 H, m, C$\underline{H}_{Ar}$), 7.55 – 7.42 (4 H, m, C$\underline{H}_{Ar}$, N$\underline{H}$CHC), 7.36 (1 H, m, C$\underline{H}_{Ar}$), 7.22 (1 H, m, C$\underline{H}_{Ar}$), 6.38 + 6.34 (1 H, 2 x d, *J* = 7.2 Hz, N$\underline{H}$CHCH$_3$), 6.15 + 6.11 (1 H, 2 x d, *J* = 7.4 Hz, NHC$\underline{H}$C), 5.57 (1 H, m, NC$\underline{H}$), 5.09 (1 H, t, *J* = 6.9 Hz, C=C$\underline{H}$), 4.83 + 4.75 (1 H, 2 x quin, *J* = 6.7 Hz, NHC$\underline{H}$CH$_3$), 3.80 – 3.68 (4 H, m, OC$\underline{H}_3$, C$\underline{H}$OSi), 3.38 (1 H, m, NHCHC$\underline{H}$H), 3.24 + 3.23 (1 H, 2 x s, SC$\underline{H}_3$), 3.01 + 2.97 (1H, 2 x s, NC$\underline{H}_3$), 2.96 (1 H, m NHCHCH$\underline{H}$), 2.24 – 2.14 (2 H, m, C$\underline{H}_2$C=O), 2.05 – 1.88 (3 H, m, C$\underline{H}_2$CH$_2$CHO, C=CHC$\underline{H}$H), 1.70 – 1.60 (3 H, m, C=CHCH$\underline{H}$, C$\underline{H}_2$CH$_2$C=O), 1.57 (3 H, s, C$\underline{H}_3$C=CH), 1.55 – 1.41 (2 H, m, C$\underline{H}_2$CHO), 1.13 + 1.12 (1 H, 2 x s, C$\underline{H}_3$CHO), 1.07 + 1.04 (1 H, 2 x d, *J* = 6.9 Hz, NHCHC$\underline{H}_3$), 0.89 (9 H, s, SiC(C$\underline{H}_3$)$_3$), 0.05 (6 H, s, SiC$\underline{H}_3$) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ 190.4 (C=O), 174.4 + 174.3 (C=O), 172.6 + 172.5 (C=O), 169.0 + 168.8 (C=O), 167.0 + 166.5 (C=O), 145.2 (C$_{Ar}$), 137.7 + 137.7 (C$_{Ar}$), 136.2 (C=CH), 134.5 + 134.4 (C$\underline{H}_{Ar}$), 134.1 (C$\underline{H}_{Ar}$), 133.9 (C$_{Ar}$), 129.5 (C$\underline{H}_{Ar}$), 129.3 (C$\underline{H}_{Ar}$), 128.8 + 128.8 (C$\underline{H}_{Ar}$), 124.3 + 124.2 (C$\underline{H}_{Ar}$), 123.1 (C=C$\underline{H}$), 115.8 + 115.7 (CBr), 68.5 (CHO), 58.4 + 57.8 (NHCHC), 56.6 (NCH), 53.4 + 53.2 (OC$\underline{H}_3$), 45.5 + 45.5 (NHCHCH$_3$), 38.9 (SC$\underline{H}_3$), 38.2 (CH$_2$CH$_2$HO), 36.0 (CH$_2$C=O), 35.9 (CH$_2$CH$_2$C=O), 32.7 (NHCHCH$_2$), 30.9 + 30.9 (NCH$_3$), 27.4 (C=CHCH$_2$), 25.9 (SiC(CH$_3$)$_3$), 25.6 + 25.6 (CH$_2$CHO), 23.8 (CH$_3$CHO), 18.1 (NHCHCH$_3$), 18.0 + 17.9 (SiC(CH$_3$)$_3$), 16.1 (CH$_3$C=CH), –4.4 (SiCH$_3$), –4.7 (SiCH$_3$) ppm.

LRMS (ES$^+$) *m/z* 896 [M^{Br81}+H]$^+$, 894 [M^{Br79}+H]$^+$.

HRMS (ES$^+$) For $C_{41}H_{60}Br^{79}N_3NaO_{10}SSi$ calculated 916.2850, found 916.2854 Da.

Appendices

X-ray crystallography data for cyclopentene 2.53

Table 1. Crystal data and structure refinement details.

Identification code	**2012sot0076 (6481 100)**
Empirical formula	$C_{36}H_{40}O_3$
Formula weight	520.68
Temperature	100(2) K
Wavelength	0.71075 Å
Crystal system	Orthorhombic
Space group	$C222_1$
Unit cell dimensions	a = 17.868(3) Å
	b = 23.467(4) Å
	c = 32.526(5) Å
Volume	13638(4) Å^3
Z	16
Density (calculated)	1.014 Mg / m^3
Absorption coefficient	0.063 mm^{-1}
F(000)	4480
Crystal	Fragment; Colourless
Crystal size	0.23 × 0.18 × 0.08 mm^3
θ range for data collection	2.93 – 25.03°
Index ranges	$-21 \le h \le 21$, $0 \le k \le 27$, $0 \le l \le 38$
Reflections collected	12037
Independent reflections	6491 [R_{int} = 0.0368]
Completeness to θ = 25.03°	99.7 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9950 and 0.9857
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6491 / 0 / 709
Goodness-of-fit on F^2	1.170
Final R indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0590, *wR2* = 0.1433
R indices (all data)	*R1* = 0.0670, *wR2* = 0.1473
Largest diff. peak and hole	0.296 and –0.197 e Å^{-3}

Diffractometer: *Rigaku AFC12* goniometer equipped with an enhanced sensitivity (HG) *Saturn724+* detector mounted at the window of an *FR-E+ SuperBright* molybdenum rotating anode generator with HF *Varimax* optics (100µm focus). **Cell determination, Data collection, Data reduction and cell refinement & Absorption correction**: CrystalClear-SM Expert 2.0 r7 (Rigaku, 2011) , **Structure solution**: SHELXS97 (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). S**tructure refinement**: SHELXL97 (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** CrystalMaker: a crystal and molecular structures program for Mac and Windows. CrystalMaker Software Ltd, Oxford, England (www.crystalmaker.com)

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model, except OH which were refined using restraints.

Appendix

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [$Å^2$ × 10^3] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
O1	2549(1)	1432(1)	809(1)	23(1)	1
O2	2846(1)	768(1)	1290(1)	27(1)	1
O3	1805(1)	267(1)	576(1)	24(1)	1
C1	3220(2)	2631(2)	728(1)	24(1)	1
C2	3399(2)	3163(2)	462(1)	26(1)	1
C3	3451(2)	3138(2)	32(1)	31(1)	1
C4	3547(2)	3629(2)	−204(1)	39(1)	1
C5	3614(3)	4150(2)	−16(2)	46(1)	1
C6	3557(3)	4189(2)	409(2)	46(1)	1
C7	3444(2)	3703(2)	640(1)	36(1)	1
C8	3640(2)	2633(2)	1145(1)	26(1)	1
C9	4322(2)	2905(2)	1193(1)	32(1)	1
C10	4737(2)	2854(2)	1553(1)	40(1)	1
C11	4485(2)	2527(2)	1872(1)	42(1)	1
C12	3806(2)	2249(2)	1830(1)	36(1)	1
C13	3388(2)	2304(2)	1475(1)	29(1)	1
C14	2351(2)	2678(2)	776(1)	25(1)	1
C15	2023(2)	2908(2)	1120(1)	32(1)	1
C16	1245(2)	3004(2)	1131(1)	38(1)	1
C17	796(2)	2886(2)	796(1)	36(1)	1
C18	1144(2)	2665(2)	444(1)	31(1)	1
C19	1905(2)	2568(2)	435(1)	26(1)	1
C20	3479(2)	2074(2)	497(1)	22(1)	1
C21	4328(2)	2089(2)	402(1)	29(1)	1
C22	4565(2)	1610(2)	111(1)	28(1)	1
C23	4389(2)	1030(2)	304(1)	29(1)	1
C24	3562(2)	1002(2)	426(1)	24(1)	1
C25	3345(2)	1497(2)	713(1)	23(1)	1
C26	2381(2)	1028(2)	1090(1)	21(1)	1
C27	1543(2)	930(2)	1129(1)	24(1)	1
C28	1323(2)	356(2)	926(1)	22(1)	1
C29	513(2)	451(2)	784(1)	28(1)	1
C30	463(2)	1082(2)	728(1)	28(1)	1
C31	1044(2)	1349(2)	907(1)	28(1)	1
C32	1346(2)	919(2)	1594(1)	26(1)	1
C33	1446(2)	1500(2)	1795(1)	29(1)	1
C34	1847(2)	1622(2)	2123(1)	36(1)	1
C35	1886(3)	2222(2)	2288(1)	41(1)	1
C36	2322(4)	1195(2)	2356(2)	78(2)	1
O4	7606(1)	3876(1)	1032(1)	25(1)	1
O5	7880(2)	3221(1)	545(1)	30(1)	1
O6	6819(1)	4187(1)	195(1)	26(1)	1
C37	8329(2)	3939(2)	1881(1)	27(1)	1
C38	8545(2)	4272(2)	2280(1)	32(1)	1
C39	8629(2)	4864(2)	2288(1)	41(1)	1
C40	8762(3)	5153(2)	2655(1)	53(1)	1
C41	8794(3)	4858(2)	3020(1)	54(1)	1
C42	8713(3)	4271(2)	3022(1)	49(1)	1
C43	8587(2)	3987(2)	2658(1)	38(1)	1
C44	8712(2)	3346(2)	1848(1)	31(1)	1
C45	9414(2)	3249(2)	2019(1)	38(1)	1
C46	9773(3)	2727(2)	1955(1)	45(1)	1

C47	9455(3)	2308(2)	1715(1)	49(1)	1
C48	8757(3)	2407(2)	1545(1)	45(1)	1
C49	8393(3)	2917(2)	1609(1)	35(1)	1
C50	7464(2)	3905(2)	1937(1)	26(1)	1
C51	7122(2)	3431(2)	2114(1)	34(1)	1
C52	6362(3)	3430(2)	2206(1)	37(1)	1
C53	5922(2)	3909(2)	2128(1)	34(1)	1
C54	6259(2)	4392(2)	1963(1)	29(1)	1
C55	7020(2)	4385(2)	1868(1)	27(1)	1
C56	8567(2)	4283(2)	1487(1)	27(1)	1
C57	9420(2)	4416(2)	1489(1)	32(1)	1
C58	9627(2)	4845(2)	1152(1)	38(1)	1
C59	9431(2)	4594(2)	733(1)	31(1)	1
C60	8595(2)	4425(2)	721(1)	26(1)	1
C61	8406(2)	4013(2)	1067(1)	24(1)	1
C62	7426(2)	3493(2)	741(1)	24(1)	1
C63	6588(2)	3431(2)	687(1)	27(1)	1
C64	6355(2)	3700(2)	266(1)	24(1)	1
C65	5537(2)	3888(2)	334(1)	29(1)	1
C66	5523(2)	3998(2)	798(1)	29(1)	1
C67	6103(2)	3754(2)	982(1)	26(1)	1
C68	6390(2)	2787(2)	694(1)	31(1)	1
C69	6511(2)	2521(2)	1112(1)	36(1)	1
C70	6527(3)	1979(2)	1198(2)	55(1)	1
C71	6633(4)	1780(3)	1640(2)	74(2)	1
C72	6473(6)	1525(3)	870(2)	119(3)	1

Table 3. Bond lengths [Å] and angles [°].

O1–C26	1.351(4)	C41–C42	1.385(7)
O1–C25	1.465(4)	C42–C43	1.378(6)
O2–C26	1.220(4)	C44–C45	1.391(6)
O3–C28	1.440(4)	C44–C49	1.395(6)
C1–C8	1.550(5)	C45–C46	1.398(6)
C1–C2	1.551(5)	C46–C47	1.380(7)
C1–C14	1.565(5)	C47–C48	1.384(7)
C1–C20	1.577(5)	C48–C49	1.378(6)
C2–C7	1.396(6)	C50–C55	1.397(5)
C2–C3	1.402(5)	C50–C51	1.394(5)
C3–C4	1.394(6)	C51–C52	1.391(6)
C4–C5	1.372(6)	C52–C53	1.395(6)
C5–C6	1.388(7)	C53–C54	1.391(6)
C6–C7	1.381(6)	C54–C55	1.396(5)
C8–C9	1.384(5)	C56–C61	1.533(5)
C8–C13	1.396(5)	C56–C57	1.556(5)
C9–C10	1.391(5)	C57–C58	1.535(5)
C10–C11	1.369(6)	C58–C59	1.524(5)
C11–C12	1.385(6)	C59–C60	1.547(5)
C12–C13	1.381(5)	C60–C61	1.522(5)
C14–C15	1.376(5)	C62–C63	1.516(5)
C14–C19	1.389(5)	C63–C67	1.498(5)
C15–C16	1.409(6)	C63–C68	1.552(5)
C16–C17	1.382(6)	C63–C64	1.565(5)
C17–C18	1.401(6)	C64–C65	1.543(5)
C18–C19	1.379(5)	C65–C66	1.528(5)
C20–C25	1.544(5)	C66–C67	1.326(6)
C20–C21	1.549(5)	C68–C69	1.511(6)
C21–C22	1.527(5)	C69–C70	1.304(6)
C22–C23	1.530(5)	C70–C72	1.509(9)
C23–C24	1.532(5)	C70–C72	1.525(7)
C24–C25	1.538(5)	C26–O1–C25	115.7(3)
C26–C27	1.520(5)	C8–C1–C2	112.8(3)
C27–C31	1.513(5)	C8–C1–C14	113.2(3)
C27–C28	1.550(5)	C2–C1–C14	101.7(3)
C27–C32	1.552(5)	C8–C1–C20	106.0(3)
C28–C29	1.534(5)	C2–C1–C20	109.9(3)
C29–C30	1.497(6)	C14–C1–C20	113.3(3)
C30–C31	1.344(5)	C7–C2–C3	116.5(4)
C32–C33	1.523(5)	C7–C2–C1	120.8(3)
C33–C34	1.316(5)	C3–C2–C1	122.5(3)
C34–C35	1.508(6)	C4–C3–C2	121.5(4)
C34–C36	1.515(7)	C5–C4–C3	120.1(4)
O4–C62	1.344(4)	C4–C5–C6	119.7(4)
O4–C61	1.469(4)	C7–C6–C5	119.8(4)
O5–C62	1.213(4)	C6–C7–C2	122.3(4)
O6–C64	1.432(4)	C9–C8–C13	116.9(3)
C37–C44	1.554(6)	C9–C8–C1	121.6(3)
C37–C50	1.558(5)	C13–C8–C1	121.0(3)
C37–C38	1.562(5)	C8–C9–C10	121.6(4)
C37–C56	1.574(5)	C11–C10–C9	120.8(4)
C38–C39	1.398(6)	C10–C11–C12	118.5(4)
C38–C43	1.401(5)	C13–C12–C11	120.9(4)
C39–C40	1.391(6)	C12–C13–C8	121.3(4)
C40–C41	1.378(7)	C15–C14–C19	118.6(3)

C15–C14–C1	122.0(3)	C48–C47–C46	118.5(5)
C19–C14–C1	118.6(3)	C49–C48–C47	120.7(5)
C14–C15–C16	120.2(4)	C48–C49–C44	121.3(4)
C17–C16–C15	121.4(4)	C55–C50–C51	117.5(4)
C16–C17–C18	117.5(4)	C55–C50–C37	120.2(3)
C19–C18–C17	121.0(4)	C51–C50–C37	121.6(4)
C18–C19–C14	121.3(4)	C52–C51–C50	121.3(4)
C25–C20–C21	105.2(3)	C51–C52–C53	120.6(4)
C25–C20–C1	117.8(3)	C52–C53–C54	119.0(4)
C21–C20–C1	111.4(3)	C53–C54–C55	119.9(4)
C22–C21–C20	112.3(3)	C50–C55–C54	121.8(4)
C21–C22–C23	110.2(3)	C61–C56–C57	105.7(3)
C22–C23–C24	110.0(3)	C61–C56–C37	117.6(3)
C23–C24–C25	111.6(3)	C57–C56–C37	111.3(3)
O1–C25–C24	107.2(3)	C58–C57–C56	111.4(3)
O1–C25–C20	109.8(3)	C59–C58–C57	109.2(3)
C24–C25–C20	110.4(3)	C58–C59–C60	110.1(3)
O2–C26–O1	124.2(3)	C61–C60–C59	111.0(3)
O2–C26–C27	123.3(3)	O4–C61–C60	107.2(3)
O1–C26–C27	112.5(3)	O4–C61–C56	110.0(3)
C31–C27–C26	116.2(3)	C60–C61–C56	110.7(3)
C31–C27–C28	102.2(3)	O5–C62–O4	124.3(3)
C26–C27–C28	110.2(3)	O5–C62–C63	123.3(3)
C31–C27–C32	110.0(3)	O4–C62–C63	112.5(3)
C26–C27–C32	108.0(3)	C67–C63–C62	116.7(3)
C28–C27–C32	110.2(3)	C67–C63–C68	110.7(3)
O3–C28–C29	110.4(3)	C62–C63–C68	108.5(3)
O3–C28–C27	108.2(3)	C67–C63–C64	101.6(3)
C29–C28–C27	104.0(3)	C62–C63–C64	109.0(3)
C30–C29–C28	103.6(3)	C68–C63–C64	110.1(3)
C31–C30–C29	111.2(3)	O6–C64–C65	110.1(3)
C30–C31–C27	111.0(4)	O6–C64–C63	108.0(3)
C33–C32–C27	112.2(3)	C65–C64–C63	104.0(3)
C34–C33–C32	127.4(4)	C66–C65–C64	101.8(3)
C33–C34–C35	121.2(4)	C67–C66–C65	111.1(4)
C33–C34–C36	124.4(4)	C66–C67–C63	112.4(3)
C35–C34–C36	114.4(4)	C69–C68–C63	112.4(3)
C62–O4–C61	115.7(3)	C70–C69–C68	126.8(4)
C44–C37–C50	113.5(3)	C69–C70–C72	122.4(5)
C44–C37–C38	113.4(3)	C69–C70–C71	120.3(5)
C50–C37–C38	100.0(3)	C72–C70–C71	117.3(5)
C44–C37–C56	106.5(3)		
C50–C37–C56	112.9(3)		
C38–C37–C56	110.6(3)		
C39–C38–C43	116.8(4)		
C39–C38–C37	122.8(4)		
C43–C38–C37	120.1(4)		
C40–C39–C38	121.4(4)		
C41–C40–C39	120.0(5)		
C40–C41–C42	120.0(4)		
C43–C42–C41	119.7(4)		
C42–C43–C38	122.1(4)		
C45–C44–C49	118.2(4)		
C45–C44–C37	121.1(4)		
C49–C44–C37	120.4(3)		
C44–C45–C46	119.9(5)		
C47–C46–C45	121.3(4)		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [Å^2× 10^3]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\ h\ k\ a^*\ b^*\ U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O1	26(1)	22(1)	20(1)	1(1)	−2(1)	−5(1)
O2	28(1)	28(2)	23(1)	2(1)	0(1)	−2(1)
O3	27(1)	26(1)	20(1)	−5(1)	4(1)	−3(1)
C1	22(2)	23(2)	25(2)	1(2)	−2(2)	−3(2)
C2	21(2)	24(2)	31(2)	0(2)	2(2)	−4(2)
C3	35(2)	28(2)	32(2)	6(2)	−6(2)	−6(2)
C4	41(3)	39(3)	37(2)	15(2)	3(2)	4(2)
C5	57(3)	26(2)	55(3)	16(2)	11(3)	6(2)
C6	52(3)	24(2)	61(3)	7(2)	6(2)	1(2)
C7	43(2)	28(2)	38(2)	5(2)	5(2)	1(2)
C8	26(2)	24(2)	26(2)	−1(2)	2(2)	−1(2)
C9	32(2)	37(2)	28(2)	1(2)	2(2)	−7(2)
C10	24(2)	59(3)	36(2)	−10(2)	−5(2)	−6(2)
C11	35(2)	71(3)	21(2)	−4(2)	−7(2)	−2(2)
C12	42(3)	46(3)	20(2)	3(2)	1(2)	1(2)
C13	32(2)	28(2)	27(2)	−4(2)	2(2)	−4(2)
C14	27(2)	23(2)	24(2)	5(2)	1(2)	−4(2)
C15	33(2)	29(2)	34(2)	−2(2)	−1(2)	−3(2)
C16	36(2)	39(3)	41(2)	−6(2)	6(2)	−2(2)
C17	34(2)	30(2)	43(2)	5(2)	−5(2)	2(2)
C18	33(2)	25(2)	34(2)	3(2)	−8(2)	5(2)
C19	28(2)	22(2)	30(2)	7(2)	−1(2)	−1(2)
C20	25(2)	25(2)	18(2)	1(2)	1(2)	−5(2)
C21	29(2)	29(2)	29(2)	5(2)	1(2)	−5(2)
C22	26(2)	27(2)	32(2)	6(2)	5(2)	−1(2)
C23	32(2)	27(2)	27(2)	2(2)	4(2)	2(2)
C24	25(2)	26(2)	23(2)	3(2)	0(2)	−1(2)
C25	20(2)	28(2)	22(2)	4(2)	−2(2)	−5(2)
C26	26(2)	17(2)	20(2)	−6(2)	−1(2)	−3(2)
C27	26(2)	28(2)	18(2)	−2(2)	0(2)	−3(2)
C28	23(2)	27(2)	17(2)	2(2)	3(2)	−5(2)
C29	22(2)	37(2)	25(2)	−7(2)	−3(2)	−9(2)
C30	25(2)	35(2)	25(2)	−3(2)	−2(2)	3(2)
C31	32(2)	29(2)	24(2)	4(2)	7(2)	0(2)
C32	26(2)	32(2)	20(2)	−1(2)	3(2)	−2(2)
C33	30(2)	31(2)	26(2)	−1(2)	4(2)	−1(2)
C34	40(2)	47(3)	20(2)	−5(2)	5(2)	−8(2)
C35	43(3)	45(3)	37(2)	−17(2)	6(2)	−5(2)
C36	124(6)	54(4)	57(3)	5(3)	−43(4)	−4(4)
O4	23(1)	28(2)	23(1)	2(1)	1(1)	−3(1)
O5	31(2)	31(2)	29(1)	−1(1)	4(1)	−4(1)
O6	28(1)	30(2)	21(1)	1(1)	−1(1)	−3(1)
C37	28(2)	36(2)	18(2)	4(2)	−5(2)	−1(2)
C38	21(2)	44(3)	31(2)	1(2)	−5(2)	2(2)
C39	40(3)	54(3)	30(2)	−2(2)	−12(2)	−1(2)
C40	55(3)	57(3)	45(3)	−13(2)	−23(2)	−2(3)
C41	58(3)	69(4)	34(3)	−9(2)	−25(2)	19(3)

C42	50(3)	73(4)	25(2)	–3(2)	–11(2)	22(3)
C43	40(2)	50(3)	24(2)	8(2)	–6(2)	15(2)
C44	35(2)	38(2)	21(2)	14(2)	0(2)	1(2)
C45	35(2)	53(3)	27(2)	9(2)	7(2)	14(2)
C46	37(3)	67(3)	30(2)	17(2)	8(2)	17(2)
C47	65(3)	43(3)	39(2)	12(2)	16(2)	17(3)
C48	65(3)	35(3)	36(2)	15(2)	8(2)	5(2)
C49	47(3)	34(2)	24(2)	11(2)	2(2)	2(2)
C50	30(2)	31(2)	17(2)	2(2)	1(2)	2(2)
C51	38(2)	33(2)	32(2)	12(2)	–1(2)	–3(2)
C52	43(3)	41(3)	28(2)	10(2)	4(2)	–12(2)
C53	23(2)	56(3)	21(2)	–1(2)	5(2)	–5(2)
C54	36(2)	31(2)	20(2)	1(2)	3(2)	0(2)
C55	27(2)	37(2)	18(2)	–2(2)	0(2)	–10(2)
C56	27(2)	35(2)	20(2)	5(2)	–1(2)	–3(2)
C57	25(2)	45(3)	27(2)	7(2)	–4(2)	–1(2)
C58	35(2)	43(3)	35(2)	8(2)	–7(2)	–15(2)
C59	28(2)	34(2)	30(2)	10(2)	1(2)	–10(2)
C60	24(2)	30(2)	24(2)	6(2)	–4(2)	–4(2)
C61	21(2)	27(2)	25(2)	2(2)	0(2)	–2(2)
C62	31(2)	25(2)	18(2)	4(2)	1(2)	–2(2)
C63	30(2)	29(2)	22(2)	–3(2)	–1(2)	–7(2)
C64	27(2)	26(2)	20(2)	–1(2)	1(2)	–6(2)
C65	27(2)	32(2)	27(2)	–2(2)	–4(2)	–3(2)
C66	27(2)	29(2)	31(2)	–5(2)	3(2)	–11(2)
C67	27(2)	32(2)	20(2)	–5(2)	4(2)	–15(2)
C68	35(2)	31(2)	26(2)	0(2)	2(2)	–10(2)
C69	36(2)	37(3)	35(2)	2(2)	3(2)	–7(2)
C70	65(4)	40(3)	58(3)	15(3)	–23(3)	–8(2)
C71	86(4)	59(4)	78(4)	36(3)	–15(3)	–2(3)
C72	190(9)	56(4)	112(6)	22(4)	–73(6)	–1(5)

Table 5. Hydrogen coordinates [× 10^4] and isotropic displacement parameters [$Å^2$ × 10^3].

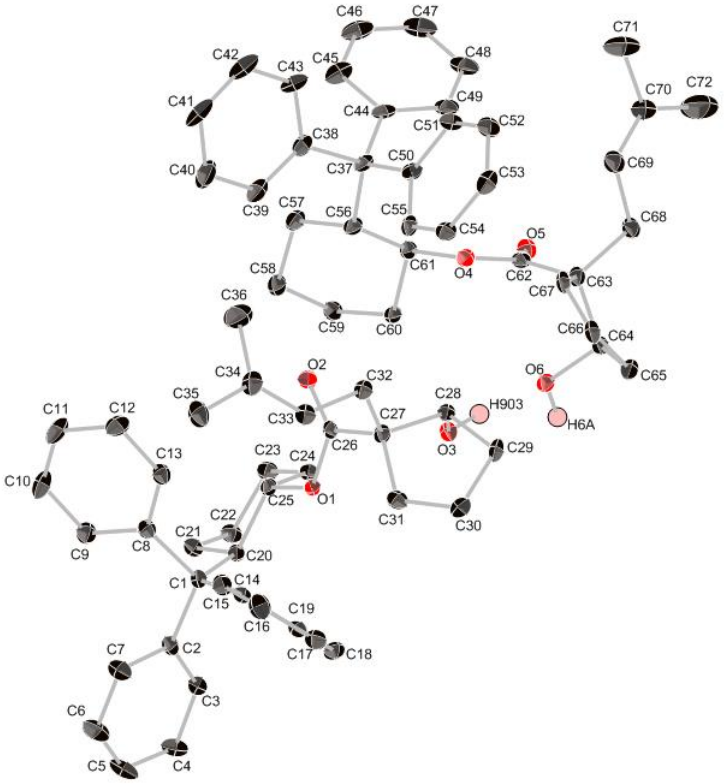
Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H903	1757	−69	492	37	1
H3	3420	2779	−101	38	1
H4	3566	3602	−495	47	1
H5	3699	4482	−176	55	1
H6	3595	4550	540	55	1
H7	3395	3738	929	43	1
H9	4511	3131	974	39	1
H10	5201	3049	1577	48	1
H11	4770	2492	2118	51	1
H12	3624	2018	2048	43	1
H13	2920	2113	1454	35	1
H15	2322	3003	1352	38	1
H16	1024	3154	1374	46	1
H17	272	2952	803	43	1
H18	851	2582	207	37	1
H19	2128	2422	192	32	1
H20	3209	2062	228	27	1
H21A	4455	2460	275	35	1
H21B	4612	2055	662	35	1
H22A	5108	1638	55	34	1
H22B	4295	1648	−153	34	1
H23A	4707	971	549	34	1
H23B	4502	724	104	34	1
H24A	3463	636	567	29	1
H24B	3248	1016	176	29	1
H25	3646	1477	972	28	1
H28	1359	33	1125	27	1
H29A	413	249	523	34	1
H29B	154	317	995	34	1
H30	72	1271	585	34	1
H31	1130	1748	896	34	1
H32A	820	794	1628	31	1
H32B	1671	638	1735	31	1
H33	1190	1809	1670	35	1
H35A	1598	2477	2110	62	1
H35B	2409	2348	2296	62	1
H35C	1678	2232	2567	62	1
H36A	2304	826	2214	118	1
H36B	2127	1152	2635	118	1
H36C	2840	1330	2367	118	1
H6A	6775	4292	−51	39	1
H39	8595	5073	2039	50	1
H40	8831	5555	2652	63	1
H41	8871	5057	3271	64	1
H42	8745	4065	3273	59	1
H43	8527	3585	2663	45	1
H45	9650	3537	2178	46	1
H46	10245	2660	2080	53	1
H47	9709	1958	1667	59	1
H48	8526	2121	1381	54	1
H49	7915	2977	1488	42	1
H51	7413	3102	2172	41	1
H52	6140	3100	2324	45	1

H53	5401	3905	2186	40	1
H54	5971	4726	1916	35	1
H55	7243	4717	1752	32	1
H56	8297	4656	1496	33	1
H57A	9563	4572	1761	39	1
H57B	9704	4058	1446	39	1
H58A	9349	5205	1194	45	1
H58B	10169	4931	1164	45	1
H59A	9745	4253	681	37	1
H59B	9536	4877	515	37	1
H60A	8282	4772	748	31	1
H60B	8479	4246	453	31	1
H61	8709	3657	1036	29	1
H64	6395	3417	37	29	1
H65A	5419	4238	177	35	1
H65B	5181	3583	256	35	1
H66	5149	4212	935	35	1
H67	6200	3782	1268	32	1
H68A	5860	2737	613	37	1
H68B	6704	2585	489	37	1
H69	6584	2776	1335	43	1
H71A	6729	2110	1817	111	1
H71B	7059	1517	1654	111	1
H71C	6179	1584	1734	111	1
H72A	6026	1293	917	179	1
H72B	6919	1282	881	179	1
H72C	6440	1707	599	179	1

Table 6. Hydrogen bonds [Å and °].

D–H···*A*	*d*(*D*–H)	*d*(H···*A*)	*d*(*D*···*A*)	∠(*D*H*A*)
O3–H903···O6^{i}	0.84	2.00	2.823(4)	166.7
O6–H6A···O3^{ii}	0.84	2.00	2.817(4)	164.3

Symmetry transformations used to generate equivalent atoms:
(i) x–1/2,y–1/2,z (ii) x+1/2,–y+1/2,–z



Thermal ellipsoids are drawn at the 35% probability level.

Appendix

X-ray crystallography data for alkyne 2.102

Table 1. Crystal data and structure refinement details.

Identification code	**2013sot0048**
Empirical formula	$C_{14}H_{20}O_3$
Formula weight	236.30
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 12.487(3) Å
	b = 5.9421(13) Å β = 92.497(5)°
	c = 18.448(4) Å
Volume	1367.5(5) Å^3
Z	4
Density (calculated)	1.148 Mg / m^3
Absorption coefficient	0.079 mm^{-1}
F(000)	512
Crystal	Fragment; Colourless
Crystal size	0.230 × 0.110 × 0.050 mm^3
θ range for data collection	3.266 – 27.484°
Index ranges	$-16 \le h \le 14$, $-4 \le k \le 7$, $-21 \le l \le 23$
Reflections collected	6858
Independent reflections	3125 [R_{int} = 0.0229]
Completeness to θ = 25.242°	99.4 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	1.000 and 0.734
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3125 / 0 / 161
Goodness-of-fit on F^2	1.061
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0446, $wR2$ = 0.1019
R indices (all data)	$R1$ = 0.0523, $wR2$ = 0.1067
Extinction coefficient	n/a
Largest diff. peak and hole	0.295 and –0.192 e Å^{-3}

Diffractometer: *Rigaku AFC12* goniometer equipped with an enhanced sensitivity (HG) *Saturn724+* detector mounted at the window of an *FR-E+ SuperBright* molybdenum rotating anode generator with HF *Varimax* optics (100µm focus). **Cell determination, Data collection, Data reduction and cell refinement & Absorption correction**: CrystalClear-SM Expert 2.0 r7 (Rigaku, 2011) , **Structure solution**: SHELXS97 (Sheldrick, G.M. (2008). *Acta Cryst*. **A64**, 112-122). **Structure refinement**: SHELXL2012 (G. M. Sheldrick (2012), University of Göttingen, Germany). **Graphics:** CrystalMaker: a crystal and molecular structures program for Mac and Windows. CrystalMaker Software Ltd, Oxford, England (www.crystalmaker.com)

Special details:

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
O1	1601(1)	6085(2)	5354(1)	20(1)	1
O2	1133(1)	9688(2)	5504(1)	20(1)	1
O3	718(1)	8983(2)	3833(1)	20(1)	1
C1	923(1)	5476(3)	5946(1)	28(1)	1
C2	1631(1)	8260(2)	5192(1)	15(1)	1
C3	2371(1)	8827(2)	4578(1)	14(1)	1
C4	2757(1)	6748(2)	4198(1)	18(1)	1
C5	3763(1)	6200(2)	4094(1)	23(1)	1
C6	3284(1)	10322(2)	4915(1)	16(1)	1
C7	3790(1)	9341(2)	5599(1)	17(1)	1
C8	3873(1)	10315(2)	6248(1)	19(1)	1
C9	4388(1)	9101(3)	6890(1)	29(1)	1
C10	3483(1)	12639(2)	6420(1)	25(1)	1
C11	1649(1)	10243(2)	4039(1)	16(1)	1
C12	2206(1)	10877(2)	3344(1)	20(1)	1
C13	1540(1)	12465(2)	2914(1)	23(1)	1
C14	967(1)	13736(3)	2591(1)	30(1)	1

Appendix

Table 3. Bond lengths [Å] and angles [°].

O1–C2	1.3274(15)	C4–C5	1.3204(18)
O1–C1	1.4555(15)	C6–C7	1.5048(16)
O2–C2	1.2113(15)	C7–C8	1.3301(17)
O3–C11	1.4210(14)	C8–C10	1.5029(18)
C2–C3	1.5307(16)	C8–C9	1.5056(17)
C3–C4	1.5094(17)	C11–C12	1.5306(17)
C3–C6	1.5531(15)	C12–C13	1.4679(18)
C3–C11	1.5592(15)	C13–C14	1.1827(19)

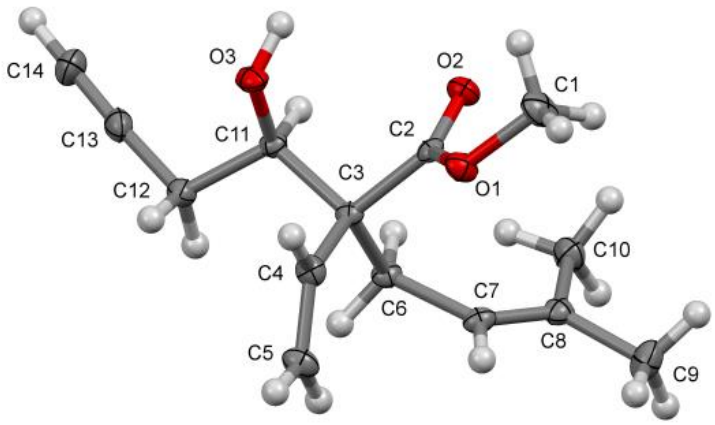
C2–O1–C1	115.72(10)	C7–C6–C3	112.88(10)
O2–C2–O1	123.73(11)	C8–C7–C6	126.91(12)
O2–C2–C3	122.37(11)	C7–C8–C10	125.14(11)
O1–C2–C3	113.89(10)	C7–C8–C9	120.87(12)
C4–C3–C2	112.24(10)	C10–C8–C9	113.99(11)
C4–C3–C6	114.22(10)	O3–C11–C12	107.61(9)
C2–C3–C6	106.58(9)	O3–C11–C3	109.24(10)
C4–C3–C11	109.44(9)	C12–C11–C3	113.32(10)
C2–C3–C11	103.94(9)	C13–C12–C11	110.11(10)
C6–C3–C11	109.91(10)	C14–C13–C12	176.87(14)
C5–C4–C3	126.49(11)		

Table 4. Anisotropic displacement parameters [Å^2× 10^3]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\ h\ k\ a^*\ b^*\ U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O1	20(1)	17(1)	24(1)	3(1)	6(1)	−1(1)
O2	19(1)	20(1)	22(1)	−2(1)	4(1)	1(1)
O3	13(1)	26(1)	22(1)	−5(1)	0(1)	−2(1)
C1	28(1)	26(1)	31(1)	9(1)	11(1)	−2(1)
C2	12(1)	16(1)	16(1)	−1(1)	−3(1)	−2(1)
C3	13(1)	14(1)	16(1)	0(1)	1(1)	−1(1)
C4	21(1)	15(1)	19(1)	−1(1)	2(1)	−2(1)
C5	22(1)	19(1)	28(1)	−3(1)	6(1)	0(1)
C6	15(1)	15(1)	19(1)	0(1)	0(1)	−3(1)
C7	15(1)	14(1)	23(1)	1(1)	−2(1)	−1(1)
C8	15(1)	20(1)	21(1)	1(1)	1(1)	−2(1)
C9	36(1)	29(1)	22(1)	1(1)	−8(1)	1(1)
C10	27(1)	25(1)	21(1)	−4(1)	2(1)	3(1)
C11	14(1)	17(1)	17(1)	−2(1)	−1(1)	0(1)
C12	17(1)	24(1)	18(1)	2(1)	1(1)	0(1)
C13	23(1)	29(1)	16(1)	−1(1)	1(1)	−3(1)
C14	31(1)	38(1)	21(1)	5(1)	−2(1)	6(1)

Table 5. Hydrogen coordinates [× 10^4] and isotropic displacement parameters [$Å^2$ × 10^3].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1A	1148	6320	6382	42	1
H1B	989	3859	6042	42	1
H1C	175	5838	5810	42	1
H4	2222	5733	4016	22	1
H5A	4327	7160	4266	28	1
H5B	3923	4846	3847	28	1
H6A	3842	10520	4555	20	1
H6B	2990	11826	5023	20	1
H7	4082	7870	5564	21	1
H9A	4588	7576	6745	44	1
H9B	3881	9017	7280	44	1
H9C	5031	9920	7062	44	1
H10A	3260	13409	5968	37	1
H10B	4062	13491	6668	37	1
H10C	2873	12534	6734	37	1
H11	1427	11652	4288	19	1
H12A	2910	11572	3471	24	1
H12B	2330	9506	3055	24	1
H14	508	14757	2332	36	1
H93	170(15)	9500(30)	4075(10)	48(5)	1



Thermal ellipsoids drawn at the 50% probability level.

List of References

1. Liu, D.-Z.; Wang, F.; Liao, T.-G.; Tang, J.-G.; Steglich, W.; Zhu, H.-J.; Liu, J.-K., *Org. Lett.*, **2006**, *8*, 5749-5752.
2. Yun, J. W., *Phytochemistry*, **2010**, *71*, 1625-1641.
3. Voshol, P. J.; Rensen, P. C. N.; van Dijk, K. W.; Romijn, J. A.; Havekes, L. M., *Biochim. Biophys. Acta (BBA) Mol. Cell. Biol. L.*, **2009**, *1791*, 479-485.
4. Schrauwen, P.; Westerterp, K., *Br. J. Nutr.*, **2000**, *84*, 417-427.
5. Jakicic, J. M.; Otto, A. D., *Am. J. Clin. Nutr.*, **2005**, *82*, 226-229.
6. Lau, D. C. W.; Douketis, J. D.; Morrison, K. M.; Hramiak, I. M.; Sharma, A. M.; Ur, E., *Can. Med. Assoc. J.*, **2007**, *176*, S1-S13.
7. WHO. http://www.who.int/mediacentre/factsheets/fs311/en/, accessed 24th March, **2014**.
8. Birari, R. B.; Bhutani, K. K., *Drug Discov. Today*, **2007**, *12*, 879-889.
9. Hill, J.; Wyatt, H.; Phelan, S.; Wing, R., *J. Nutr. Educ. Behav.*, **2005**, *37*, 206-210.
10. Padwal, R. S.; Majumdar, S. R., *Lancet*, **2007**, *369*, 71-77.
11. Chaput, J. P.; St-Pierre, S.; Tremblay, A., *Mini-Rev. Med. Chem.*, **2007**, 3-10.
12. Gloy, V.; Briel, M.; Bhatt, D.; Kashyap, S.; Schauer, P.; Mingrone, G.; Bucher, H.; Nordmann, A., *Br. Med. J.*, **2013**, *347*.
13. Arterburn, D.; Bogart, A.; Coleman, K. J.; Haneuse, S.; Selby, J. V.; Sherwood, N. E.; Sidney, S.; Theis, M. K.; Campos, G. M.; McCulloch, D.; O'Connor, P. J., *Obes. Res. Clin. Pract.*, **2013**, *7*, 258-268.
14. Bond, D.; Phelan, S.; Leahey, T.; Hill, J.; Wing, R., *Int. J. Obesity*, **2009**, *33*, 173-180.
15. Fried, M.; Yumuk, V.; Oppert, J.; Scopinaro, N.; Torres, A.; Weiner, R.; Yashkov, Y.; Fruhbeck, G., *Obes. Surg.*, **2014**, *24*, 42-55.
16. Tainter, M. L.; Cutting, W. C.; Stockton, A. B., *Am. J. Public Health Nations Health*, **1934**, *24*, 1045-1053.
17. Phillips, L.; Singer, M. A., *Neurology*, **2013**, *80*, 773-774.
18. Colman, E., *Circulation*, **2012**, *125*, 2156-2164.
19. Di Dalmazi, G.; Vicennati, V.; Pasquali, R.; Pagotto, U., *Endocrine*, **2013**, *44*, 598-609.
20. Rucker, D.; Padwal, R.; Li, S. K.; Curioni, C.; Lau, D. C., *Br. Med. J.*, **2007**, *335*, 1194-1199.
21. James, W. P.; Caterson, I. D.; Coutinho, W.; Finer, N.; Van Gaal, L. F.; Maggioni, A. P.; Torp-Pedersen, C.; Sharma, A. M.; Shepherd, G. M.; Rode, R. A.; Renz, C. L.; Investigators, S., *N. Engl. J. Med.*, **2010**, *363*, 905-917.
22. Van Gaal, L. F.; Rissanen, A. M.; Scheen, A. J.; Ziegler, O.; Rössner, S., *Lancet*, **2005**, *365*, 1389-1397.
23. Christensen, R.; Kristensen, P. K.; Bartels, E. M.; Bliddal, H.; Astrup, A., *Lancet*, **2007**, *370*, 1706-1713.
24. Winkler, F. K.; D'Arcy, A.; Hunziker, W., *Nature*, **1990**, *343*, 771-774.
25. Mukherjee, M., *J. Mol. Catal. B: Enzym.*, **2003**, *22*, 369-376.
26. McClendon, K.; Riche, D.; Uwaifo, G., *Expert Opin. Drug Saf.*, **2009**, *8*, 727-744.
27. Weibel, E. K.; Hadvary, P.; Hochuli, E.; Kupfer, E.; Lengsfeld, H., *J. Antibiot. (Tokyo)*, **1987**, *40*, 1081-1085.
28. Hadvary, P.; Lengsfeld, H.; Wolfer, H., *Biochem. J.*, **1988**, *256*, 357-361.

29. Li, Z.; Maglione, M.; Tu, W.; Mojica, W.; Arterburn, D.; Shugarman, L. R.; Hilton, L.; Suttorp, M.; Solomon, V.; Shekelle, P. G.; Morton, S. C., *Ann. Intern. Med.*, **2005**, *142*, 532-546.
30. Rossner, S.; Sjostrom, L.; Noack, R.; Meinders, A.; Noseda, G., *Obes. Res.*, **2000**, *8*, 49-61.
31. Paterson, I.; Doughty, V. A., *Tetrahedron Lett.*, **1999**, *40*, 393-394.
32. Tripathi, D.; Kumar, P., *Tetrahedron: Asymmetry*, **2012**, *23*, 884-890.
33. Venukadasula, P. K. M.; Chegondi, R.; Maitra, S.; Hanson, P. R., *Org. Lett.*, **2010**, *12*, 1556-1559.
34. Schwindt, M.; Fleming, M.; Han, Y.; Hodges, L.; Johnston, D.; Micheli, R.; Roberts, C.; Snyder, R.; Topping, R.; Puntener, K.; Scalone, M., *Org. Process Res. Dev.*, **2007**, *11*, 524-533.
35. Pons, J.-M.; Kocieński, P., *Tetrahedron Lett.*, **1989**, *30*, 1833-1836.
36. Zhou, Q.; Snider, B. B., *Org. Lett.*, **2008**, *10*, 1401-1404.
37. Zhou, Q.; Snider, B. B., *J. Org. Chem.*, **2008**, *73*, 8049-8056.
38. Zeiler, E.; Braun, N.; Bottcher, T.; Kastenmuller, A.; Weinkauf, S.; Sieber, S., *Angew. Chem. Int. Ed.*, **2011**, *50*, 11001-11004.
39. Frees, D.; Qazi, S.; Hill, P.; Ingmer, H., *Mol. Microbiol.*, **2003**, *48*, 1565-1578.
40. Böttcher, T.; Sieber, S. A., *J. Am. Chem. Soc.*, **2008**, *130*, 14400-14401.
41. Jiang, M.; Wang, F.; Yang, X.; Fang, L.; Dong, Z.; Zhu, H.; Liu, J., *Chem. Pharm. Bull.*, **2008**, *56*, 1286-1288.
42. Jiang, M.; Zhang, L.; Dong, Z.; Yang, Z.; Leng, Y.; Liu, J., *Chem. Pharm. Bull.*, **2010**, *58*, 113-116.
43. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H., *J. Am. Chem. Soc.*, **1991**, *113*, 4092-4096.
44. Andrews, R.; Walker, B., *Clin. Sci.*, **1999**, *96*, 513-523.
45. Wang, G.; Wei, K.; Feng, T.; Li, Z.; Zhang, L.; Wang, Q.; Liu, J., *J. Asian Nat. Prod. Res.*, **2012**, *14*, 115-120.
46. Wang, G.; Wei, K.; Li, Z.; Feng, T.; Ding, J.; Wang, Q.; Liu, J., *J. Asian Nat. Prod. Res.*, **2013**, *15*, 950-955.
47. Zhao, P.; Yang, Y.; Du, L.; Liu, J.; Zeng, Y., *Angew. Chem. Int. Ed.*, **2013**, *52*, 2298-2302.
48. Kroner, S. M.; DeMatteo, M. P.; Hadad, C. M.; Carpenter, B. K., *J. Am. Chem. Soc.*, **2005**, *127*, 7466-7473.
49. Grob, C. A., *Angew. Chem. Int. Ed.*, **1969**, 535-546.
50. Yang, H.; Zhao, C.; Romo, D., *Tetrahedron*, **1997**, *53*, 16471-16488.
51. Racherla, U. S.; Brown, H. C., *J. Org. Chem.*, **1991**, *56*, 401-404.
52. Ma, G.; Zancanella, M.; Oyola, Y.; Richardson, R. D.; Smith, J. W.; Romo, D., *Org. Lett.*, **2006**, *8*, 4497-4500.
53. Pons, J.-M.; Pommier, A.; Lerpiniere, J.; Kocienski, P., *J. Chem. Soc. Perkin Trans. 1*, **1993**, 1549-1551.
54. Pommier, A.; Pons, J.-M.; Kocienski, P. J., *J. Org. Chem.* **1995**, *60*, 7334-7339.
55. J. Kocienski, P.; Pelotier, B.; Pons, J.-M.; Prideaux, H., *J. Chem. Soc. Perkin Trans. 1*, **1998**, 1373-1382.
56. Bates, R. W.; Fernandez-Moro, R.; Ley, S. V., *Tetrahedron*, **1991**, *47*, 9929-9938.
57. Bates, R. W.; Fernández-Moro, R.; Ley, S. V., *Tetrahedron Lett.*, **1991**, *32*, 2651-2654.
58. Wu, Y.; Sun, Y. P., *J. Org. Chem.*, **2006**, *71*, 5748-5751.

59. Crimmins, M. T.; King, B. W.; Tabet, E. A., *J. Am. Chem. Soc.*, **1997**, *119*, 7883-7884.
60. Case-Green, S. C.; Davies, S. G.; Roberts, P. M.; Russell, A. J.; Thomson, J. E., *Tetrahedron: Asymmetry*, **2008**, *19*, 2620-2631.
61. Baker, R. W.; Davies, S. G., *Tetrahedron: Asymmetry*, **1993**, *4*, 1479-1480.
62. Mineeva, I., *Russ. J. Org. Chem.*, **2013**, *49*, 1647-1654.
63. Ihara, M.; Takahashi, M.; Niitsuma, H.; Taniguchi, N.; Yasui, K.; Fukumoto, K., *J. Org. Chem.*, **1989**, *54*, 5413-5415.
64. Corey, E. J.; Ensley, H. E., *J. Am. Chem. Soc.*, **1975**, *97*, 6908-6909.
65. Ihara, M.; Taniguchi, N.; Kai, T.; Satoh, K.; Fukumoto, K., *J. Chem. Soc. Perkin Trans. 1*, **1992**, 221-227.
66. Moreno-Mañas, M.; Sebastián, R. M.; Vallribera, A.; Molins, E.; Espinosa, E., *Tetrahedron: Asymmetry*, **1997**, *8*, 1525-1527.
67. Jones, M. C.; Marsden, S. P.; Muñoz Subtil, D. M., *Org. Lett.*, **2006**, *8*, 5509-5512.
68. Ihara, M.; Takahashi, M.; Taniguchi, N.; Yasui, K.; Niitsuma, H.; Fukumoto, K., *J. Chem. Soc. Perkin Trans. 1*, **1991**, 525-535.
69. Peddle, G. J. D., *J. Organomet. Chem.*, **1968**, *14*, 115-121.
70. Al Hazmi, A. M., Post-Doctorate Thesis, **2010**.
71. Watkin, S., Post-Doctorate Thesis, **2013**.
72. Rodríguez, J. B.; Markey, S. P.; Ziffer, H., *Tetrahedron: Asymmetry*, **1993**, *4*, 101-108.
73. Corey, E. J.; Ensley, H. E.; Suggs, J. W., *J. Org. Chem.*, **1976**, *41*, 380-381.
74. Arisawa, M.; Akamatsu, K.; Yamaguchi, M., *Org. Lett.*, **2001**, *3*, 789-790.
75. Ohnuma, T.; Hata, N.; Fujiwara, H.; Ban, Y., *J. Org. Chem.*, **1982**, *47*, 4713-4717.
76. Brunce, R. A.; Burns, S. E., *Org. Prep. Proced. Int.*, **1999**, 99-106.
77. Baader, S.; Ohlmann, D.; Goossen, L., *Chem. Eur. J.*, **2013**, *19*, 9807-9810.
78. Hegedus, L. S.; Williams, R. E.; McGuire, M. A.; Hayashi, T., *J. Am. Chem. Soc.*, **1980**, *102*, 4973-4979.
79. Seefelder, M., *Liebigs Ann. Chem.*, **1962**, 107-114.
80. Sylla, M.; Joseph, D.; Chevallier, E.; Camara, C.; Dumas, F., *Synthesis*, **2006**, 1045-1049.
81. Herrmann, J.; Kieczyko.C. R; Schlessi. R. H., *Tetrahedron Lett.*, **1973**, 2433-2436.
82. Okrasa, K.; Levy, C.; Wilding, M.; Goodall, M.; Baudendistel, N.; Hauer, B.; Leys, D.; Micklefield, J., *Angew. Chem. Int. Ed.*, **2009**, *48*, 7691-7694.
83. Sugikubo, K.; Omachi, F.; Miyanaga, Y.; Inagaki, F.; Matsumoto, C.; Mukai, C., *Angew. Chem. Int. Ed.*, **2013**, *52*, 11369-11372.
84. Sato, Y.; Oonishi, Y.; Mori, M., *J. Org. Chem.*, **2003**, *68*, 9858-9860.
85. Millán, A.; Álvarez de Cienfuegos, L.; Miguel, D.; Campaña, A. G.; Cuerva, J. M., *Org. Lett.*, **2012**, *14*, 5984-5987.
86. Bissember, A.; Banwell, M., *Tetrahedron*, **2009**, *65*, 8222-8230.
87. Shiraishi, S.; Nomoto, S., *Agric. Biol. Chem.*, **1988**, *52*, 1601-1602.
88. Jones, D. N.; Mundy, D.; Whitehouse, R. D., *J. Chem. Soc. Chem. Commun.*, **1970**, 86-87.
89. Kocienski, P.; Yeates, C., *J. Chem. Soc. Perkin Trans. 1*, **1985**, 1879-1883.
90. Grachan, M. L.; Tudge, M. T.; Jacobsen, E. N., *Angew. Chem. Int. Ed.*, **2008**, 1469-1472.
91. Ayers, T. A., *Tetrahedron Lett.*, **1999**, *40*, 5467-5470.

92. Adam, W.; Baeza, J.; Liu, J.-C., *J. Am. Chem. Soc.*, **1972**, *94*, 2000-2006.
93. Coulombel, L.; Favier, I.; Dunach, E., *Chem. Commun.*, **2005**, 2286-2288.
94. Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, G.; Rothe-Streit, P.; Schwarzenbach, F., *J. Am. Chem. Soc.*, **1992**, *114*, 2321-2336.
95. Le Flohic, A.; Meyer, C.; Cossy, J., *Org. Lett.*, **2004**, *7*, 339-342.
96. Hopkins, C. D.; Schmitz, J. C.; Chu, E.; Wipf, P., *Org. Lett.*, **2011**, *13*, 4088-4091.
97. Wullschleger, C. W.; Gertsch, J.; Altmann, K.-H., *Org. Lett.*, **2010**, *12*, 1120-1123.
98. Gauthier, D. R.; Carreira, E. M., *Angew. Chem. Int. Ed.*, **1996**, *35*, 2363-2365.
99. Linclau, B.; Cini, E.; Oakes, C. S.; Josse, S.; Light, M.; Ironmonger, V., *Angew. Chem. Int. Ed.*, **2012**, *51*, 1232-1235.
100. Iwaoka, M.; Tomoda, S., *J. Chem. Soc. Chem. Commun.*, **1992**, 1165-1167.
101. Ha, M. W.; Hong, S.; Park, C.; Park, Y.; Lee, J.; Kim, M.-h.; Lee, J.; Park, H.-g., *Org. Biomol. Chem.*, **2013**, *11*, 4030-4039.
102. Hong, S.; Lee, J.; Kim, M.; Park, Y.; Park, C.; Kim, M.-h.; Jew, S.-s.; Park, H.-g., *J. Am. Chem. Soc.*, **2011**, *133*, 4924-4929.
103. Kirkland, T. A.; Grubbs, R. H., *J. Org. Chem.*, **1997**, *62*, 7310-7318.
104. Dinger, M. B.; Mol, J. C., *Organometallics*, **2003**, *22*, 1089-1095.
105. Dinger, M. B.; Mol, J. C., *Eur. J. Inorg. Chem.*, **2003**, 2827-2833.
106. Louie, J.; Bielawski, C. W.; Grubbs, R. H., *J. Am. Chem. Soc.*, **2001**, *123*, 11312-11313.
107. Hoye, T. R.; Zhao, H., *Org. Lett.*, **1999**, *1*, 1123-1125.
108. Hoye, T.; Jeffrey, C.; Tennakoon, M.; Wang, J.; Zhao, H., *J. Am. Chem. Soc.*, **2004**, *126*, 10210-10211.
109. Hoye, T. R.; Jeon, J.; Tennakoon, M. A., *Angew. Chem. Int. Ed.*, **2011**, 2141-2143.
110. Lee, J.; Parker, K. A., *Org. Lett.*, **2012**, *14*, 2682-2685.
111. Cardillo, G.; Fabbroni, S.; Gentilucci, L.; Gianotti, M.; Tolomelli, A., *Synthetic Commun.*, **2003**, *33*, 1587-1594.
112. Clark, J. R.; French, J. M.; Jecs, E.; Diver, S. T., *Org. Lett.*, **2012**, *14*, 4178-4181.
113. Healy, M. P.; Parsons, A. F.; Rawlinson, J. G. T., *Org. Lett.*, **2005**, *7*, 1597-1600.
114. Kinoshita, A.; Mori, M., *Synlett*, **1994**, 1020-1022.
115. Lippstreu, J. J.; Straub, B. F., *J. Am. Chem. Soc.*, **2005**, *127*, 7444-7457.
116. Lloyd-Jones, G. C.; Margue, R. G.; de Vries, J. G., *Angew. Chem. Int. Ed.*, **2005**, 7442-7447.
117. Galan, B. R.; Giessert, A. J.; Keister, J. B.; Diver, S. T., *J. Am. Chem. Soc.*, **2005**, *127*, 5762-5763.
118. Villar, H.; Frings, M.; Bolm, C., *Chem. Soc. Rev.*, **2007**, *36*, 55-66.
119. Grotevendt, A. G. D.; Lummiss, J. A. M.; Mastronardi, M. L.; Fogg, D. E., *J. Am. Chem. Soc.*, **2011**, *133*, 15918-15921.
120. Mori, M.; Sakakibara, N.; Kinoshita, A., *J. Org. Chem.*, **1998**, *63*, 6082-6083.
121. Leeuwenburgh, M. A.; Appeldoorn, C. C. M.; van Hooft, P. A. V.; Overkleeft, H. S.; van der Marel, G. A.; van Boom, J. H., *Eur. J. Org. Chem.*, **2000**, 873-877.
122. Benneche, T.; Gundersen, L.; Undheim, K., *Acta Chem. Scand. B*, **1988**, *42*, 384-389.
123. Chevallier, O.; Migaud, M., *Beilstein J. Org. Chem.*, **2006**, *2*.

124. Williams, D. R.; Li, J., *Tetrahedron Lett.*, **1994**, *35*, 5113-5116.
125. DiLauro, A.; Seo, W.; Phillips, S., *J. Org. Chem.*, **2011**, *76*, 7352-7358.
126. Trost, B. M.; Hipskind, P. A., *Tetrahedron Lett.*, **1992**, *33*, 4541-4544.
127. Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H., *J. Am. Chem. Soc.*, **2005**, *127*, 17160-17161.
128. Iizuka, T.; Fudou, R.; Jojima, Y.; Ogawa, S.; Yamanaka, S.; Inukai, Y.; Ojika, M., *J. Antibiot. (Tokyo)*, **2006**, *59*, 385-391.
129. Sumiya, E.; Shimogawa, H.; Sasaki, H.; Tsutsumi, M.; Yoshita, K.; Ojika, M.; Suenaga, K.; Uesugi, M., *ACS Chem. Biol.*, **2011**, *6*, 425-431.
130. Fang, X.; Zhang, M.; Tang, Q.; Wang, Y.; Zhang, X., *Sci. Rep.*, **2014**, *4*.
131. Hausbeck, M.; Lamour, K., *Plant Dis.*, **2004**, *88*, 1292-1303.
132. Mo, H.; Kim, S.; Wai, K.; Siddique, M.; Yoo, H.; Kim, B., *Hortic. Environ. Biotechnol.*, **2014**, *55*, 50-55.
133. Xie, J.; Cardenas, E. S.; Sammis, T. W.; Wall, M. M.; Lindsey, D. L.; Murray, L. W., *Agr. Water Manage.*, **1999**, *42*, 127-142.
134. Babadoost, M., *Plant Dis.*, **2000**, *84*, 1345-1345.
135. Sanogo, S.; Ji, P., *Can. J. Plant Pathol.*, **2012**, *34*, 479-492.
136. Dawid, W., *Fems Microbiol. Rev.*, **2000**, *24*, 403-427.
137. Irschik, H.; Gerth, K.; Hofle, G.; Kohl, W.; Reichenbach, H., *J. Antibiot.*, **1983**, *36*, 1651-1658.
138. Mancuso, A.; Oudard, S.; Sternberg, C. N., *Crit. Rev. Oncol. Hemat.*, **2007**, *61*, 176-185.
139. Kunze, B.; Bohlendorf, B.; Reichenbach, H.; Hofle, G., *J. Antibiot.*, **2008**, *61*, 18-26.
140. Kunze, B.; Steinmetz, H.; Hofle, G.; Huss, M.; Wieczorek, H.; Reichenbach, H., *J. Antibiot.*, **2006**, *59*, 664-668.
141. Jansen, R.; Washausen, P.; Kunze, B.; Reichenbach, H.; Hofle, G., *Eur. J. Org. Chem.*, **1999**, 1085-1089.
142. Gerth, K.; Schummer, D.; Hofle, G.; Irschik, H.; Reichenbach, H., *J. Antibiot.*, **1995**, *48*, 973-976.
143. Gerth, K.; Irschik, H.; Reichenbach, H.; Trowitzsch, W., *J. Antibiot.*, **1980**, *33*, 1474-1479.
144. Trowitzsch, W.; Reifenstahl, G.; Wray, V.; Gerth, K., *J. Antibiot.*, **1980**, *33*, 1480-1490.
145. Ojika, M.; Suzuki, Y.; Tsukamoto, A.; Sakagami, Y.; Fudou, R.; Yoshimura, T.; Yamanaka, S., *J. Antibiot.*, **1998**, *51*, 275-281.
146. Sasse, F.; Bohlendorf, B.; Hermann, M.; Kunze, B.; Forche, E.; Steinmetz, H.; Hofle, G.; Reichenbach, H., *J. Antibiot.*, **1999**, *52*, 721-729.
147. Fudou, R.; Iizuka, T.; Yamanaka, S., *J. Antibiot.*, **2001**, *54*, 149-152.
148. Fudou, R.; Iizuka, T.; Sato, S.; Ando, T.; Shimba, N.; Yamanaka, S., *J. Antibiot.*, **2001**, *54*, 153-156.
149. Sasse, F.; Leibold, T.; Kunze, B.; Hofle, G.; Reichenbach, H., *J. Antibiot.*, **2003**, *56*, 827-831.
150. Ojika, M.; Inukai, Y.; Kito, Y.; Hirata, M.; Iizuka, T.; Fudou, R., *Chem. Asian J.*, **2008**, *3*, 126-33.
151. Fujii, K.; Ikai, Y.; Oka, H.; Suzuki, M.; Harada, K.-i., *Anal. Chem.*, **1997**, *69*, 5146-5151.
152. Martin, B. J.; Clough, J. M.; Pattenden, G.; Waldron, I. R., *Tetrahedron Lett.*, **1993**, *34*, 5151-5154.
153. Williams, D. R.; Patnaik, S.; Clark, M. P., *J. Org. Chem.*, **2001**, *66*, 8463-8469.

154. Kato, K.; Nishimura, A.; Yamamoto, Y.; Akita, H., *Tetrahedron Lett.*, **2002**, *43*, 643-645.
155. Kato, K.; Sasaki, T.; Takayama, H.; Akita, H., *Tetrahedron*, **2003**, *59*, 2679-2685.
156. DeRoy, P. L.; Charette, A. B., *Org. Lett.*, **2003**, *5*, 4163-4165.
157. Clough, J.; Dube, H.; Martin, B.; Pattenden, G.; Reddy, K.; Waldron, I., *Org. Biomol. Chem.*, **2006**, *4*, 2906-2911.
158. Chakor, N. S.; Musso, L.; Dallavalle, S., *J. Org. Chem.*, **2008**, *74*, 844-849.
159. Chakor, N. S.; Dallavalle, S.; Musso, L.; Sardi, P., *Tetrahedron Lett.*, **2012**, *53*, 228-231.
160. Shao, J.; Panek, J. S., *Org. Lett.*, **2004**, *6*, 3083-3085.
161. Gebauer, J.; Arseniyadis, S.; Cossy, J., *Org. Lett.*, **2007**, *9*, 3425-3427.
162. Colon, A.; Hoffman, T.; Gebauer, J.; Dash, J.; Rigby, J.; Arseniyadis, S.; Cossy, J., *Chem. Commun.*, **2012**, *48*, 10508-10510.
163. Iwaki, Y.; Akita, H., *Chem. Pharm. Bull.*, **2007**, *55*, 1610-1614.
164. Inanaga, J.; Baba, Y.; Hanamoto, T., *Chem. Lett.*, **1993**, 241-244.
165. Iwaki, Y.; Kaneko, M.; Akita, H., *Tetrahedron Lett.*, **2008**, *49*, 7024-7026.
166. Iwaki, Y.; Kaneko, M.; Akita, H., *Tetrahedron: Asymmetry*, **2009**, *20*, 298-304.
167. Schmidt, A.; Hall, M., *Annu. Rev. Cell Dev. Biol.*, **1998**, *14*, 305-338.
168. Fenteany, G.; Zhu, S., *Curr. Top. Med. Chem.*, **2003**, *3*, 593-616.
169. Spector, I.; Braet, F.; Shochet, N.; Bubb, M., *Microsc. Res. Tech.*, **1999**, *47*, 18-37.
170. Allingham, J.; Klenchin, V.; Rayment, I., *Cell. Mol. Life Sci.*, **2006**, *63*, 2119-2134.
171. Pettit, G.; Kamano, Y.; Kizu, H.; Dufresne, C.; Herald, C.; Bontems, R.; Schmidt, J.; Boettner, F.; Nieman, R., *Heterocycles*, **1989**, *28*, 553-558.
172. Hiroyuki, I.; Hiroki, S.; Hideo, K.; Kiyoyuki, Y., *Tetrahedron*, **1994**, *50*, 12853-12882.
173. Senderowicz, A. M. J.; Kaur, G.; Sainz, E.; Laing, C.; Inman, W. D.; Rodriguez, J.; Crews, P.; Malspeis, L.; Grever, M. R.; Sausville, E. A.; Duncan, K. L. K., *J. Natl. Cancer Inst.*, **1995**, *87*, 46-51.
174. Sasse, F.; Kunze, B.; Gronewold, T. M. A.; Reichenbach, H., *J. Natl. Cancer Inst.*, **1998**, *90*, 1559-1563.
175. Bai, R.; Covell, D.; Liu, C.; Ghosh, A.; Hamel, E., *J. Biol. Chem.*, **2002**, *277*, 32165-32171.
176. Entschladen, F.; Drell, T.; Lang, K.; Joseph, J.; Zaenker, K., *Lancet Oncol.*, **2004**, *5*, 254-258.
177. Friedl, P.; Wolf, K., *Nat. Rev. Cancer.*, **2003**, *3*, 362-374.
178. Hayot, C.; Debeir, O.; Van Ham, P.; Van Damme, M.; Kiss, R.; Decaestecker, C., *Toxicol. Appl. Pharm.*, **2006**, *211*, 30-40.
179. Grieco, P.; Hon, Y.; Perezmedrano, A., *J. Am. Chem. Soc.*, **1988**, *110*, 1630-1631.
180. Corey, E.; Hase, T., *Tetrahedron Lett.*, **1979**, 335-338.
181. Schmidt, U.; Siegel, W.; Mundinger, K., *Tetrahedron Lett.*, **1988**, *29*, 1269-1270.
182. Chu, K.; Negrete, G.; Konopelski, J., *J. Org. Chem.*, **1991**, *56*, 5196-5202.
183. Rao, A.; Gurjar, M.; Nallaganachu, B.; Bhandari, A., *Tetrahedron Lett.*, **1993**, *34*, 7081-7084.
184. Rao, A.; Gurjar, M.; Nallaganachu, B.; Bhandari, A., *Tetrahedron Lett.*, **1993**, *34*, 7085-7088.

185. Ghosh, A. K.; Moon, D. K., *Org. Lett.*, **2007**, *9*, 2425-2427.
186. Schmauder, A.; Müller, S.; Maier, M. E., *Tetrahedron*, **2008**, *64*, 6263-6269.
187. Schmauder, A.; Sibley, L.; Maier, M., *Chem. Eur. J.*, **2010**, *16*, 4328-4336.
188. Eggert, U.; Diestel, R.; Sasse, F.; Jansen, R.; Kunze, B.; Kalesse, M., *Angew. Chem. Int. Ed.*, **2008**, *47*, 6478-6482.
189. Waldmann, H.; Hu, T.-S.; Renner, S.; Menninger, S.; Tannert, R.; Oda, T.; Arndt, H.-D., *Angew. Chem. Int. Ed.*, **2008**, 6473-6477.
190. Hintermann, T.; Seebach, D., *Helv. Chim. Acta*, **1998**, 2093-2126.
191. Brown, H. C.; Bhat, K. S., *J. Am. Chem. Soc.*, **1986**, *108*, 293-294.
192. Tannert, R.; Hu, T.; Arndt, H.; Waldmann, H., *Chem. Commun.*, **2009**, 1493-1495.
193. Schultz, K., Post-Doctorate Thesis, **2010**.
194. Schultz, K.; Stief, L.; Kazmaier, U., *Synthesis*, **2012**, 600-604.
195. Wenkert, E.; Michelotti, E. L.; Swindell, C. S.; Tingoli, M., *J. Org. Chem.*, **1984**, *49*, 4894-4899.
196. Kocienski, P.; Pritchard, M.; Wadman, S.; Whitby, R.; Yeates, C., *J. Chem. Soc. Perkin Trans. 1*, **1992**, 3419-3429.
197. Kocienski, P.; Wadman, S.; Cooper, K., *J. Am. Chem. Soc.*, **1989**, *111*, 2363-2365.
198. Black, F.; Kocienski, P., *Org. Biomol. Chem.*, **2010**, *8*, 1188-1193.
199. Gao, X.; Liu, Y.; Kwong, S.; Xu, Z.; Ye, T., *Org. Lett.*, **2010**, *12*, 3018-3021.
200. Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S., *J. Am. Chem. Soc.*, **1987**, *109*, 5856-5858.
201. Mashima, K.; Kusano, K.-h.; Sato, N.; Matsumura, Y.-i.; Nozaki, K.; Kumobayashi, H.; Sayo, N.; Hori, Y.; Ishizaki, T., *J. Org. Chem.*, **1994**, *59*, 3064-3076.
202. Reis, J. S.; Andrade, L. H., *Tetrahedron: Asymmetry*, **2012**, *23*, 1294-1300.
203. Kocieński, P.; Dixon, N. J.; Wadman, S., *Tetrahedron Lett.*, **1988**, *29*, 2353-2356.
204. Taber, D. F.; Kong, S., *J. Org. Chem.*, **1997**, *62*, 8575-8576.
205. White, K. N.; Konopelski, J. P., *Org. Lett.*, **2005**, *7*, 4111-4112.
206. Li, H.; Jiang, X.; Ye, Y.-h.; Fan, C.; Romoff, T.; Goodman, M., *Org. Lett.*, **1999**, *1*, 91-94.
207. Seashore-Ludlow, B.; Villo, P.; Häcker, C.; Somfai, P., *Org. Lett.*, **2010**, *12*, 5274-5277.
208. Shiina, I.; Kubota, M.; Ibuka, R., *Tetrahedron Lett.*, **2002**, *43*, 7535-7539.
209. Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M., *Bull. Chem. Soc. Jpn.*, **1979**, *52*, 1989-1993.
210. Boden, E. P.; Keck, G. E., *J. Org. Chem.*, **1985**, *50*, 2394-2395.
211. Corey, E. J.; Nicolaou, K. C., *J. Am. Chem. Soc.*, **1974**, *96*, 5614-5616.
212. Armarego, W. L. F.; Perrin, D. D.; Perrin, D. R., Butterworth-Heinemann Ltd: Oxford, **1997**.
213. Padwa, A.; Filipkowski, M. A.; Meske, M.; Murphree, S. S.; Watterson, S. H.; Ni, Z., *J. Org. Chem.*, **1994**, *59*, 588-596.
214. Bird, R.; Stirling, C. J. M., *J. Chem. Soc. Perkin Trans. 2*, **1973**, 1221-1226.
215. Su, T.; Xie, S.; Wei, H.; Yan, J.; Huang, L.; Li, X., *Bioorg. Med. Chem.*, **2013**, *21*, 5830-5840.
216. Ronan, B.; Kagan, H. B., *Tetrahedron: Asymmetry*, **1992**, *3*, 115-122.
217. Westermann, J.; Schneider, M.; Platzek, J.; Petrov, O., *Org. Process Res. Dev.*, **2007**, *11*, 200-205.

218. Niwayama, S.; Cho, H.; Lin, C., *Tetrahedron Lett.*, **2008**, *49*, 4434-4436.
219. Martin-Matute, B.; Bunuel, E.; Mendez, M.; Nieto-Oberhuber, C.; Cardenas, D.; Echavarren, A., *J. Organomet. Chem.*, **2003**, *687*, 410-419.
220. Martínez, M. M.; Hoppe, D., *Eur. J. Org. Chem.*, **2005**, 1427-1443.
221. Wang, L.; Clive, D. L. J., *Org. Lett.*, **2011**, *13*, 1734-1737.
222. Swarén, P.; Massova, I.; Bellettini, J. R.; Bulychev, A.; Maveyraud, L.; Kotra, L. P.; Miller, M. J.; Mobashery, S.; Samama, J.-P., *J. Am. Chem. Soc.*, **1999**, *121*, 5353-5359.
223. Kobayashi, Y.; Kumar, G. B.; Kurachi, T.; Acharya, H. P.; Yamazaki, T.; Kitazume, T., *J. Org. Chem.*, **2001**, *66*, 2011-2018.
224. Conway, J. C.; Quayle, P.; Regan, A. C.; Urch, C. J., *Tetrahedron*, **2005**, *61*, 11910-11923.
225. PLC, S. B., Patent US2004/176370 A1, **2004**.
226. Fleming, W. J.; Muller-Bunz, H.; Lillo, V.; Fernandez, E.; Guiry, P. J., *Org. Biomol. Chem.*, **2009**, *7*, 2520-2524.
227. Yang, J.-H.; Yang, G.-C.; Lu, C.-F.; Chen, Z.-X., *Tetrahedron: Asymmetry*, **2008**, *19*, 2164-2166.
228. Bryant, V. C.; Kishore Kumar, G. D.; Nyong, A. M.; Natarajan, A., *Bioorg. Med. Chem. Lett.*, **2012**, *22*, 245-248.
229. Schmidt, B.; Riemer, M.; Karras, M., *J. Org. Chem.*, **2013**, *78*, 8680-8688.