Total Synthesis of Phomapyrone B and Paecilopyrone A, and Two Serrulatanes from *Eremophila neglecta*

A thesis submitted for the fulfilment of the degree of Doctor of Philosophy

By

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Declaration

I certify that this thesis does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text.

Nicholas J. Rudgley

31st August 2017

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Presentations

Synthetic Studies Towards the EN3 and EN4 Serrulatanes
Oral presentation given at the Adelaide Organic Symposium, Adelaide, South Australia, 8th December, 2015

Synthetic Studies Towards the EN3 and EN4 Serrulatanes
Poster presentation at the RACI National Congress, Adelaide, South Australia, 7th-12th December, 2014.

Total Synthesis of Paecilopyrone A and Phomapyrone B.
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Publications

Total Synthesis of Paecilopyrone A and Phomapyrone B.
Rudgley, N.; Perkins, M. V.; *In Preparation*

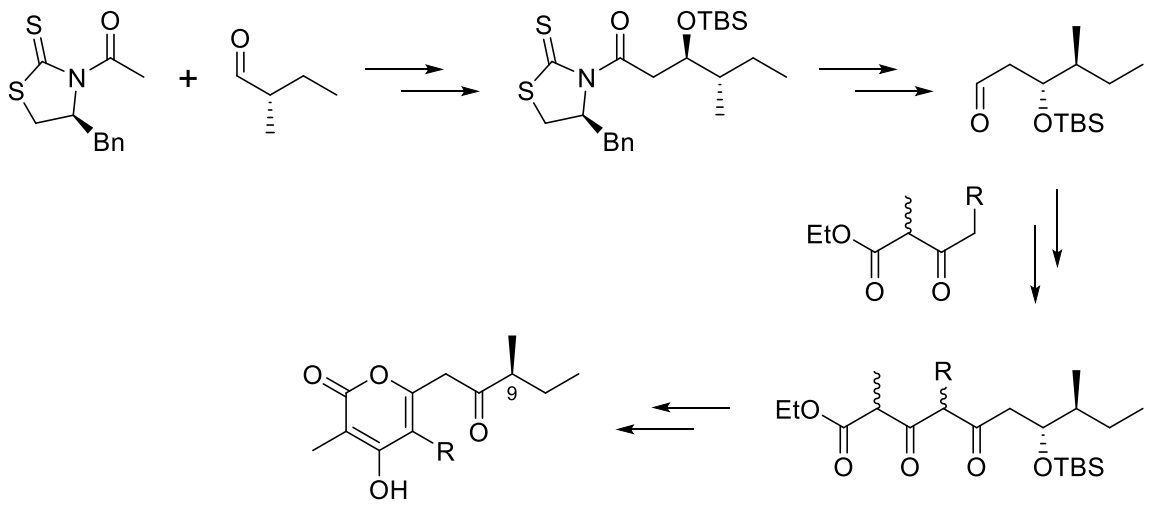
Total Synthesis of 8, 19-dihydroxyserrulat-14-ene and 8-hydroxyserrulat-14-en-19-oic acid. Rudgley, N.; Perkins, M. V.; *In Preparation*

Thesis Summary

This thesis describes the first total synthesis of two α-pyrone natural products isolated from *Leptosphaeria maculans* and *Paecilomyces lilacinus*. The first total synthesis of two serrulatane diterpenoids from *Eremophila neglecta* is also discussed. Due to the segmented nature of the two projects, literature reviews and discussions for each project are separated by chapters.

The first two chapters are concerned with the total synthesis of the pyrone natural products, phomapyrone B and paecilopyrone A. **Chapter 1** gives a brief overview of pyrones, with the isolation, biological activity and biosynthetic origins discussed, as well as literature examples pertaining to the elaboration of pyrone rings in total synthesis. The isolation of micropyrone (**65**) and ascosalipyrone (**66**), as well as their respective syntheses has been detailed, forming the foundation for the following chapter.

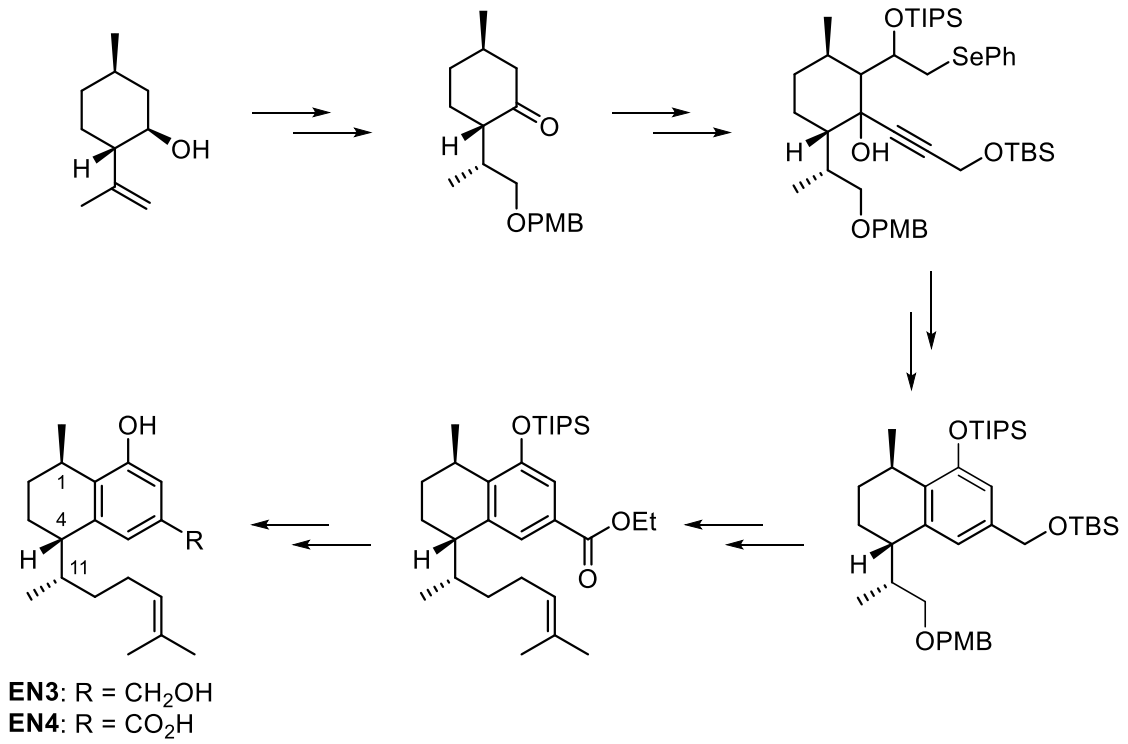
Chapter 2 details the total synthesis of two structurally related natural products, phomapyrone B (**76**) and paecilopyrone A (**78**). The known (*S*)-2-methylbutyraldehyde was used as a starting material for introduction of the stereogenic center at C9 of the natural products. Key steps in the synthesis were dianion addition of β-keto esters to a common aldehyde fragment and diketo ester cyclisation. Phomapyrone B (**76**) and paecilopyrone A (**78**) were obtained in 11% and 22% yields respectively over 9 steps. The stereochemistry was determined as (9*R*)-phomapyrone B (**76**) and (9*S*)-paecilopyrone A (**78**) based on comparison of the synthesised natural products' optical rotations to literature sources.



*Overview of phomapyrone B (**76**) and paecilopyrone A (**78**) synthesis*

Chapter 3 serves as an introduction to the diterpene natural products which are encountered predominantly amongst the plant kingdom. This chapter gives a brief overview of diterpene biosynthesis, with particular interest in radiolabelled feeding studies for determination of biosynthetic origins. SAR studies are discussed, with the goal being development of a suitable antimicrobial agent for the treatment of biofilms. Relevant literature regarding the synthesis of diterpene natural products is presented. This includes the total synthesis of leubethanol and the 8-hydroxycalamenenes, which possess similar carbon frameworks and substitution patterns to EN3 and EN4.

Chapter 4 reports the total synthesis of the EN3 and EN4 serrulatane natural products that were isolated from the Australian desert plant, *Eremophila neglecta*. The synthesis elaborates on the previous total syntheses by our group, which utilised a silver catalysed cycloisomerisation of 5-alkoxy-1,5-enynes for construction of the aromatic ring. The total syntheses of 8, 19-dihydroxyserrulat-14-ene (EN3) and 8-hydroxyserrulat-14-en-19-oic acid (EN4) were achieved in 17 steps. Analysis of the spectroscopic data as well as the specific rotations allowed for the determination of the stereochemistry at C1, C4 and C11 as (1*R*, 4*S*, 11*S*) for both natural products.



*Overview of the synthesis of EN3 (**146**) and EN4 (**147**)*

General concluding remarks can be found in **chapter 5**, which summarises the main findings of the previous four chapters as well as possible future directions for chapters 2 and 4. **Chapter 6** is divided into two sub-sections containing experimental procedures for chapters 2 and 4. Finally, the **appendices** contain ^{1}H, ^{13}C, COSY, HMQC and HMBC NMR spectra for selected compounds in Chapters 2 and 4.

Abbreviations

The abbreviations used throughout this thesis are listed below with their corresponding systematic or standard (trivial) names.

Abbreviation	**Standard Name**
°C	degrees Celsius
1D	one dimensional
2D	two dimensional
$A^{1,3}$	allylic 1, 3 strain
Ac_2O	acetic anhydride
AcOH	acetic acid
ACP	acyl carrier protein
aq.	aqueous
app	apparent
AT	acyl transferase
$BF_3.Et_2O$	boron trifluoride diethyl etherate
$BH_3.SMe_2$	borane-dimethyl sulphide complex
BH_3.THF	borane-tetrahydrofuran complex
Bn	benzyl
BnBr	benzyl bromide
Bu_2BOTf	dibutylboron triflate
n-BuLi	butyl lithium
t-Bu	tertiary-butyl
t-BuOH	tertiary-butanol
t-BuLi	tertiary-butyl lithium
c	concentration (g/100 mL)
C_6H_6	benzene
ca.	*circa* - approximately
CaH_2	calcium hydride
calcd.	calculated
cat.	catalytic
CCl_4	carbon tetrachloride
CH_2Cl_2	dichloromethane
CH_3CN	acetonitrile
$CHCl_3$	chloroform
CoA	coenzyme A
COSY	correlation spectroscopy
CS_2	carbon disulfide
CSA	camphor sulfonic acid
$CDCl_3$	deuterated chloroform
CD_3OD	deuterated methanol
$(CD_3)_2CO$	deuterated acetone

δ	chemical shift (parts per million)
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1, 2-dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DH	dehydratase
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminium hydride
DIPEA	*N*,*N*-diisopropylethylamine
iPr_2NEt	diisopropylethylamine
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
E	*entgegen* (opposite)
e.e.	enantiomeric excess
ent	enantiomer
equiv.	equivalents
ER	enoyl reductase
ESI	electrospray ionisation
Et	ethyl
Et_2O	diethyl ether
Et_3N	triethylamine
et. al.	*et alia* (and others)
EtOAc	ethyl acetate
$(EtO)_2CO$	diethyl carbonate
EtOH	ethanol
h	hours
H_2	Hydrogen
HCl	hydrogen chloride
HF	hydrogen Fluoride
HMBC	heteronuclear multiple bond connectivity
HMDS	hexamethyldisilazide
HMQC	heteronuclear multiple quantum coherence
HRESIMS	high resolution electrospray ionisation mass spectroscopy
HTS	high throughput screening
Hz	hertz
IBX	2-iodoxybenzoic acid
IC_{50}	half maximal inhibitory concentration
IR	infrared
*i*Pr	*iso*-propyl
i-PrMgCl	*iso*-propylmagnesium chloride

J	coupling constant (Hz)
K_2CO_3	potassium carbonate
$KMnO_4$	potassium permanganate
KOH	potassium hydroxide
KR	ketoreductase
KS	ketosynthase
LDA	lithium diisopropylamine
$LiAlH_4$	lithium aluminium hydride
$LiBH_4$	lithium borohydride
LiHMDS	lithium hexamethyldisilazide
lit.	literature
M^+	molecular ion (mass spectrum)
*m*CPBA	*meta*-chloroperbenzoic acid
Me	methyl
MeCN	acetonitrile
$(MeO)_2CO$	dimethyl carbonate
MeOH	methanol
$MeOSO_2F$	methyl fluorosulfonate (magic methyl)
MHz	megahertz
MIC	minimum inhibitory concentration
min	minutes
mmol	millimole
mol	mole
m.p.	melting point
MS	mass spectrum
m/z	mass-to-charge ratio
NA	not active
$Na_2S_2O_3.5H_2O$	sodium thiosulfate pentahydrate
Na_2SO_4	sodium sulfate
$NaBH_4$	sodium borohydride
NADH	nicotinamide adenine dinucleotide hydride
NaH	sodium hydride
$NaHCO_3$	sodium bicarbonate
NaHMDS	sodium hexamethyldisilazide
NaOH	sodium hydroxide
NaSEt	sodium ethanethiolate
NBS	*N*-Bromosuccinimide
NH_4Cl	ammonium chloride
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NT	not tested
[O]	oxidation
OTf	trifluoromethanesulfonate
Oxone®	potassium peroxymonosulfate

PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
PhMe	toluene
PKS	polyketide synthase
PMB	*para*-methoxybenzyl
PMBCl	*para*-methoxybenzyl chloride
PMP	*para*-methoxyphenyl
PPh_3	triphenylphosphine
ppm	part per million
quant.	quantitative
(*R*)	*Rectus* (right)
R_f	retention factor
rt	room temperature
SAR	Structure-Activity-Relationship
sat.	saturated
(*S*)	*Sinister* (left)
SiO_2	silica gel
SM	starting material
$Sn(OTf)_2$	tin(II) trifluoromethanesulfonate
TBAF	tetrabutylammonium fluoride
TBS	tertiary-butyl dimethylsilyl
TBSCl	tertiary-butyl dimethylsilyl chloride
TBSOTf	tertiary-butyl dimethylsilyl triflate
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TfOH	trifluoromethanesulfonic acid (triflic acid)
THF	Tetrahydrofuran
$TiCl_4$	Titanium tetrachloride
TIPS	triisopropylsilyl
TIPSOTf	triisopropylsilyl triflate
THF	tetrahydrofuran
$TiCl_4$	titanium tetrachloride
TLC	Thin Layer Chromatography
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
TMSOTf	trimethylsilyl trifluoromethanesulfonate
TM	trade mark
X4	mixed hexanes
Z	*zusammen* (together)
<	less than
>	greater than

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Chapter 2

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Chapter 1
Isolation, Biological Activity and Synthesis of Pyrone Natural Products

Chapter 1 Summary

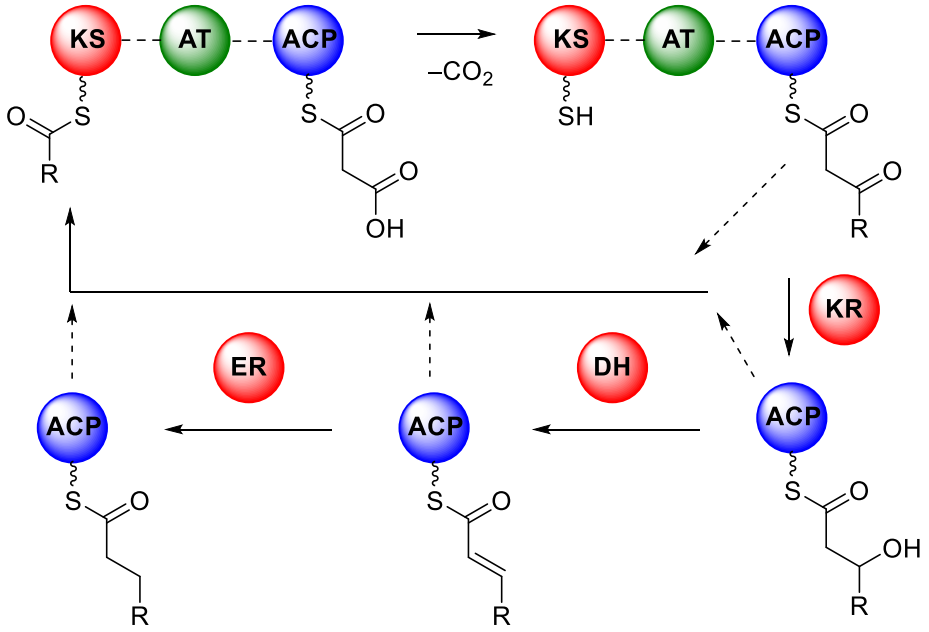
Chapter 1 introduces polyketide natural products and discusses their biosynthetic origins as well as biological activities. Literature examples detailing construction of the pyrone moiety in total syntheses are reviewed, along with methodology used previously by the Perkins research group. The isolation of phomapyrone B (**76**) and paecilopyrone A (**78**) from *Leptosphaeria maculans* and *Paecilomyces lilacinus* is also detailed.

1.1 Polyketide Biosynthesis

Metabolites within an organism can be divided into two groups. The first are the primary metabolites and consist of compounds such as common fats, sugars and amino acids. These molecules perform critical roles within the organism and therefore the structures are highly conserved amongst species. The second class are termed the secondary metabolites and include the terpenoids, phenols, alkaloids and polyketides to name a few. These are not essential for survival of the organism but instead convey some specific evolutionary advantage. As such, species have evolved the ability to synthesise different secondary metabolites to perform roles relating to predation, defence and signalling. Although fundamentally different in their roles within organisms, the fatty acids and polyketides are synthesised by similar enzymatic machinery.

The mechanisms involved in both fatty acid and polyketide biosynthesis employ enzymes termed ketosynthases (KS), acyl transferases (AT) and acyl carrier proteins (ACP), which are attached to the growing chain.[1] Both processes employ acetyl-coenzyme A (CoA) and malonyl-CoA units in decarboxylative thioester Claisen condensations to assemble the growing chain (Scheme 1.1). A ketoreductase (KR) enzyme may catalyse the reduction of the newly introduced carbonyl to the secondary alcohol. The dehydratase (DH) enzyme may then catalyse the dehydration of this alcohol to the alkene, which may be reduced further by enoyl reductase (ER) to the saturated alkyl chain.

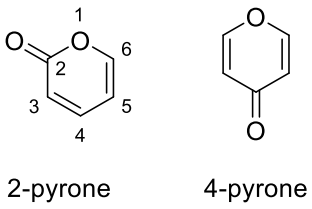
During fatty acid biosynthesis, all of these steps occur during each iteration until a fatty acid with highly controlled chain length is produced with an even number of carbon atoms. The chain length is typically 14, 16 or 18 carbons long, but shorter fatty acids such as butyric acid are also possible.[2] However, Polyketide Synthases (PKS) can vary markedly not only in the number of iterations (chain length) but also in the starter units employed. PKS's have been observed to utilise acetate, propionate and butyrate units in the construction of growing polyketide chains. Furthermore, the essential KR, DH and ER enzymes in fatty acid biosynthesis are not obligatory during polyketide biosynthesis. This leads to polyketide chains with varying levels of reduction, and following chain formation, events such as condensations, cyclisations and rearrangements can increase diversity in the structures of polyketide chains generated.[2]



Scheme 1.1: Generic representation of biosynthesis of fatty acids and polyketides

1.2 Biosynthetic Origin of Pyrones

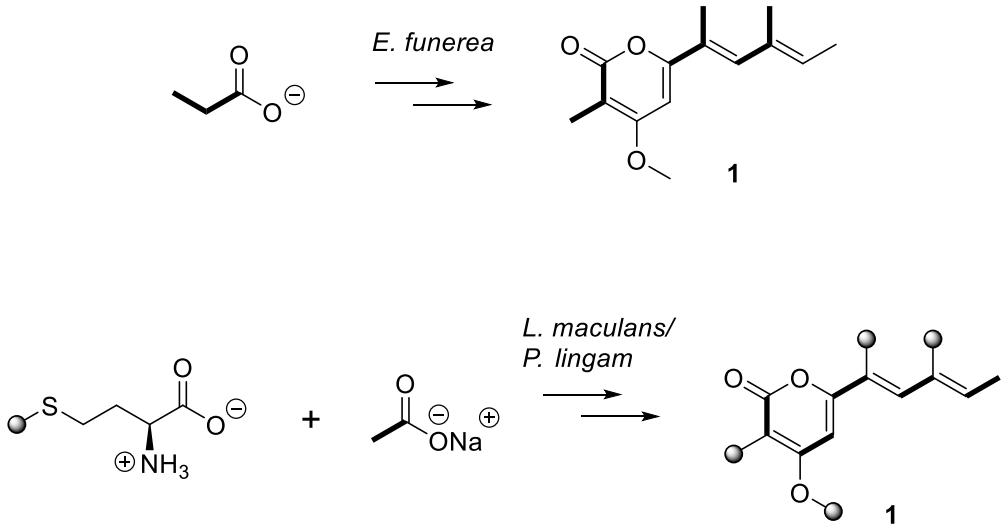
Pyrones are polyketide secondary metabolites formed through cyclisation of a growing polyketide chain. They are frequently encountered in both marine and terrestrial organisms, possessing a vast array of biological activities including: plant growth regulation,[3] germicidal activities,[4] antitumor[5], antibacterial[6] and antiparasitic[7] activities. Pyrones have also been implicated as quorum sensing agents, which are small diffusible molecules used for the cell-cell communication between bacteria.[8] In their simplest forms, pyrones can be described as either 2-pyrones (α-pyrones) or 4-pyrones (γ-pyrones) based on the position of the ketone (Scheme 1.2). Substitution is possible at any of the four remaining carbons numbered 3-6.



Scheme 1.2: General structures of pyrones

Depending on the Kingdom or phyla of the particular organism, the secondary metabolites may be biosynthesised by evolutionarily distinct pathways. For example, fungi synthesise apparent polypropionate natural products through elongation of a polyacetate chain, with methyl substituents introduced with S-adenosyl methionine.[9] Conversely, marine gastropods have been shown to incorporate intact C_3 propionate units, along with the capability of utilising a mixed acetate/propionate pathway to generate diverse structures. Bacteria have been observed to synthesise polypropionates through either of these two pathways, leading to ambiguity as to the biosynthetic origin of secondary metabolites from marine organisms known to have symbiotic relationships with bacteria.

In relatively few examples, the same secondary metabolites have been synthesised by entirely different taxa employing distinct sequences of PKS and different building blocks. Independent studies by Pedras[10] and Fontana[11] have shown that two structurally similar natural product classes; the phomapyrones and the placidenes, are biosynthesised by two different pathways (Scheme 1.3).

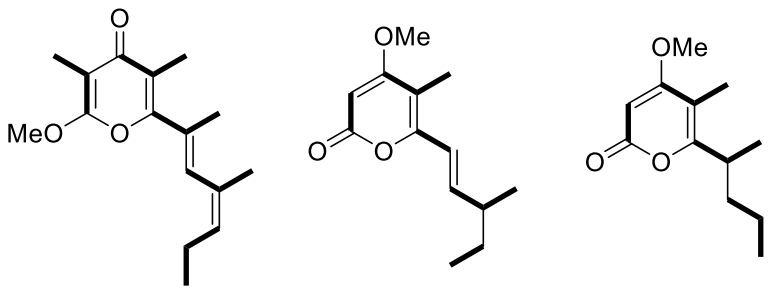


*Scheme 1.3: Biosynthesis of phomapyrone A (7-methyl-cyercene-1) (**1**) in E. funerea and L. maculans*

The phomapyrones were initially isolated in 1994 by Pedras *et al.* from the terrestrial fungus *Leptosphaeria maculans*.[12] The fungi was cultured in the presence of various ^{13}C radiolabelled building blocks and NMR spectroscopy used to determine the percentage of incorporation within phomapyrone A (**1**).[10] Pedras showed that during the biosynthesis of **1**, radiolabelled acetate and malonate units were incorporated as

identified by the increase in ^{13}C abundance at the highlighted positions. There was no observable increase in ^{13}C abundance upon incubation of *L. maculans/P. lingam* with radiolabelled propionate units, however upon incubation with deuterated methionine, incorporation was observed at the four methyl positions. It was therefore determined that phomapyrone A (**1**) was biosynthesised through an acetate/malonate pathway with methyl substituents introduced *via* S-adenosyl methionine.

Radiolabelled feeding studies by Fontana *et al.* examined the incorporation of acetate and propionate units in the biosynthesis of the compound they reported as 7-methyl-cyercene-1 (**1**) (same chemical structure as phomapyrone A), which was isolated from the marine mollusc *E. funerea.*[13] Addition of ^{13}C labelled propionate resulted in incorporation of propionate units at the highlighted positions (Scheme 1.4). Fontana *et al.* also investigated the biosynthesis of the placidenes, which were isolated from the Mediterranean mollusc *P. dendritica.*[14,15] It was observed that for placidene A (**2**), there was no incorporation of radiolabelled acetate units, whilst placidene C (**3**) showed incorporation between C2-C3, C6-C7 and C10-C11.[11] Placidene E (**4**) showed incorporation of radiolabelled acetate at C2-C3 indicating that the biosynthesis of these natural products is due to PKS's capable of incorporating either acetate or propionate units at different stages. This is distinct from the phomapyrones isolated from the fungus *Leptosphaeria maculans*, which utilises methylation of a preformed polyacetate chain to form the same polypropionate structure.



placidene A (**2**) placidene C (**3**) placidene E (**4**)

*Scheme 1.4: structures of placidenes A (**2**), C (**3**) and E (**4**) and incorporation of radiolabelled acetate (C_2) and propionate (C_3) units*

1.3 Isolation and Biological Activities of Pyrones

Natural products, whether of marine or terrestrial origin, are highly sought after mainly for their biological activity and therapeutic potential. Quite often, when a secondary

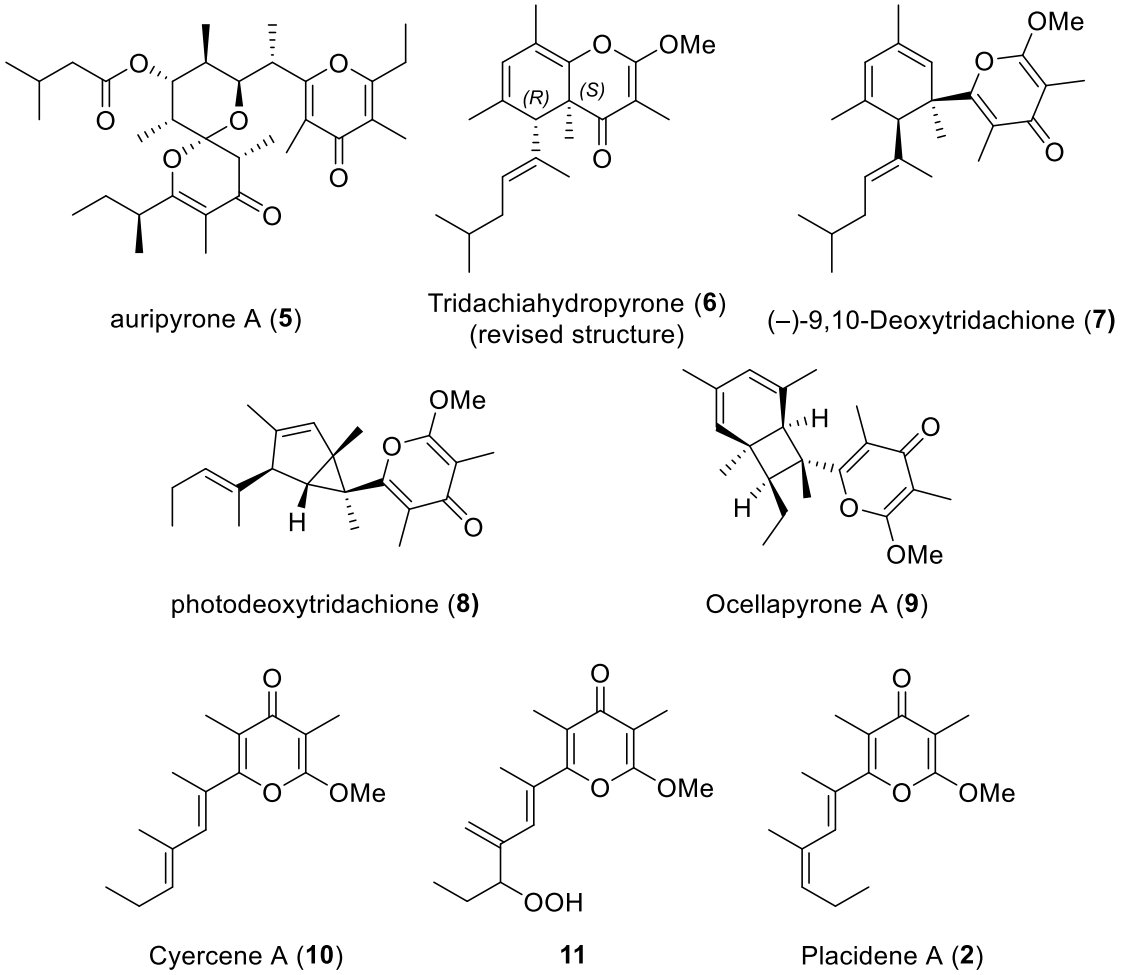
metabolite is isolated from a natural source, the primary role of the metabolite within the organism is unknown. It is therefore not surprising when they are reported as having no significant biological activity, especially when the researchers are interested in a specific function and therefore submit the molecule to a narrow scope of bioassays. Furthermore, they are often assessed for their activity against human cell lines, and considering that this would not be their intended target in most cases, it is probable that they may not show activity. Nevertheless, there has been increasing interest surrounding both marine and terrestrial natural products.

One particularly interesting class of organisms are the marine molluscs, which are soft bodied creatures that are vulnerable to predation. Due to this susceptibility, it has been hypothesised that they may produce an array of bioactive molecules associated with defence of the organism. The cytotoxic polypropionate constituent Auripyrone A (**5**) was isolated from the sea hare *Dolabella auricularia* (Aplysiidae) in 1996 by Suenaga and co-workers (Scheme 1.5).[16] Auripyrone A (**5**) had potent activity against HeLa S_3 cells with an IC_{50} value of 0.26 μg/mL, leading our group[17,18], Jung *et al.*[19,20] and Kigoshi *et al.*[21,22] to investigate its synthesis.

Another γ-pyrone metabolite, tridachiahydropyrone (**6**), was isolated from the Caribbean sacoglossan mollusc *Tridachia crispate* by Cimino *et al*. in 1996.[23] Although no biological activities were reported for this compound, its bicyclic fused pyrone ring and adjacent stereocenters represented an appealing target for the development of synthetic methodology. Jeffery *et al.* developed methodology applicable to the synthesis of the tridachiones through a common cyclohexenone synthon.[24] This methodology was applied to the synthesis of the reported structure of *trans*-tridachiahydropyrone (**4*R***, **9*R*)-6**.[25–27] The spectroscopic and physical properties of the *trans*-diastereomer were inconsistent with the reported literature data. Notably, the ^{1}H and ^{13}C NMR data for C9 and C17 of the *trans*-diastereomer did not match the natural product. This led Jeffery to propose that the structure of tridachiahydropyrone (**6**) needed to be revised to the *cis*-diastereomer **(4*S*, 9*R*)-6**, which was later supported through total synthesis by Moses and co-workers.[28,29] In addition, a number of biosynthetically related natural products have also been isolated (**7**-**9**) and their photochemical relationships examined by multiple groups.

Scheuer and Faulkner have shown that (−)-9, 10-deoxytridachione (**7**) undergoes a photochemical conversion to (−)-photodeoxytridachione (**8**) both *in vivo* and *in vitro*

when exposed to sunlight.[30,31] Furthermore, Moses was able to successfully synthesise (±)-ocellapyrone A (**9**) and (±)-9,10-deoxytridachione (**7**) through either thermal or photochemical electrocyclisation involving geometric isomers of a linear polyene precursor. Moses rationalised that because these two natural products had previously been co-isolated, their synthesis demonstrated a plausible biosynthetic pathway from a common polyene fragment. The above studies highlight the photochemical relationships between these co-isolated natural products.



*Scheme 1.5: Complex 4-pyrone secondary metabolites and oxygenated derivative **11***

The α-methoxy γ-pyrone cyercene A (**10**) has been isolated from the dorsal appendages (cerata) of the autotomizing ascoglossan mollusc *Cyerce cristallina*.[32] Cimino *et al.*[15] hypothesised that cyercene A (**10**) was involved in defence of the mollusc due to its ichthyotoxic activity as well as being implicated in the mollusc's regenerative processes. Aside from cyercene A (**10**), a number of other structurally related natural products such as placidene A (**2**) have been isolated with varying geometries of polyene

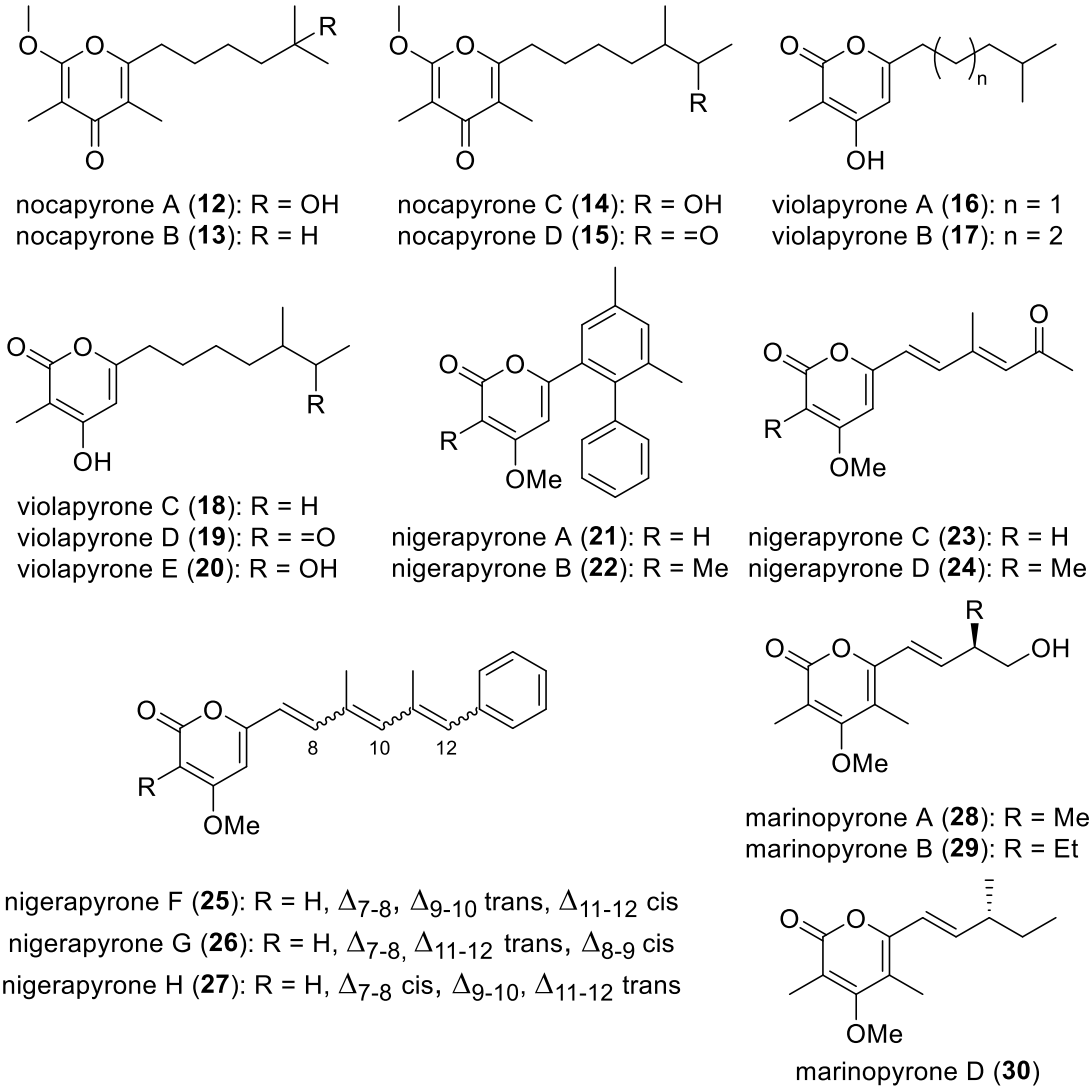
chains. Notably, cyercene A (**10**) has been shown to interconvert to placidene A (**2**) and isoplacidene A in sunlight through photoisomerisation.[33]

Studies by Jones and Zuidema in 2006 investigated the photosensitising activity of several 2-methoxy γ-pyrones as well as their 4-methoxy α-pyrone analogues.[34] They determined that the 2-methoxy γ-pyrones were more effective photosensitising agents, capable of producing singlet oxygen. Furthermore, they have previously shown that irradiation of cyercene A (**10**) in the presence of oxygen leads to the hydroperoxide **11**, leading them to suggest that metabolites from molluscs may be a form of biological prodrug, with the hydroperoxides likely irritants to predators such as fish. It is interesting to note that these molluscs or associated bacteria have evolved the enzymatic capabilities of methylating specific pyrone positions, as there seems to be a disproportionate number of 2-methoxy γ-pyrones isolated compared to the α-pyrone analogues, potentially due to their triplet photosensitising ability.[34]

Nocapyrones A-D (**12-15**) were isolated from the organic extract of the *Nocardiopsis* strain HB383 from the marine sponge *Halichondria panacea* in 2010 (Scheme 1.6).[35] Each possessed an α-methoxy γ-pyrone moiety with C3 and C5 methyl substitution, but differed in the alkyl chain appended at C6. All compounds were tested for cytotoxicity and antimicrobial properties, but were found to be inactive. The structurally related violapyrones A-E (**16-20**) were extracted from *Streptomyces violascens* isolated from *Hylobates hoolock* feces in 2013 by Huang and co-workers. Interestingly, the violapyrones possess a very similar carbon framework to that of the nocapyrones, with the key difference being the 4-hydroxy α-pyrone ring. Violapyrones D-E (**19-20**) possessed no biological activity, whereas A-C (**16-18**) exhibited moderate activity against *Bacillus subtilis* and *Staphylococcus aureus* with MIC values between 4−32 μg/mL.[6]

The nigerapyrones (**21-27**) were isolated from the marine mangrove-derived endophytic fungus *Aspergillus niger* MA-132 in 2011.[36] They possess an unsaturated alkyl chain appended to an α-pyrone moiety. Wang observed that although the nigerapyrones exhibited some weak cytotoxic activities against tumour cell lines, only the α-pyrones with C3 methyl substitution exhibited the cytotoxic activities, with the unsubstituted analogues having no observable activity. The marinopyrones (**28-30**) were isolated from a marine-derived actinomycetes, with marinopyrone D (**30**) exhibiting a 13 μM nitric oxide inhibitory activity in LPS-stimulated RAW 264.7 macrophage cells.[37]

Marinopyrones A and B (**28-29**) did not exhibit any significant activity, which was rationalised as being due to the hydrophilic nature of the side chain.



Scheme 1.6: Pyrones isolated from natural sources

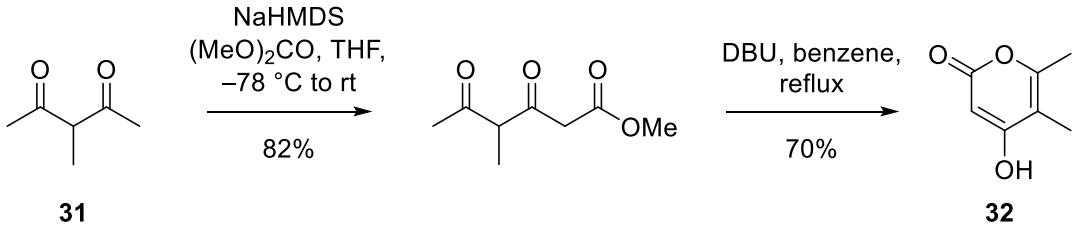
Analysis of the structures of the aforementioned natural products and their biological activities reveals some interesting aspects. For instance, the biological properties appeared to be predominantly determined by the side chain. Methylation of the pyrone ring at C3 resulted in increased activity, whilst the substituent at C5 was less important. There was no apparent difference in biological activity between the two structural isomers of pyrones (α or γ), although the α-methoxy γ-pyrones had been shown to be more efficient triplet photosensitising agents. Cytotoxic activity was observed for the nigerapyrones and marinopyrone D (**30**), indicating that this may be due to unsaturation

of the side chain. Cytotoxic activity was less when the side chain was fully saturated, with oxygenation of the side chain resulting in loss of antimicrobial activity.

1.4 Literature Methods for Pyrone Synthesis

Following the isolation and identification of new compounds, there is often insufficient material to perform exhaustive testing for bioactivity. It may not be possible to simply increase the quantity of material available for extraction, as it may not be ecologically viable to obtain kilogram quantities of the organism to isolate milligrams of the target compound. Instead, synthetic methodology must be developed to access sufficient quantities for testing and further structural identification. To date, a variety of different methods have been published for the formation of pyrones starting from either β-keto esters or diketones. Although not all methods for pyrone formation are presented here, a representative selection is shown. Examples are given that include construction of the pyrone moiety both before and after introduction of other functionality such as side chains.

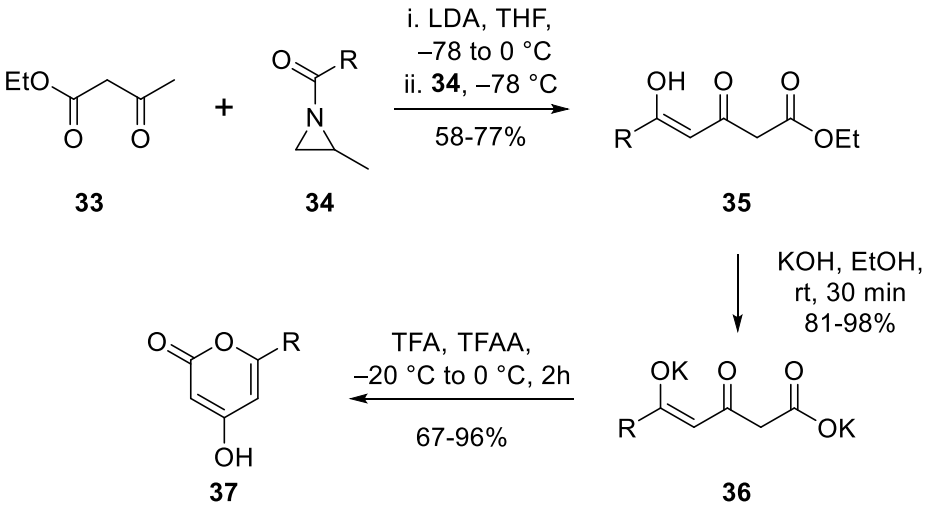
The known 3-methylpentane-2,4-dione **31** has been used to synthesise the α-pyrone **32** (Scheme 1.7).[38–40] Treatment of diketone **31** with NaHMDS at −78 °C followed by the addition of dimethyl carbonate afforded the diketo ester, which was heated under reflux in benzene to afford the α-pyrone **32**.



*Scheme 1.7: Synthesis of pyrone **32** from 3-methylpentane-2,4-dione **31***

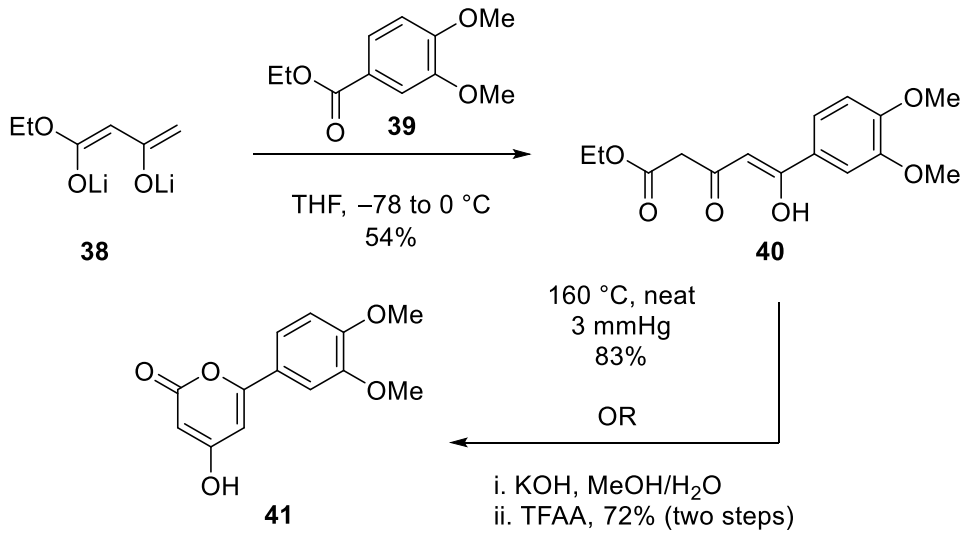
Beifuss *et al.* synthesised a variety of α-pyrones starting from the commercially available ethyl-2-methyl acetoacetate (**33**) (Scheme 1.8).[41] Formation of the dianion with 2 equivalents of LDA, followed by addition of the aziridine **34** led to formation of the enol tautomer **35**. The ester was hydrolysed to the bis-potassium salt of the carboxylate **36**, which then underwent a facile cyclisation at −20 °C with TFA and TFAA affording the α-pyrone **37** in 67-96% yields. Whilst this synthesis is high

yielding and does not require oxidation following addition of the dianion, it still requires formation of the *N*-acyl aziridine **34** possessing other functionality present in the molecule.



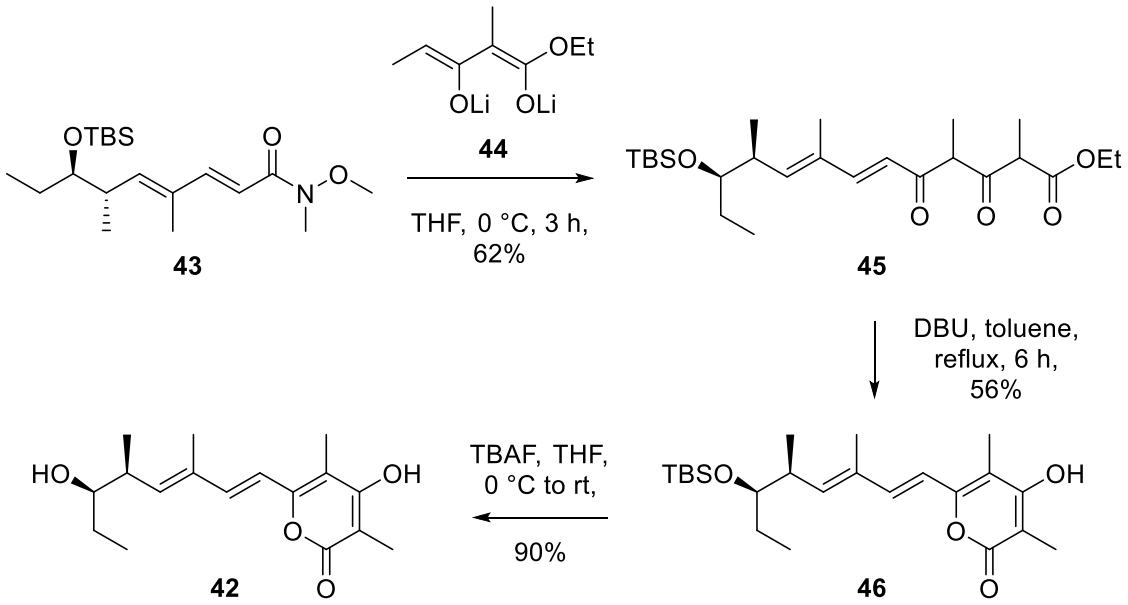
Scheme 1.8: Synthesis of α-pyrones from the bis-potassium salts of 5-hydroxy-3-oxopent-4-enoic acids.[41]

Hua *et al.* employed the *dilithio*-bisenolate **38** as a nucleophile for addition to methyl 3,4-dimethoxybenzoate **39** affording the enol tautomer **40** (Scheme 1.9).[42] In order to effect cyclisation the neat enol tautomer **40** was heated to 160 °C under reduced pressure (3 mmHg), affording the α-pyrone **41** in 83% yield. As an alternative to these forcing reaction conditions, Jung *et al.*[43] hydrolysed the ester to the bis-potassium carboxylate using the aforementioned reaction conditions, then cyclised the bis-potassium salt with TFAA in Et_2O at room temperature. The aryl pyrone **41** was obtained in slightly lower yield than the reduced pressure procedure, but the conditions employed were less forcing, meaning they were applicable to more sensitive substrates.



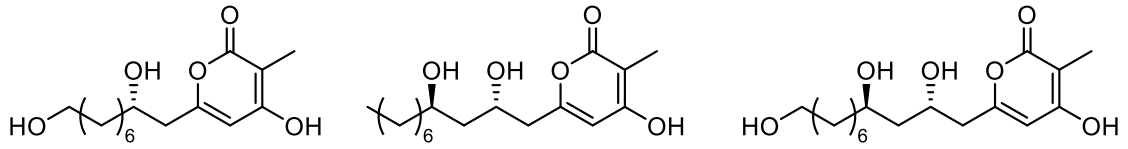
*Scheme 1.9: Synthesis of aryl pyrone **41** from ethyl acetoacetate*[42,43]

Meshram *et al*. synthesised salinipyrone A (**42**) through nucleophilic addition to a Weinreb amide (Scheme 1.10).[44] Cannulation of the Weinreb amide **43** to the pre-formed bisenolate **44** afforded diketo ester **45** in 62% yield. The crude mixture was dissolved in toluene and heated at reflux with DBU affording pyrone **46** in 56% yield. Salinipyrone A (**42**) was obtained in 90% yield following deprotection of the silyl protecting group.



*Scheme 1.10: Meshram's synthesis of Salinipyrone A (**42**)*[44]

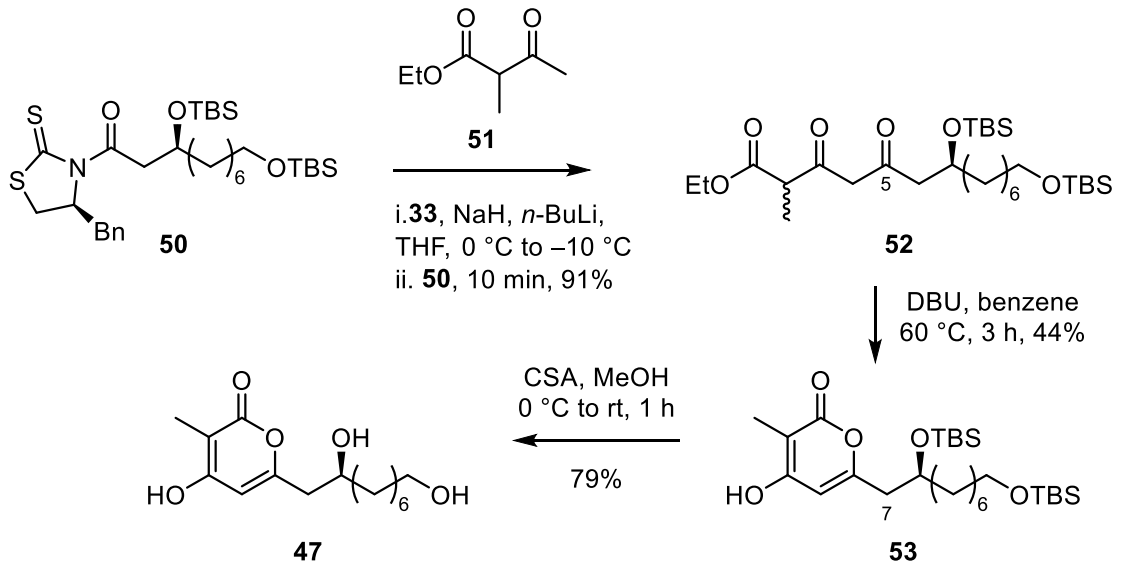
A further addition to this methodology was made by Yadav *et al.* during the reported synthesis of the three α-pyrones **47-49** (Scheme 1.11). They were isolated from *Penicillium corylophilum* DAOM 242293, which was collected from damp building materials in Halifax, Canada.[45,46] One particularly interesting aspect of their synthesis utilised the chiral thiazolidinethione as a leaving group. Yadav and co-workers were able to successfully displace the chiral auxiliary **50** through addition of the dianion formed from ethyl-2-methyl acetoacetate **51** to access **52**. This circumvented the need to manipulate the oxidation state at C5 (Scheme 1.12).[45]



47 **48** **49**

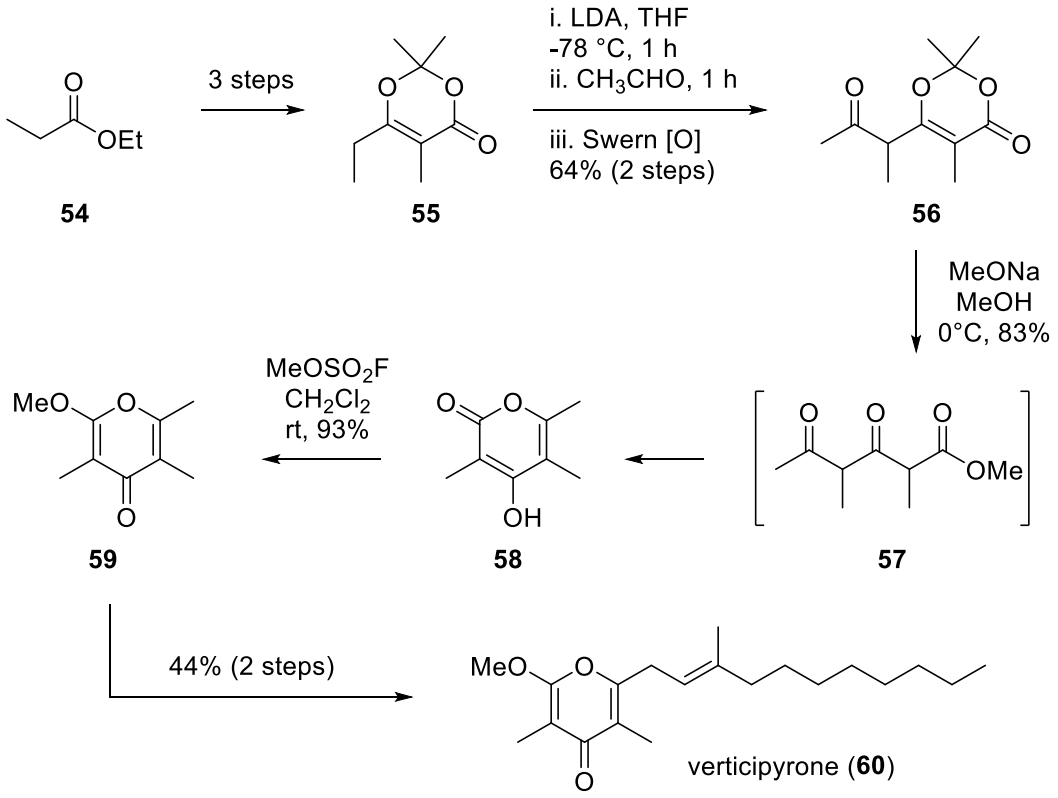
Scheme 1.11: α-pyrones isolated from Penicillium corylophilum[45]

Subsequent cyclisation of the linear β, δ-diketo ester **52** to the corresponding pyrone **53** proceeded in 44% yield. The yield for this type of cyclisation was lower than previous literature examples. One possible reason for this low yield may be the presence of the β-silyloxy substituent, which may be prone to β-elimination due to the acidic nature of the C7 hydrogens of pyrone **53**. Overall, Yadav *et al.* were able to successfully synthesise pyrones **47-49** through nucleophilic displacement of *N*-acyl thiazolidinethiones with the dianion formed from ethyl-2-methylacetoacetate **51**. Following DBU mediated cyclisation, this allowed for the expedient construction of the pyrone moiety and hence synthesis of the natural products **47-49**.



*Scheme 1.12: Yadav's synthesis of pyrone **47***[45]

Dioxinones have been shown by Barrett *et al.* to be excellent substrates for alkylation and cyclisation.[47] Further work by Omura *et al.* have shown that alkylation of 1,3-dioxin-4-ones is possible with aldehydes when treated with one equivalent of lithium diisopropylamide (LDA) (Scheme 1.13).[7] Starting from the commercially available ethyl propionate **54**, Omura synthesised dioxinone **55** in three steps. Subsequent aldol reaction with acetaldehyde and LDA as the base afforded the secondary alcohol, which was immediately oxidised to ketone **56** using standard Swern oxidation reaction conditions.[48,49] Subjection of ketone **56** to a solution of sodium methoxide in methanol at 0 °C afforded the intermediate diketo ester **57** through acetonide deprotection, which then underwent cyclisation under the basic conditions to afford pyrone **58** in 83% yield. Methylation of the α-oxygen with methyl fluorosulfonate occurred in 93% yield to afford γ-pyrone **59**. Omura and coworkers were then able to append a side chain through deprotonation of pyrone **59** with LDA and alkylation with an α-phenylsulfonyl aldehyde in 74% yield. Subsequent acetylation and reductive elimination of the hydroxy sulfone afforded verticipyrone (**60**) in 59% yield.



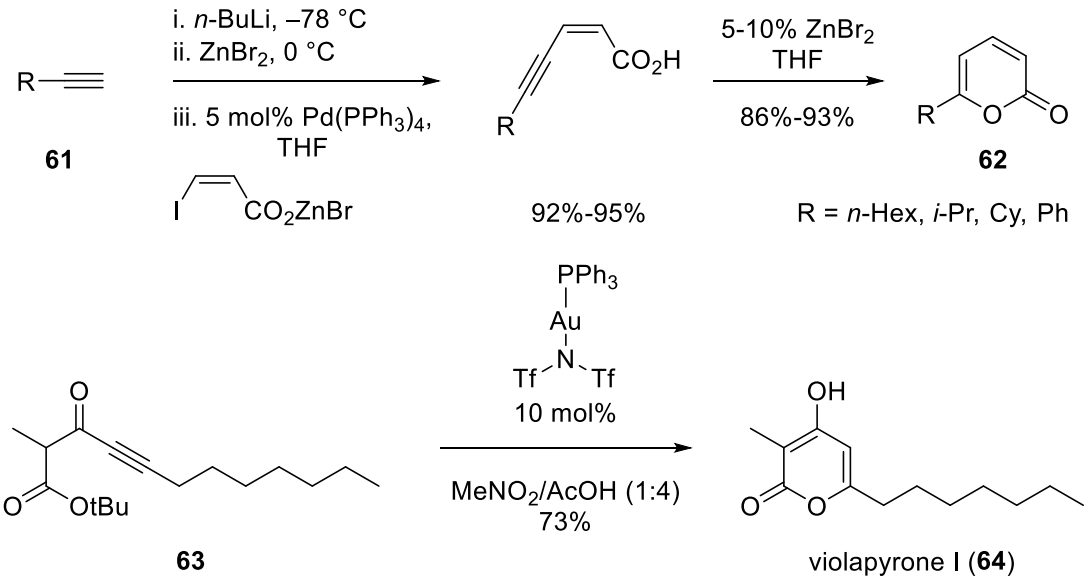
54 **55** **56** **57** **58** **59**

*Scheme 1.13: Omura's synthesis of verticipyrone **60***[7]

Since verticipyrone (**60**) was initially reported to have significant NADH-fumarate reductase inhibitory activity, Omura also tested a variety of analogues to determine the Structure-Activity Relationships (SAR). During their investigations, they observed that the pyrone ring with no side chain had less activity, whilst the derivative with no methyl substituents on the pyrone ring was also inactive. Incorporating *cis* double bond geometry increased the activity to 2.0 nM, whilst there was little difference observed when the position of the double bond was altered or removed or the δ-methyl substituent of the alkyl chain was removed. The greatest activity was observed when there was hydroxyl functionality at the β-position, with IC_{50} values between 0.65 and 0.3 nM.

Aside from the use of dioxinones, β-diketones, β-keto esters and amides, synthetic efforts have also been made using transition metals as catalysts for 2-pyrone formation. Work by Negishi *et al.* utilised a palladium catalysed alkynylzinc-haloacrylic acid coupling with alkyne **61**, followed by a zinc catalysed lactonisation for the formation of 6-alkyl 2-pyrones **62** in two steps (Scheme 1.14).[50] Lee *et al.* have also shown that the tert-butyl ynoate **63** is capable of undergoing a 6-*endo-dig* cyclisation in the presence of a gold(I) catalyst to afford the corresponding violapyrone I (**64**).[51] For more examples of

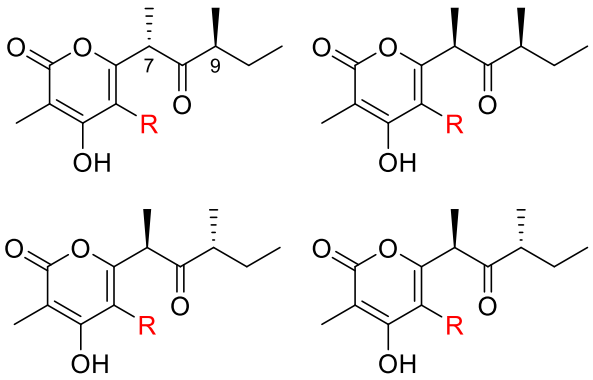
transition metal catalysed formation of 2-pyrones see Lee's review on the Recent Advances in the Synthesis of 2-Pyrones.[52]



Scheme 1.14: transition metal catalysed synthesis of 2-pyrones[50,51]

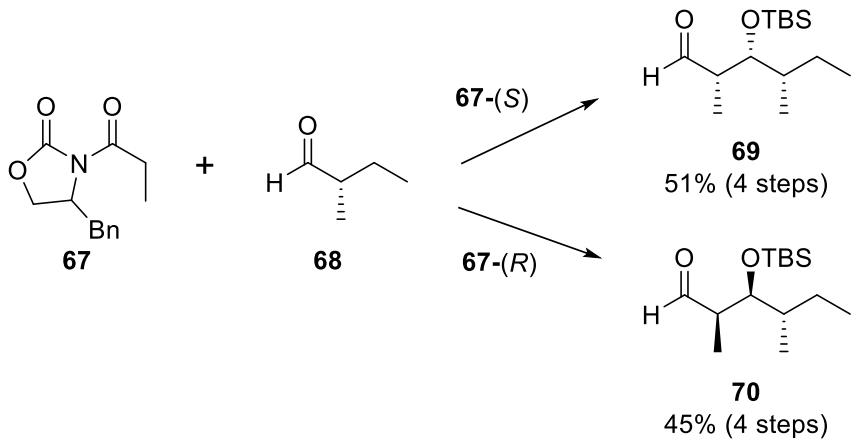
1.5 Isolation and Synthesis of Micropyrone and Ascosalipyrone

Previous work by the Perkins research group has established methodology pertinent to the synthesis of two marine polyketide metabolites; ascosalipyrone and micropyrone (Scheme 1.15).[53] Micropyrone (**65**) was isolated from the plant *Helichrysum italicum ssp. microphyllum* in 2007 by Appendino *et al.*,[54] whilst ascosalipyrone (**66**) was isolated from the marine fungus *Ascochyta salicorniae* of the green alga *Ulva sp.* in 2000 by König and coworkers.[55] The structures were determined based on 1D and 2D NMR experiments, as well as mass spectrometry. Although the skeletal structures were determined, the stereochemistry at C7 and C9 was not established. Since there are two stereocenters in each natural product, there are four potential stereoisomers; two diastereomers and their associated enantiomers.



*Scheme 1.15: Potential stereoisomers of micropyrone **65** (R=Me) and ascosalipyrone **66** (R=H)*[53]

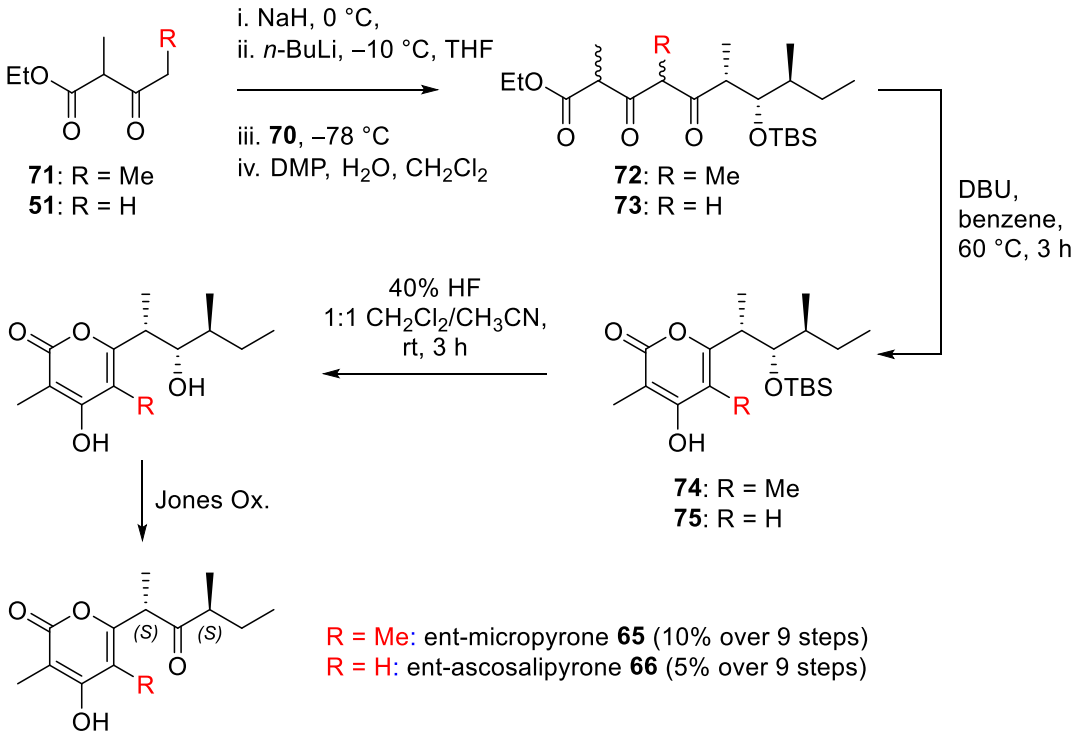
The synthetic strategy developed by C. Gregg[53] employed a diastereoselective boron aldol[56] reaction between *N*-acyl oxazolidinone **67-*S*** (synthesised in 3 steps from (*S*)-phenylalanine)[57] and (*S*)-2-methylbutyraldehyde (**68**) (Scheme 1.16). This allowed the installation of the *syn-syn* stereochemistry of the C2 methyl and C3 hydroxyl, which was protected as the silyl ether. Reduction of the auxiliary and oxidation of the corresponding alcohol to aldehyde **69** was achieved in 51% yield over 4 steps. By using the (*R*) stereochemistry of the Evans auxiliary **67-*R***, the corresponding *syn* diastereomeric aldehyde **70** was also obtained in 45% yield over 4 steps.



*Scheme 1.16: Greg's synthesis of the diastereomeric aldehyde fragments **69** and **70***[53]

Formation of the *sodio-lithio* bisenolate[58] of the β-keto esters **71** and **51** was achieved using sodium hydride and *n*-butyl lithium, with addition of aldehyde **70** resulting in formation of the β-keto δ-hydroxy esters (Scheme 1.17). Subsequent oxidation with Dess-Martin Periodinane[59–62] (DMP) afforded the diketo esters, which underwent cyclisation to the silyl protected pyrones when treated with base. To achieve the total

synthesis of *ent*-micropyrone (**65**), the silyl protecting group was removed and secondary alcohol oxidised to furnish the *anti*-isomer **65** in 9 linear steps and 10% overall yield.

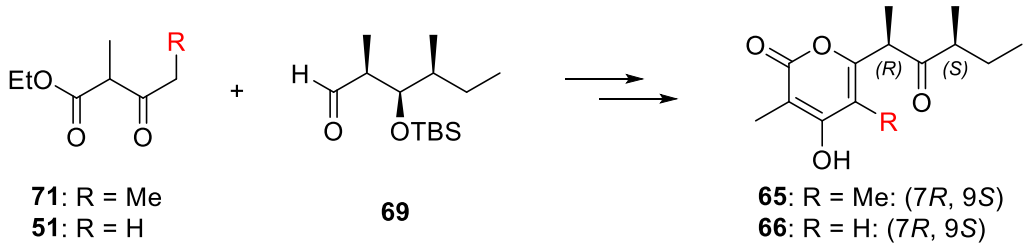


*Scheme 1.17: Gregg's synthesis of ent-micropyrone (**65**) and ent-ascosalipyrone (**66**)*[53]

This process was repeated using the diastereomeric aldehyde **69** to obtain the (7*R*)-diastereomers (Scheme 1.18). By comparison of the NMR spectra and optical rotations for the two diastereomers to micropyrone (**65**), the stereochemistry of micropyrone (**65**) was determined as (7*S*, 9*S*) through synthesis of (7*R*, 9*R*)-*ent*-micropyrone (**65**).

The difference in overall yield observed between *ent*-ascosalipyrone (**66**) and *ent*-micropyrone (**65**) is due primarily to the substituent at C5 of the pyrone ring. During the base mediated cyclisation, diketo ester **72** underwent a smooth reaction affording pyrone **74** in modest yield (45% after trituration) as a single stereoisomer. However, when subjected to the same cyclisation conditions, the linear diketo ester **73** returned pyrone **75** as the major product (25%) as well as its C7 epimer as an inseparable mixture. C. Gregg attributed this marked difference in reactivity to the C5 methyl substituent of pyrone **74**. X-ray analysis of *ent*-micropyrone (**65**) and its C7 epimer revealed that the conformation about C6-C7 was such that the C7 hydrogen eclipsed the

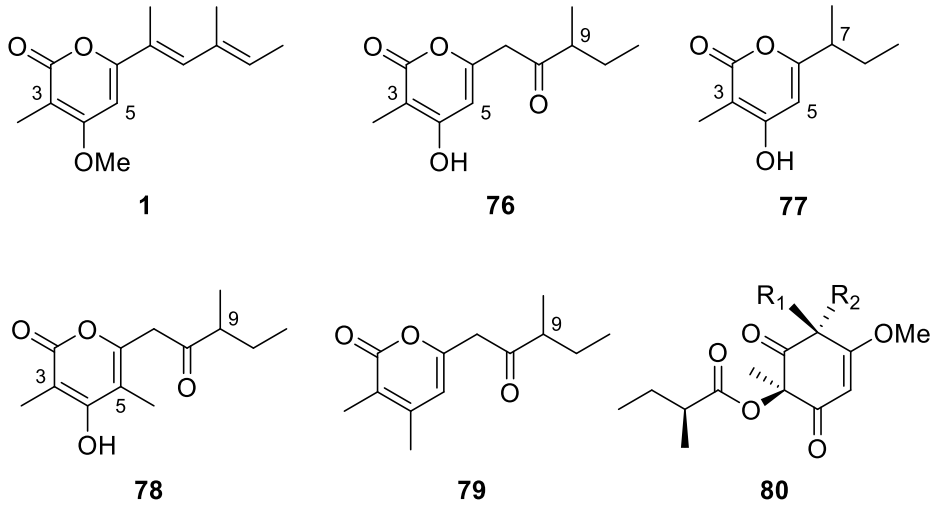
C5 methyl in both cases. It was rationalised by C. Gregg that this minimises the A^{1-3} strain experienced by the methyl substituent.



*Scheme 1.18: Gregg's synthesis of the 7R, 9S-diastereomers using aldehyde fragment **69***[53]

1.6 Isolation of Paecilopyrone A and Phomapyrone B

Phomapyrones A−C (**1, 76-77**) were isolated by Pedras *et al.*[12] in 1994 from the pathogenic fungus *Leptosphaeria maculans*; which is associated with the plant disease known as Blackleg in cruciferous crops (Scheme 1.19).[10] Although phomapyrone B (**76**) had no clinically significant biological activity in the limited assays, it was identified as a potential marker for detection of Blackleg in crucifers. The structures of phomapyrones A-C were determined based on HRESIMS and NMR spectroscopy.



*Scheme 1.19: natural products isolated from Leptosphaeria maculans (**1**, **76-77**)*[12] *and Paecilomyces lilacinus (**78-80**)*[63]

All three metabolites possessed a methyl substituent at C3 of the α-pyrone ring, as well as oxygen functionality at C4. For phomapyrone A (**1**), the oxygen was methylated, whilst phomapyrones B-C (**76-77**) possessed the free hydroxyl group. Phomapyrone A (**1**) also contained two degrees of unsaturation in its side chain as well as three vinylic

methyl groups. The molecular formula for phomapyrone B (**76**) was determined as $C_{12}H_{16}O_4$ based on the observed 224.1048 m/z indicating five degrees of unsaturation. The position of the ketone at C8 and methyl at C9 was determined based on long range NMR correlation experiments. Phomapyrones B (**76**) and C (**77**) were optically active indicating that they were present with some degree of enantiomeric excess at C9 for phomapyrone B (**76**) and C7 for phomapyrone C (**77**).

In 2009 a structurally related secondary metabolite, paecilopyrone A (**78**) was reported by Elbandy *et al.* [63] from the fungus *Paecilomyces lilacinus* associated with the marine sponge *Petrosia* sp. (Scheme 1.19). The marine sponge was collected from waters around Jeju Island in October 2004. The sponge was dissected following sterilisation and the fungal and yeast colonies from the sponge tissue were cultured on agar plates with PMG medium. The *Paecilomyces lilacinus* strain (J04J-1) F-9 was determined based on morphology and its 18S rDNA sequence.

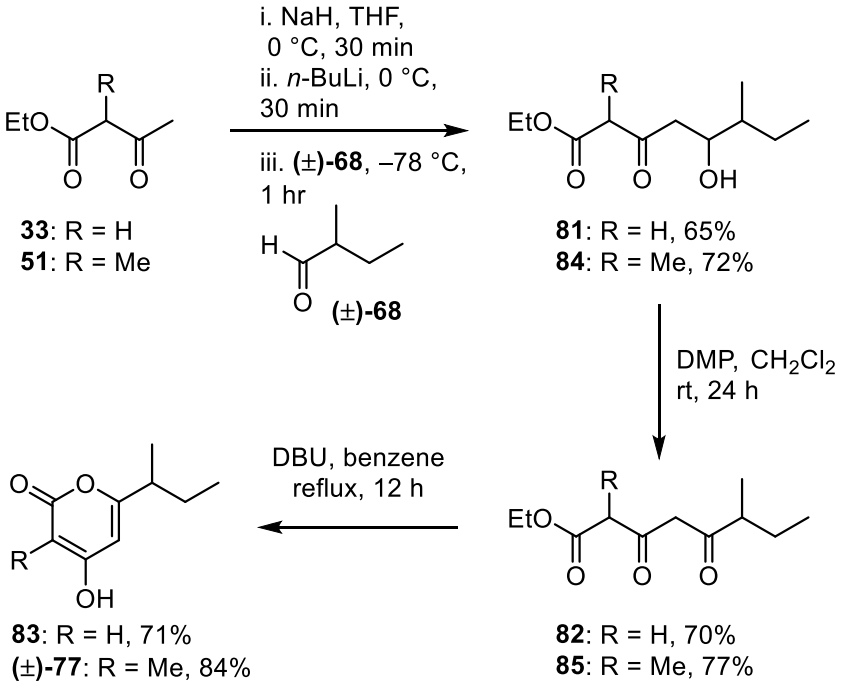
Interestingly, Elbandy *et al.* also isolated natural products consistent with phomapyrone B (**76**) and phomapyrone C (**77**) alongside paecilopyrone B (**79**) and a number of phomaligols (**80**), where the substituents at R_1 and R_2 could be variations of; Me, OH, OCH_3, $OCOCH_3$ or OOH. The structures were determined based on NMR spectroscopic analysis as well as mass spectrometry. The structure of paecilopyrone A (**78**) was determined based on the molecular formula of $C_{13}H_{18}O_4$, which was obtained from the HRFABMS ion of 283.0916 m/z corresponding to the $[M+2Na-H]^+$ ion. NMR analysis revealed two methyl singlets associated with the pyrone ring, whilst Elbandy also compared the NMR data to the previously isolated phomapyrone B (**76**) for structural confirmation.

Paecilopyrone A (**78**) was reported to be optically active, indicating that one enantiomer was present in an enantiomeric excess. The reported optical rotation for phomapyrone B (**76**) from *Paecilomyces lilacinus* was opposite in sign to phomapyrone B (**76**) isolated from *Phoma lingam/ Leptosphaeria maculans* indicating they are enantiomeric. This is probably not too surprising considering the distant genera to which the respective fungi belong but it does imply a different biosynthesis. Because the *ent*-phomapyrone B (**76**) was co-isolated with paecilpyrone A (**78**), it is probable that they possess the same stereochemical relationship at C9 since they may have been processed by the same polyketide synthase. In terms of the biosynthetic origin of paecilopyrone A (**78**) and phomapyrone B (**76**), being isolated from fungi indicates they are most likely derived

through an acetate/malonate and S-adenosyl methionine pathway, with only one methylation step involving S-adenosyl methionine resulting in the different structures.

1.7 Synthesis of (±)-Phomapyrone C

The structural similarities between paecilopyrone A (**78**), phomapyrone B (**76**), ascosalipyrone (**66**) and micropyrone (**65**) indicated that methodology developed by Gregg could be applicable to their synthesis. The carbon skeleton of the co-isolated phomapyrone C (**77**) could be easily accessed in three steps; constituting model studies for the dianion addition and cyclisation protocol (Scheme 1.20). This formed the basis of my Honours research project,[64] as well as part of my PhD research project.



*Scheme 1.20: Three-step synthesis of pyrones including (±)-phomapyrone C (**77**)*[64]

Treatment of ethyl acetoacetate (**33**) with sodium hydride at 0 °C, followed by addition of *n*-butyl lithium afforded the bis-enolate (Scheme 1.20). Subsequent addition of (±)-2-methylbutyraldehyde (**68**) at −78 °C afforded the δ-hydroxy-β-keto ester **81** in 65% yield as a complex mixture of diastereomers. The secondary alcohol at C5 was oxidised with DMP giving the β, δ-diketo ester **82** in 70% yield. Cyclisation with DBU and heating at reflux in benzene for 12 hours afforded pyrone **83** in 71% yield. The same synthetic sequence was applied with ethyl-2-methyl acetoacetate (**51**). The δ-hydroxy-β-

keto ester **84** was obtained in 72% yield, whilst oxidation with DMP afforded diketo ester **85** in a comparable 77% yield. Cyclisation gave the racemic (±)-phomapyrone C (**77**) as an amorphous solid in 84% yield.

Whilst initial synthetic efforts were made towards phomapyrone B during my Honours research project,[64] the total synthesis was not achieved. The upcoming chapter details the optimisation of methodology as well as its application to the first reported total syntheses of phomapyrone B (**76**) and paecilopyrone A (**78**).

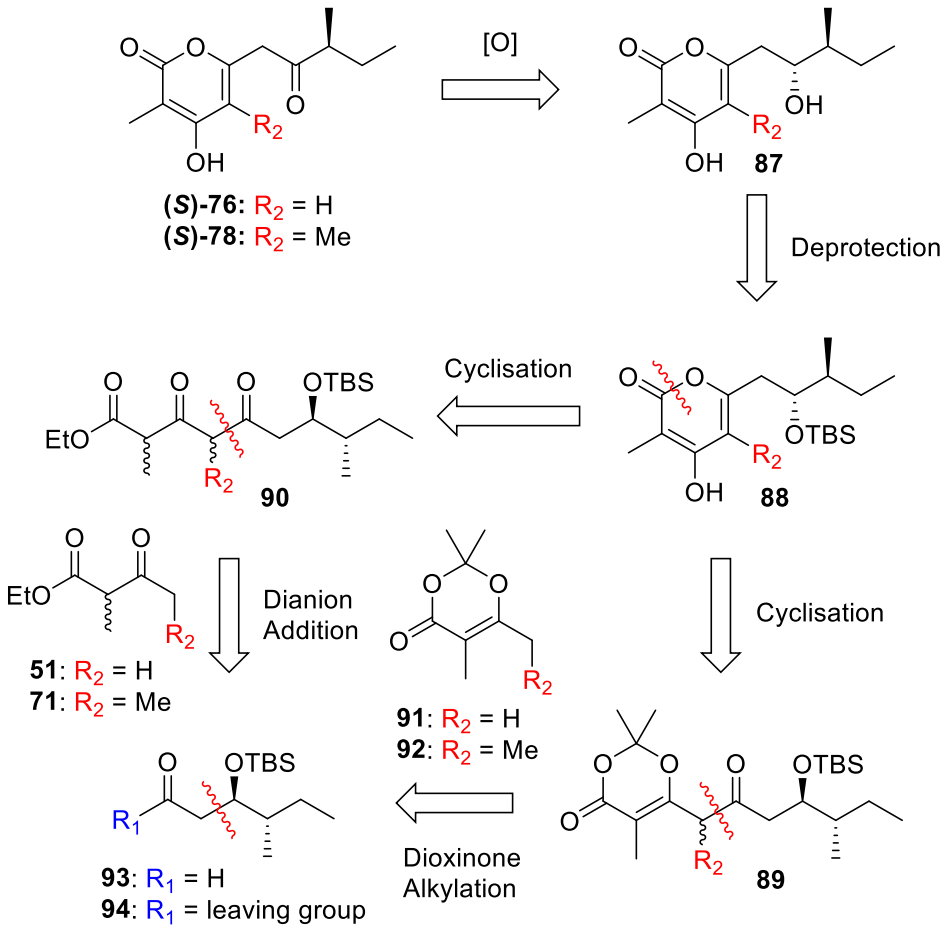
Chapter 2
Total Synthesis of Paecilopyrone A and Phomapyrone B

Chapter 2 Summary

This chapter details the continuation of my Honours research project.[64] The total synthesis of *ent*-phomapyrone B (**76**) and paecilopyrone A (**78**); two structurally related α-pyrone secondary metabolites is described. The (*S*)-stereochemistry at C9 was installed using the known (*S*)-2-methylbutyraldehyde (**68**) as a starting material. The total syntheses featured coupling of the *sodio-lithio bis*-enolates derived from β-keto esters **71** and **51** with the common aldehyde fragment **93**, as well as a base-catalysed cyclisation of the diketo esters for pyrone ring formation. The configuration at C9 for each natural product was determined through comparison of the optical rotations for the synthesised material with the natural products.

2.1 Retrosynthetic Analysis of Phomapyrone B (**76**) and Paecilopyrone A (**78**)

As eluded to in chapter 1, there are a variety of syntheses for both 2-pyrones and 4-pyrones. They vary markedly in reaction conditions, with temperatures ranging from −20 °C to 160 °C. Gregg has previously shown that dianions prepared from β-keto esters can be coupled with aldehydes and converted into the corresponding α-pyrones.[53] The prolonged reaction times for full conversion of the starting material at high temperatures leads to side product formation. Milder conditions have been reported using dioxinones to affect cyclisation at 0 °C for 1 hour. The number of linear steps may also be minimised by coupling β-keto esters with amides directly, resulting in the linear diketo ester.



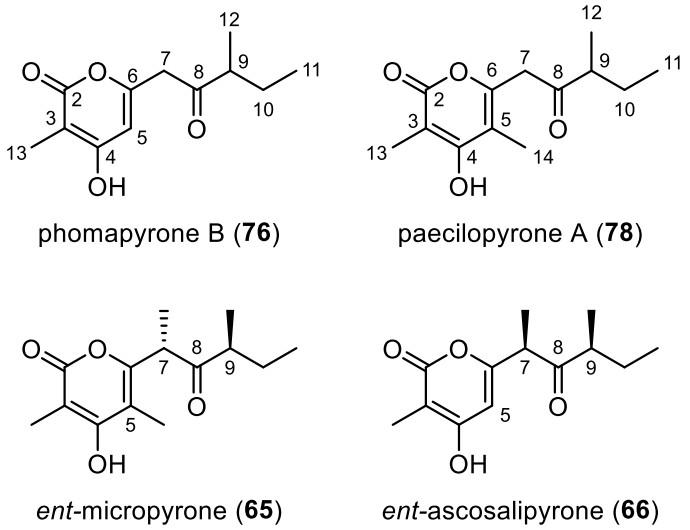
*Scheme 2.1: Retrosynthesis of pyrone (**S**)-**76** and pyrone (**S**)-**78***

The retrosynthetic analysis is depicted in Scheme 2.1. Both compounds may be obtained through oxidation of the appropriate 7-hydroxypyrone **87**, which in turn could

be accessed through deprotection of the appropriate silyloxy pyrone **88**. Disconnection of the pyrone moiety reveals two potential linear precursors; the acetonide **89** and the β, δ-diketo ester **90**. Disconnection of the acetonide affords either dioxinone **91** or **92** and the common aldehyde fragment **93**, which possesses controlled (3*R*, 4*S*) stereochemistry. The β, δ-diketo esters **90** may be accessed through coupling of β-keto esters **51** and **71** with the common aldehyde fragment **93**, followed by oxidation of the secondary alcohol. Alternatively, coupling with a substrate where R_1 represents a suitable leaving group (**94**) would afford the desired C5 oxidation state directly.

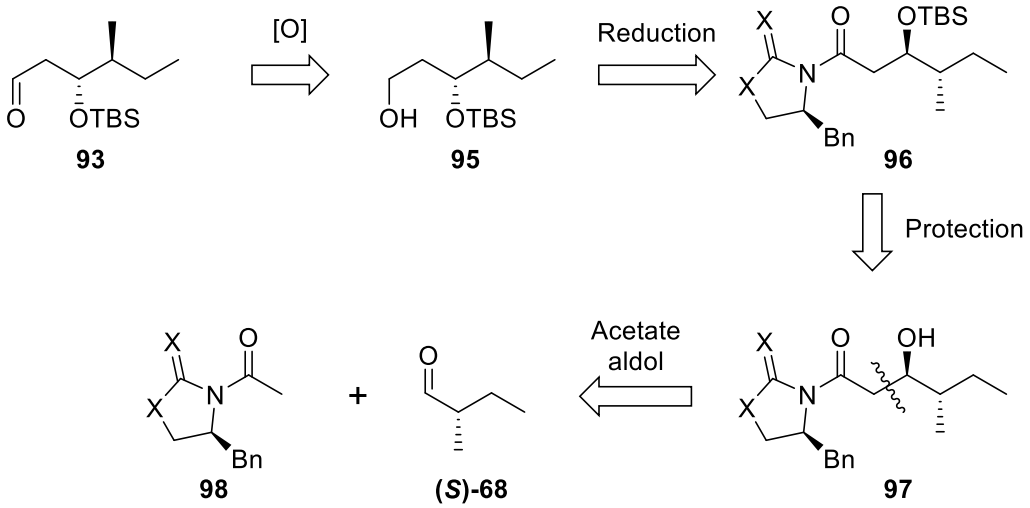
These two approaches follow a similar synthetic sequence; however, cyclisation from the corresponding acetonide **89** could be achieved at 0 °C with sodium methoxide for one hour. In contrast, cyclisation of the β, δ-diketo ester **90** could require heating at reflux in benzene for multiple hours, which could result in degradation and side-product formation.

Although alternative methods for diketo ester and pyrone ring formation would be investigated, the stereochemistry at C8 and C9 could be obtained in a similar manner to micropyrone (**65**) and ascosalipyrone (**66**). The two key variations in chemical structure between the four natural products (Scheme 2.2) are the substituents at C5 and C7, which can be either a hydrogen atom or methyl group. Both phomapyrone B (**76**) and paecilopyrone A (**78**) possess no substituent at C7, whilst they have a hydrogen atom and methyl substituent at C5, respectively. By alternating the β-keto ester or dioxinone used, the methyl substituent at C5 may be introduced allowing for synthesis of both natural products.



*Scheme 2.2: Structures of phomapyrone B (**76**), paecilopyrone A (**78**), ent-micropyrone (**65**) and ent-ascosalipyrone (**66**)*

In terms of the absence of a methyl substituent at C7, both natural products may be accessed through use of the common aldehyde fragment **93** possessing no α-branching (Scheme 2.3). The diastereomeric aldehyde fragment **93** possessing the (3*S*, 4*S*) stereochemistry may be obtained from the corresponding alcohol **95**, which in turn may be obtained from the reductive cleavage of chiral auxiliary **96**. The silyloxy substituent may be introduced through protection of the aldol product **97**. Because the required aldehyde fragment possesses no α-branching, the *N*-acetyl chiral auxiliary **98** could be used in an asymmetric acetate aldol reaction, where X represents either oxygen or sulfur atoms. The stereochemistry at C3 could be obtained through use of the known (*S*)-2-methylbutyraldehyde (**68**), which could be easily obtained through oxidation of the commercially available (*S*)-2-methylbutan-1-ol.



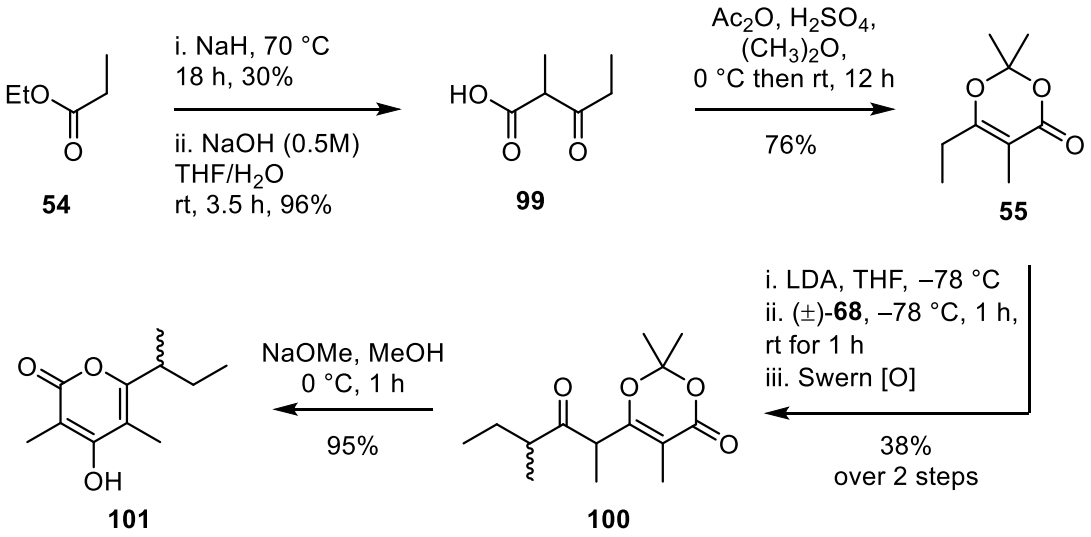
*Scheme 2.3: Retrosynthesis of aldehyde **93** (X = O or S)*

Of the three synthetic strategies, Gregg's previously developed methodology would afford the natural products, but the other two plausible synthetic routes could be investigated for their potential to increase overall yield and minimise the number of linear steps.

2.2 Model Systems for Dioxinone Formation

The first synthetic strategy investigated was the use of dioxinones as protected β-keto esters. Omura has shown that they can be easily converted to the corresponding α-pyrones through acetonide deprotection and cyclisation of the intermediate diketo ester with sodium methoxide.[7] The reaction conditions are relatively mild, with the temperature maintained at 0 °C for the duration of the reaction. It was believed that the low temperatures employed may suppress side reactions such as elimination.

In order to test this methodology, a simplified model system could be used with a commercially available aldehyde. The sequence began with synthesis of the known dioxinone **55** (Scheme 2.4).[7] Self-condensation of ethyl propionate **54** with sodium hydride[65] and subsequent hydrolysis afforded the β-keto acid **99**, which was protected as the acetonide through addition of acetic anhydride and a catalytic quantity of sulfuric acid. Dioxinone **55** was obtained as a yellow oil, with the ^{1}H NMR and ^{13}C NMR spectra matching the reported literature spectra.[7]



*Scheme 2.4: synthesis of pyrone **101***

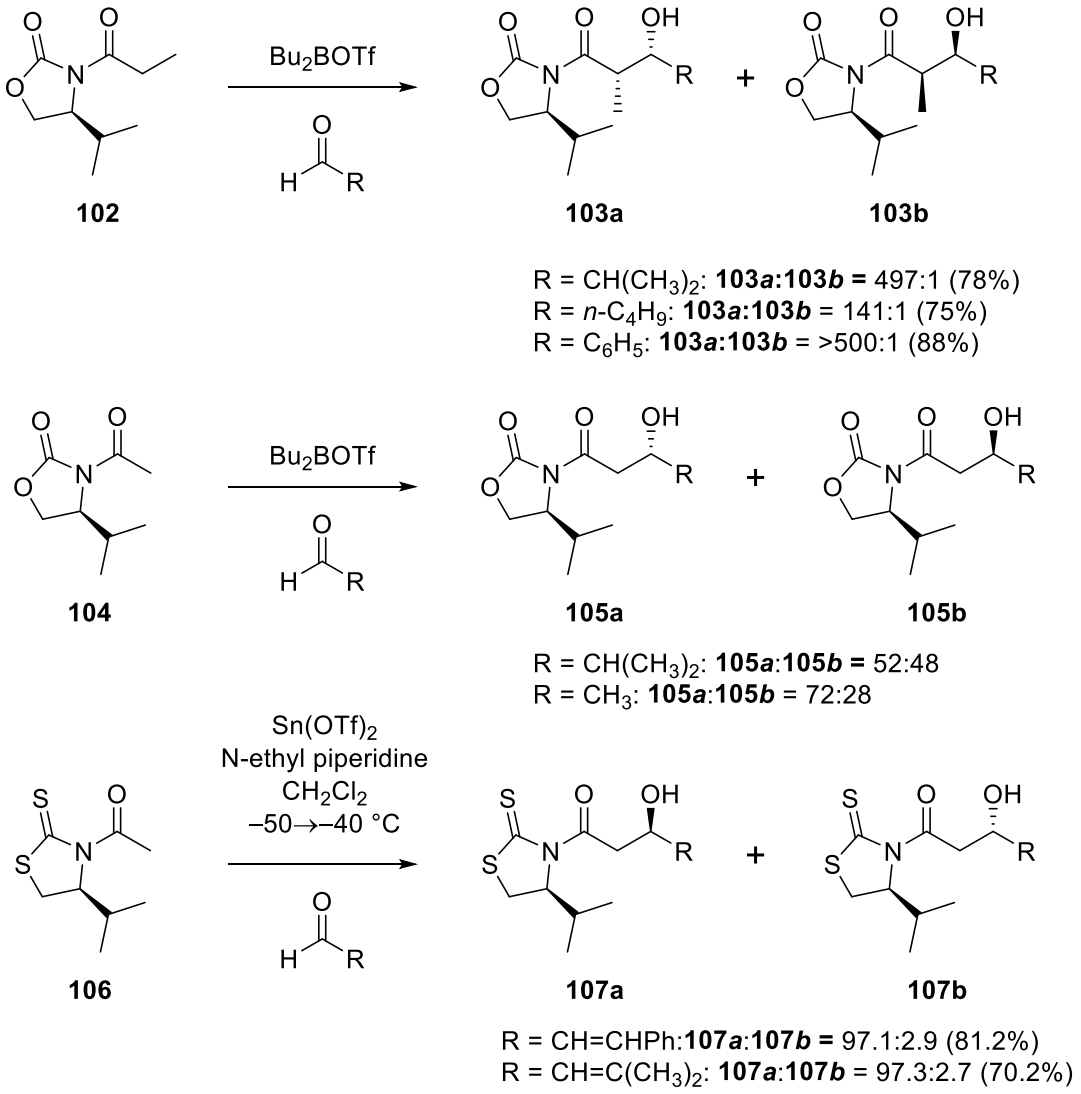
Dioxinone **55** was deprotonated with LDA, then 2-methylbutyraldehyde **(±)-68** was added *via* cannulation. Immediately following purification, the secondary alcohol was oxidised using standard Swern oxidation conditions.[49] Ketone **100** was isolated as a colourless oil and mixture of isomers in 38% yield over two steps. In order to complete the model study, acetonide deprotection and subsequent cyclisation afforded pyrone **101** as a white amorphous solid in 95% yield after slow crystallisation.

2.3 Selection of an Appropriate Chiral Auxiliary

With the model system completed, the next step in the synthesis was the construction of the aliphatic aldehyde **93**. The stereochemistry of the hydroxyl functionality in the intermediates was inconsequential as this position would be oxidised to align with the carbonyl of the natural products. However, for the purposes of NMR characterisation, synthesis of one diastereomer of aldehyde **93** would be beneficial. The common aldehyde fragment **93** could be synthesised through a stereoselective aldol reaction between the known (*S*)-2-methylbutyraldehyde (**68**) and an appropriate *N*-acetyl substituted auxiliary.

The *N*-acetyl group of chiral auxiliaries can have a marked effect on diastereoselectivities compared to the *N*-propionyl analogues. For instance, the stereochemical outcome of the boron mediated aldol reaction with chiral oxazolidinones is often poor when the acetate is used (Scheme 2.5).[56] Pioneering work by Evans has

previously described the use of chiral *N*-acyl oxazolidinones in aldol condensations with various aldehydes. When the *N*-propionyl auxiliary **102** was used, treatment with dibutyl boron triflate followed by diisopropylethylamine at 0 °C afforded the *Z*-enolate, which was then cooled to −78 °C and the aldehyde added. Evans observed that of the four diastereomers possible, the major constituents were the *erythro* diastereomers **103*a*** and **103*b***. The *threo* diastereomers (*anti* configuration of methyl and hydroxyl) constituted less than 1% of the reaction mixture. Selectivity for the *erythro* isomer **103*a*** over **103*b*** ranged from 141:1 to >500:1, indicating high levels of stereoinduction with *N*-propionyl oxazolidinones. Conversely, use of the *N*-acetyl oxazolidinone **104** in the boron aldol reaction resulted in poor diastereoselectivities, some of which approached 1:1 mixtures of **105*a*** to **105*b***.

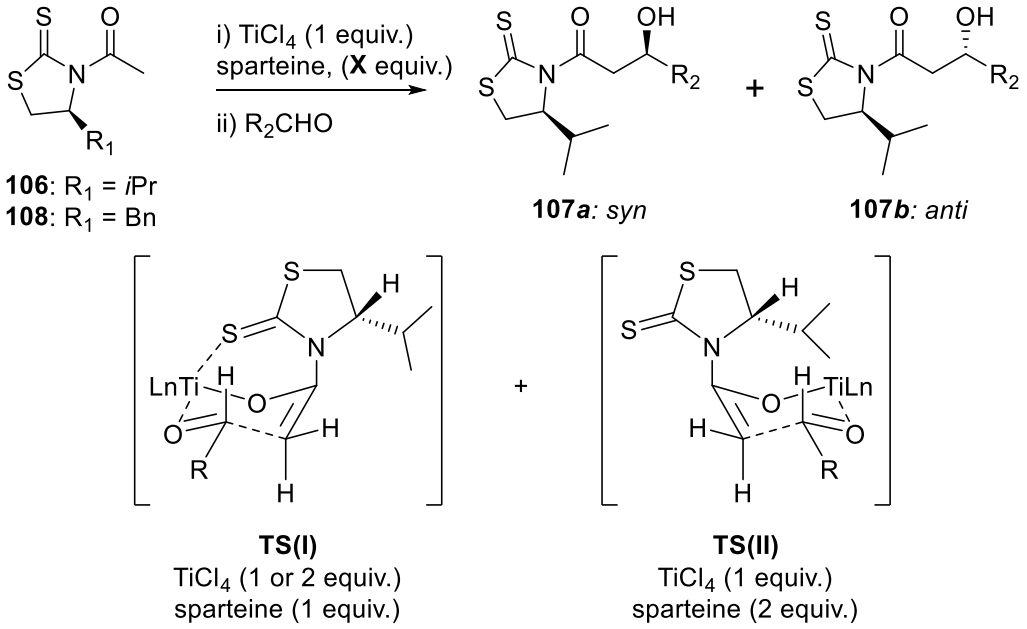


Scheme 2.5: Evans' erythro-selective aldol condensations with boron enolates and Nagao's tin (II) mediated acetate aldol

Simply by changing the heteroatoms of the auxiliary and the Lewis acid used for enolisation, Nagao[66,67] was able to obtain good diastereoselectivities with *N*-acetyl thiazolidinethione **106**. Treatment with Tin(II) triflate and *N*-ethylpiperidine at −50 °C followed by addition of the aldehyde resulted in formation of the non-Evans *syn* acetate aldol adduct **107*a*** (Scheme 2.5). Here the terms *syn* and *anti* refer to the stereochemical relationship as drawn between the hydroxyl group and the C4 stereocenter of the auxiliary. The diastereoselectivities were comparable to Evans earlier work with boron mediated aldols; however stereochemistry at the β-hydroxyl position was reversed.

Further work by Olivo[68] investigated the stoichiometry effects on the acetate aldol reaction of *N*-acetyl thiazolidinethione **106** with a variety of unsaturated aldehydes, aromatic aldehydes and aliphatic aldehydes (Table 2.1). Titanium(IV) chloride and (−)-sparteine (1 equivalent) were used for the mild enolisation of the auxiliary, resulting in the non-Evans *syn* acetate aldol product **107*a*** as the major diastereomer. This was attributable to the reaction proceeding through transition state **TS(I)** where the thiocarbonyl was coordinated with the titanium. For the range of aldehydes tested, the unsaturated and aromatic aldehydes gave the highest diastereoselectivities (85−96 *dr*) for the *syn* diastereomer, whilst the aliphatic aldehydes gave the lowest diastereoselectivities (70−86 *dr*).

Table 2.1: Stoichiometry effects on the acetate aldol reaction with thiazolidinethiones[68]



		Base (1 equiv.)		Base (2 equiv.)	
Entry	**Aldehyde: R_2 =**	**Ratio *Syn : Anti***	**Yield**	**Ratio *Syn : Anti***	**Yield**
1	*t*-CH=CH-C_6H_5	92:8	73	18:82	73
2	-CH=C$(CH_3)_2$	91:9	60	26:74	60
3	−CH=CH−CH=CH−Br	96:4	94	–	–
4	−CH=CH_2	–	–	27:73	65
5	−C_6H_5	85:15	69	93:7	69
6	*p*-C_6H_4−br	95:5	50	63:37	50
7	−C$(CH_3)_3$	100:0	70	100:0	70
8	−CH$(C_6H_5)_2$	70:30	87	60:40	99
9	−CH_2CH_3	83:17	63	33:67	63
10	−$CH_2CH_2C_6H_5$	86:14	52	36:64	52

Increasing the equivalents of base employed (2 equivalents) resulted in a reversal of selectivity for the *anti* diastereomer **107*b*** as the major product. This was rationalised to proceed through transition state **TS(II)** with no coordination between the metal and thiocarbonyl group. Again, diastereoselectivities were greatest for the unsaturated aldehydes (73−82 *dr*) favouring the *anti* diastereomer **107*b***. An interesting result was observed for the aromatic aldehydes, which favoured the *syn* diastereomer **107*a*** (63 and 93 *dr*). The aliphatic aldehydes gave poorer results, with diastereoselectivities ranging

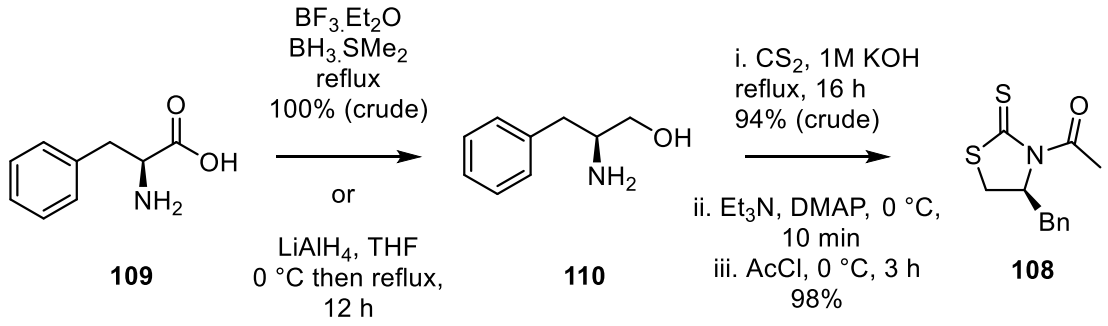
from 40−67 *dr* for the *anti* diastereomer **107*b***. Olivo also investigated the *N*-acetyl thiazolidinethione **108** with 3-phenylpropionaldehyde and observed a marked increase in diastereoselectivity for the *anti* diastereomer with 2 equivalents of base.

Differentiation of the *syn* and *anti* diastereomers was achieved through analysis of the chemical shifts and coupling constants for the α-protons.[68] For the major diastereomer, the most de-shielded α-proton exhibited a small vicinal coupling constant (<4 Hz), compared to >9 Hz for the more shielded α-proton. Conversely, the minor diastereomer possessed a large vicinal coupling constant (>9 Hz) for the most de-shielded α-proton, whilst the more shielded α-proton exhibited a small vicinal coupling constant (< 4 Hz). Both diastereomers showed large geminal coupling constants greater than 17 Hz. Olivo used this trend to assign the configurations of the synthesised diastereomers, as well as X-ray analysis of the major *syn* acetate aldol product formed from 4-bromobenzaldehyde.[68]

Based on these previous studies, the use of a thiazolidinethione would be beneficial over the analogous oxazolidinone, as superior diastereoselectivities could be obtained in the acetate aldol reaction. A simple enolisation with the commercially available titanium(IV) chloride (1M in CH_2Cl_2) could also be performed. This would be preferable to the alternative tin(II) triflate, which is normally prepared from tin(II) chloride. A chiral auxiliary derived from phenylalanine could be used, as this would afford a bulky phenyl substituent and hopefully better diastereoselectivities than the valine-derived auxiliary.[68]

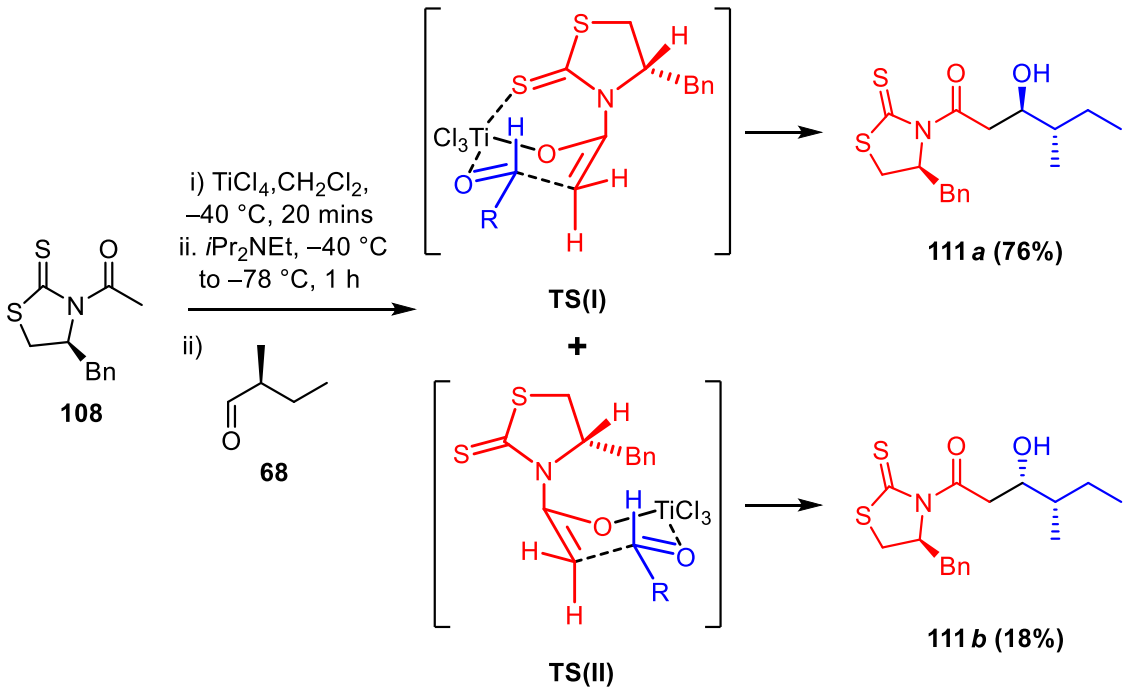
2.3.1 Installation of the C8 hydroxyl functionality

Starting from (*S*)-phenylalanine (**109**), reduction of the carboxylic acid could be achieved through complexation of the carbonyl with boron trifluoride then treatment with borane.[57,69] Although this procedure afforded (*S*)-phenylalanol **110** in high purity as white needles and quantitative yield, the procedure was quite involved. Therefore larger scale preparations made use of the operationally simpler reduction with lithium aluminium hydride ($LiAlH_4$).[70] Although the product obtained was not crystalline; instead it was an oily yellow residue, following cyclisation with CS_2 under basic conditions, the crude thiazolidinethione was obtained (Scheme 2.6).[71,72] Acylation of the crude thiazolidinethione with Et_3N, DMAP and AcCl afforded the crude *N*-acetyl thiazolidinethione **108**. Following column chromatography, the *N*-acetyl thiazolidinethione **108** was isolated as yellow needles in high purity.



*Scheme 2.6: Synthesis of the chiral auxiliary **108***

In order to install the hydroxyl functionality that would later be oxidised to align with the ketone of the natural products, methodology by Crimmins[73,74] and Olivo[68] was employed in an asymmetric acetate aldol reaction. Treatment of the *N*-acyl thiazolidinethione **108** with $TiCl_4$ at −40 °C allowed for complexation with the oxygen and sulfur atoms (Scheme 2.7). Subsequent treatment with diisopropylethylamine (1 equivalent) and stirring for a further hour at −40 °C afforded the deprotonated transition states **TS(I)** and **TS(II)**, with the major transition state being rationalised by the stability afforded from chelation of the titanium and sulfur atom.[68] The reaction mixture was cooled to −78 °C, and an excess of (*S*)-2-methylbutyraldehyde (**68**) added *via* cannulation. The reaction mixture was allowed to stir at −78 °C, with reaction progress monitored by TLC. After disappearance of the starting *N*-acetyl thiazolidinethione **108**, the reaction mixture was quenched and allowed to warm to room temperature. Analysis of the ^{1}H NMR of the crude reaction mixture revealed that the major diastereomer **111*a*** was present in a ratio of 81:19 with the minor diastereomer **111*b***.



*Scheme 2.7: Titanium(IV) mediated acetate aldol with thiazolidinethione **108***

The stereochemistry of the two diastereomers could be determined using the coupling constants observed for the two diastereomers in accordance with the trends that Olivo reported for the C'2 and C'3 hydrogens of the acetate aldol products.[68] This analysis relies on the hydrogen bonding that exists between the C'1 carbonyl and C'3 hydroxyl, as well as the restricted rotation of the amide bond. The ^{1}H NMR for the α-protons of the major diastereomer **111*a*** (Figure 2.1); 3.61 (1H, dd, *J*=17.8, 2.0 Hz, H_a) and 3.16 (1H, dd, *J*=17.8, 10.1 Hz, H_b) were compared to those of the minor diastereomer **111*b***; 3.54 (1H, dd, *J*=17.3, 10.2 Hz, H_a) and 3.27 (1H, dd, *J*=17.3, 2.1 Hz, H_b).

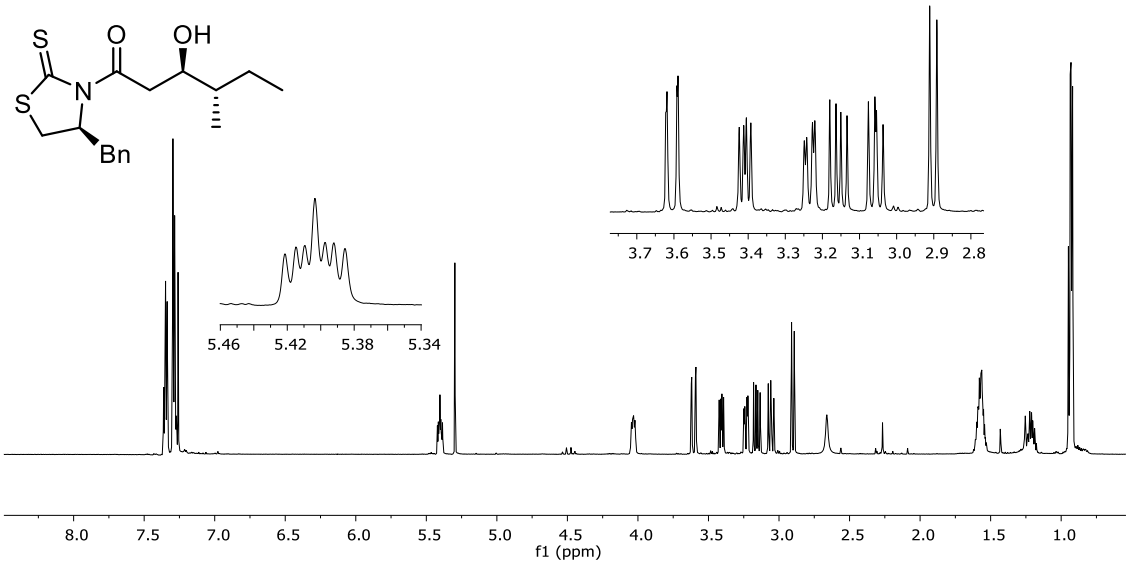
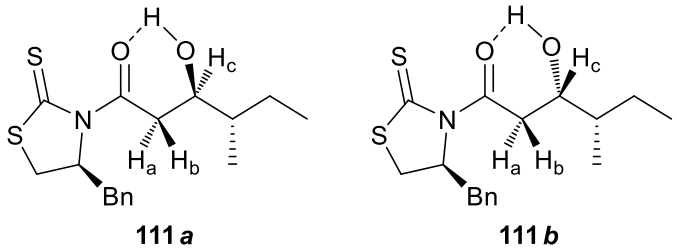


*Figure 2.1: ^{1}H NMR spectrum of major diastereomer **111a***

For the major diastereomer, the signal at 3.61 ppm was assigned using the trend reported by Olivo as the H_a proton.[68] This hydrogen exhibited a large geminal coupling constant of 17.8 Hz with H_b, whilst the smaller coupling constant of 2.0 Hz was observed with H_c (Scheme 2.8). The small coupling constant indicates a small dihedral angle, thus a *gauche* relationship between the two protons (3*R*, 4*S* stereochemistry). Conversely, the proton H_b at 3.16 ppm had coupling constants of 17.8 Hz and 10.1 Hz. The larger coupling constant of 10.1 Hz with H_c indicates a larger dihedral angle and therefore an *anti*-relationship (H_b–H_c). For the minor diastereomer, this trend was reversed, with the larger coupling constant (10.2 Hz) observed for the most de-shielded α-proton H_a (3.54 ppm), indicating an *anti*-relationship between H_a–H_c and therefore assignment of the stereochemistry as 3*S*, 4*S*.



Scheme 2.8: Stereochemistry of the two acetate aldol diastereomers

In addition to NMR analysis, the minor diastereomer **111*b*** crystallised on standing after 1 week at ~4 °C. In order to grow crystals suitable for X-ray analysis, **111*b*** was dissolved in the minimum amount of diethyl ether required for solvation, and a small

volume of hexanes added. The mixture was allowed to stand overnight and upon analysis the following morning revealed yellow block-like crystals. X-ray analysis[75] revealed that the minor diastereomer was the acetate-*anti* diastereomer **111*b*** as expected (Figure 2.2), supporting the NMR assignment of the diastereomers.

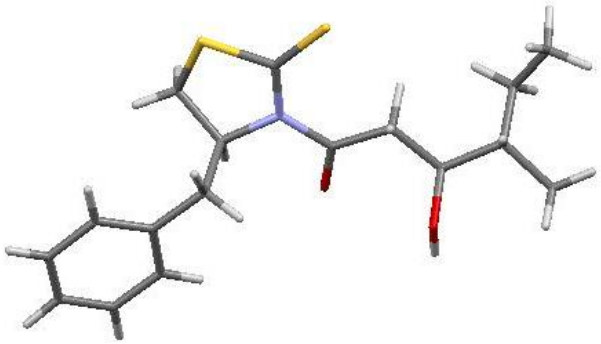
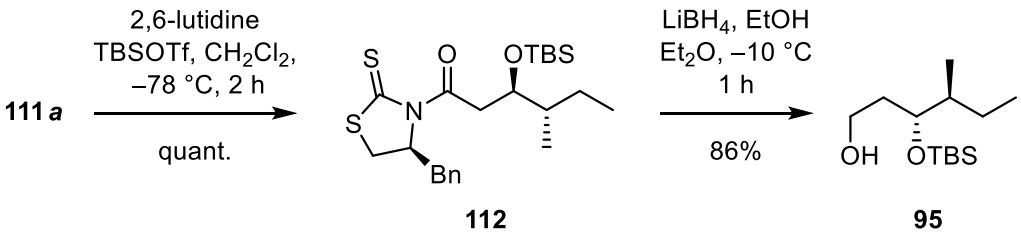


*Figure 2.2: Wire frame diagram of the minor diastereomer **111b***

*2.4 Synthesis of Aliphatic Aldehyde **93***

With installation of the C8 and C9 stereochemistry complete, attention was turned to the protection and subsequent removal of the chiral auxiliary. The major diastereomer **111*a*** was protected as the *t*-butyldimethylsilyl ether **112** by treatment with 2, 6-lutidine and TBSOTf (Scheme 2.9).[76,77] ^{1}H NMR analysis revealed that the reaction was successful, with the characteristic *t*-butyl group appearing at 0.84 ppm as a sharp singlet and integrating for 9H. Two signals from methyl groups attached to the silicon atom also appeared at 0.1 and 0.04 ppm, each integrating for 3H and appearing as sharp singlets. The remaining ^{1}H NMR signals were similar to that observed for the starting material, except the proton under the silyloxy substituent had shifted downfield to 4.36 ppm compared to 4.02 ppm for the hydroxyl substituent of the starting material.



*Scheme 2.9: TBS protection and reduction of the major diastereomer **111a***

Reduction of the auxiliary was conducted through portionwise addition of $LiBH_4$ to silyl ether **112**. During the reaction, the apparent yellow colour from the starting material dissipated, leaving a colourless solution indicating that the auxiliary had been cleaved. The primary alcohol **95** was easily separable from the free auxiliary through trituration and chromatography, which afforded alcohol **95** in 86% isolated yield.

Analysis of the ^{1}H NMR spectrum revealed a signal at 3.79 ppm (1H, m) attributable to the silyloxy methine hydrogen. There was also a peak at 3.73 ppm (2H, dt) that was assigned as the 2 hydrogens of the oxymethylene. The ^{13}C NMR spectrum revealed signals at 74.8 and 60.9 ppm, which were assigned to the silyloxy methine and oxymethylene carbons. There were also no signals characteristic of the free thiazolidinethione, indicating that both the reduction worked well and the alcohol was of high purity. The HRESIMS was obtained for the alcohol, with the observed m/z of 269.1912 in good agreement with the calculated m/z (269.1913 for $C_{13}H_{30}O_2SiNa^{+}$).

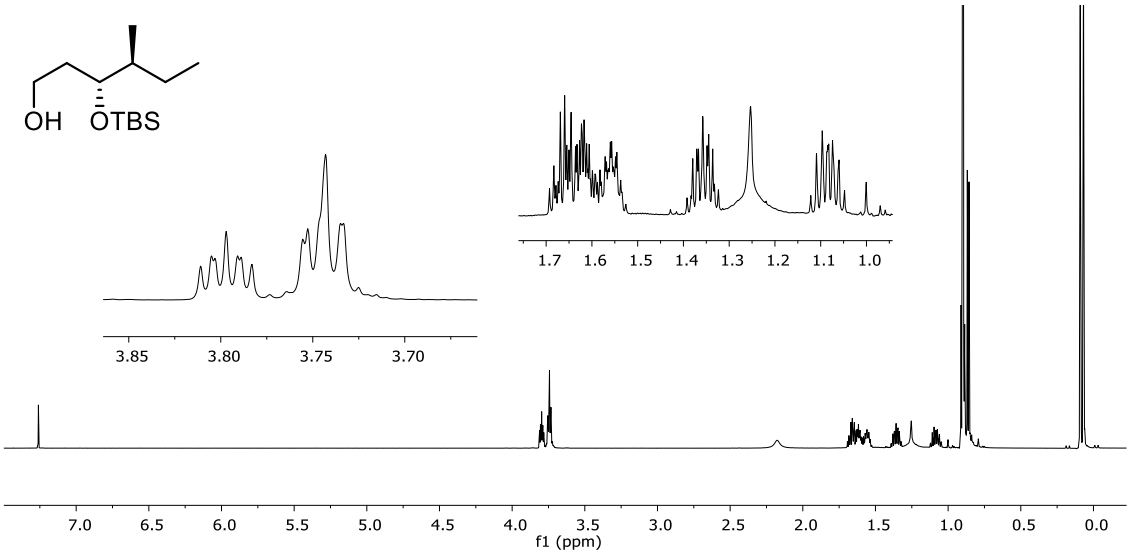
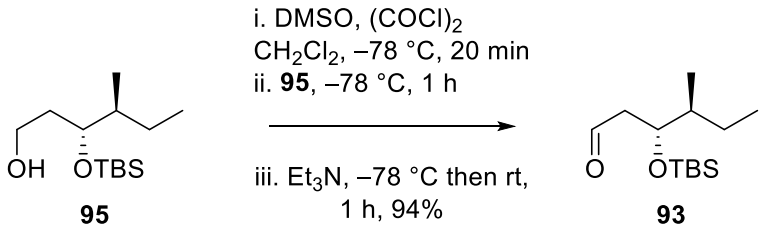


*Figure 2.3: ^{1}H NMR spectrum of alcohol **95***

Treatment of alcohol **95** under standard Swern oxidation conditions afforded the corresponding aldehyde **93** in 94% yield (Scheme 2.10). The ^{1}H NMR contained a characteristic signal at 9.81 ppm integrating for 1H that was indicative of an aldehyde. The peak previously present at 3.73 ppm in the starting material had also disappeared, with appearance of signals at 2.51 ppm and 2.35 ppm indicative of methylene hydrogens α to the carbonyl. There was characteristic coupling observed to the aldehyde proton (*J* 3.2 Hz) as well as the silyloxy methine proton (*J* 8.1 Hz) from the methylene hydrogen at 2.51 ppm. The ^{13}C NMR spectrum showed a signal at 203.1 ppm, which

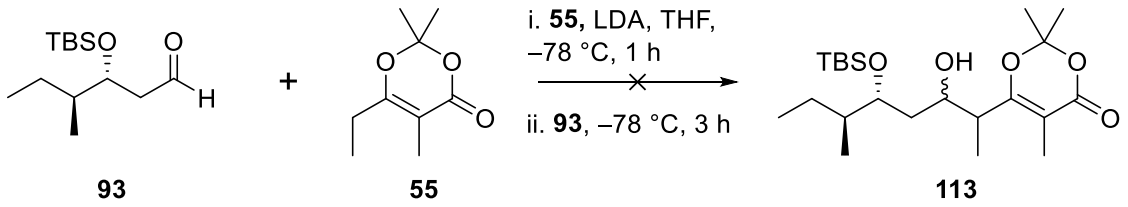
was assigned to the aldehyde, whilst there was only 1 signal at 71.4 ppm indicative of the silyloxy methine carbon. Because of the instability of aldehyde **93**, it was not subjected to prolonged storage, and was used without further characterisation.



*Scheme 2.10: Synthesis of aldehyde **93**.*

*2.4.1 Attempted coupling of aldehyde **93** with dioxinones*

Using the same experimental conditions as the model system, dioxinone **55** was deprotonated with LDA and aldehyde **93** added after 1 hour (Scheme 2.11). The reaction mixture was stirred for 3 hours at −78 °C then warmed to 0 °C. Unfortunately, only starting dioxinone and decomposed aldehyde were observed in the crude ^{1}H NMR spectrum. Alterations were made to reaction times and temperatures for enolate formation and aldehyde addition. The stoichiometry and concentration were also varied but in each case, only starting dioxinone was observed. The inability to synthesise alcohol **113** in addition to the low yields observed in the model system led to the abandonment of this approach.

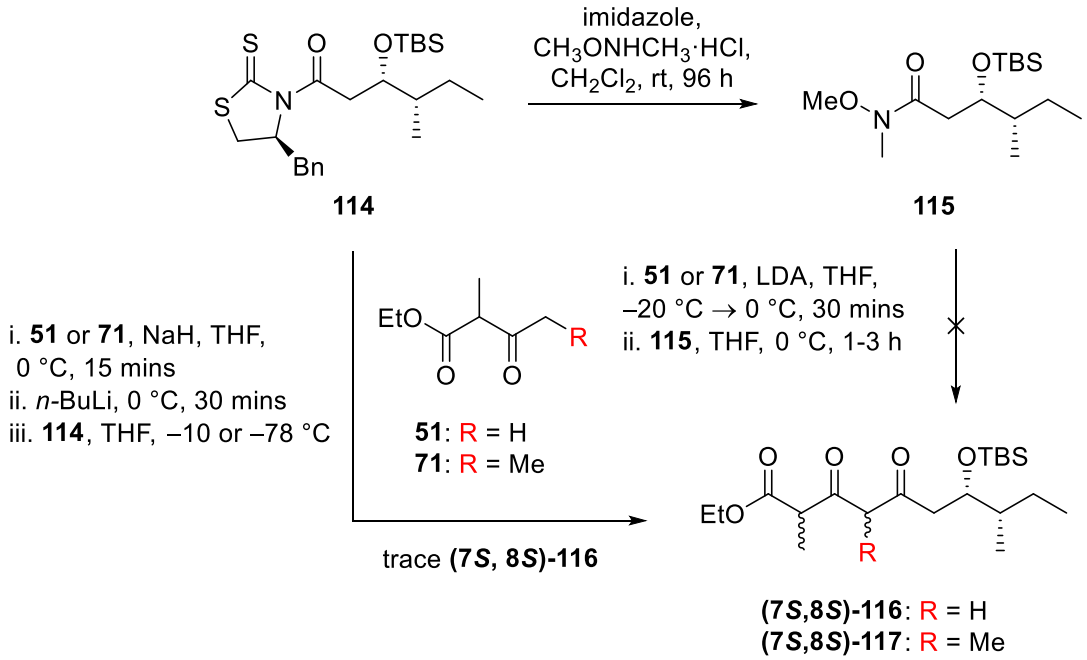


*Scheme 2.11: Attempted coupling of aldehyde **93** and dioxinone **55***

2.4.2 Attempted coupling of β-keto esters and amides

Meshram *et al.* have reported that bisenolates formed from β-keto esters were able to nucleophilically displace Weinreb amides during the synthesis of salinipyrone A (**42**).[44] To test this methodology, additional material in the form of the minor isomer was protected as the silyl ether **114** in quantitative yield. The thioamide was converted into the Weinreb amide **115** following treatment with N,O-hydroxylamine hydrochloride in CH_2Cl_2 over 96 hours (Scheme 2.12).[78] Formation of the dianion from either ethyl-2-

methyl acetoacetate **51** or β-keto ester **71** occurred following deprotonation with LDA, with the Weinreb amide **115** then added *via* cannulation. In each case, only starting materials were observed.

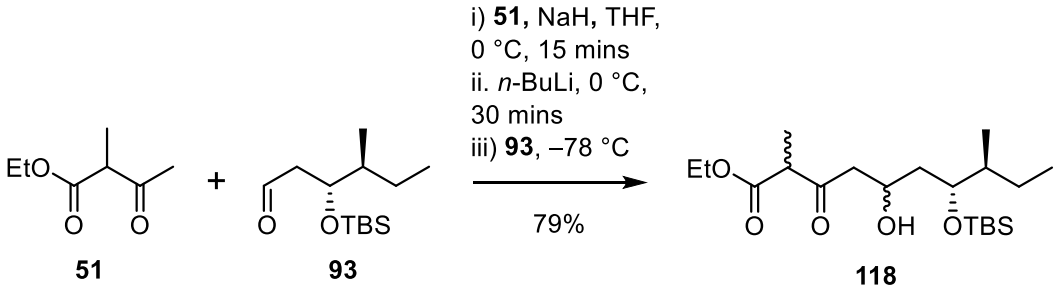


*Scheme 2.12: attempted synthesis of diketo esters **116** and **117** through displacement of amides*

Following methodology from Yadav *et al.*, [45] the dianion addition was performed using the *N*-acyl thiazolidinethione **114** as electrophile. No product was observed when R was a methyl substituent. When R was a hydrogen atom for the commercially available ethyl-2-methyl acetoacetate (**51**), only trace quantities of the β, δ-diketo ester **116** was observed, even when the temperature was lowered to −78 °C for addition of thiazolidinethione **114**. Interestingly, as the reaction duration increased, decomposition of the starting *N*-acyl thiazolidinethione **114** was observed, with appearance of a lower R_f spot attributed to the free auxiliary. This indicates that thiazolidinethione **114** may not necessarily be stable to the conditions used. One possible explanation for this may be due to LiOH, which may be present in low concentrations in the *n*-butyl lithium solution. Thiazolidinethione **114** also possesses α-branching adjacent to the silyloxy substituent, which may account for the decreased reactivity. All attempts to synthesise diketo ester **117** from the dianion of β-keto ester **71** were unsuccessful.

2.4.3 Coupling of aldehyde **93** with β-keto esters

With the two aforementioned approaches failing to improve yield or minimise the number of linear steps, Gregg's methodology was applied for the coupling of common aldehyde fragment **93** with β-keto esters.[53] The *sodio-lithio* bisenolate formed from ethyl-2-methyl acetoacetate (**51**) was added to aldehyde **93** (Scheme 2.13). The δ-hydroxy-β-keto ester **118** was isolated as a colourless oil in 79% yield. It is important to note that due to the two uncontrolled stereocenters, the hydroxy ester was isolated as an inseparable mixture of diastereomers. This also meant that the ^{1}H and ^{13}C NMR spectra for the oil obtained were complicated. It was therefore decided to not fully characterise this compound but instead treat it as an intermediate.



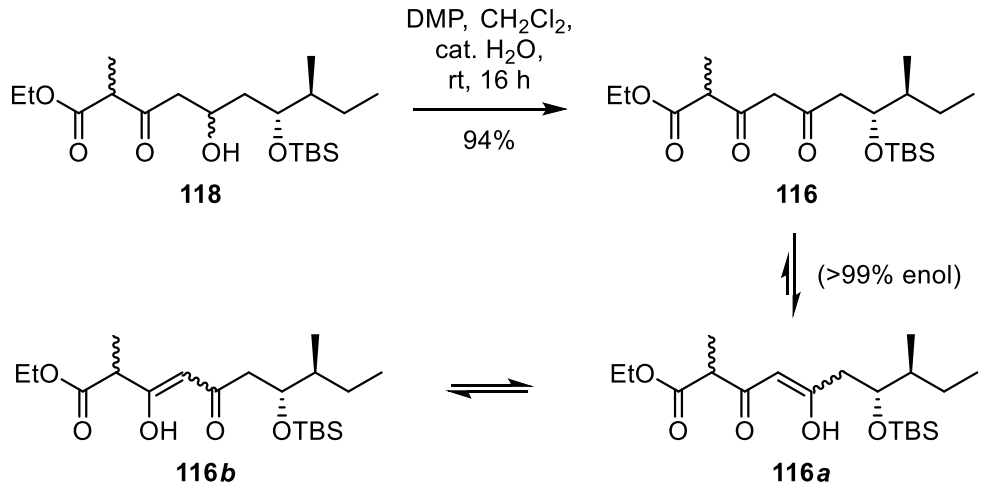
*Scheme 2.13: Dianion addition with ethyl-2-methyl acetoacetate **51** and aldehyde **93***

2.4.4 Dess-Martin periodinane oxidation of alcohol ***118***

The alcohol **118** was dissolved in CH_2Cl_2 and DMP added (Scheme 2.14).[60] In order to increase the rate of oxidation a catalytic amount of water in CH_2Cl_2 was added every 5 minutes for 1 hour. Following workup and purification, the diketo ester **116** was obtained as a light yellow oil in 94% yield.

Analysis of the ^{1}H NMR spectrum (Figure 2.4) revealed a signal at 5.6 ppm (s, 1H), which initially seemed erroneous considering the structure of diketo ester **116**. However, a chemical shift of 5.6 ppm is indicative of vinylic protons, and was determined through 2D NMR spectroscopy as belonging to the proton of either enol tautomer **116*a*** or **116*b***. The hydroxyl proton from the enol tautomers was apparent at 15.21 ppm (d, 1H). The signal at 4.17 ppm (m, 2H) belonged to the oxymethylene of the ester, whilst the signal at 4.09–4.06 ppm (m, 1H) belonged to the silyloxy methine proton. The signal at 3.38–3.34 ppm was attributable to the methine proton *alpha* to the

two carbonyls, whilst the signal at 2.31–2.23 ppm was attributable to the methylene *alpha* to the silyloxy methine.



*Scheme 2.14: Oxidation of δ-hydroxy β-keto ester **118** and subsequent tautomerism*

The ^{1}H NMR integration for the C4 vinyl proton at 5.6 ppm indicates that the enol tautomers predominate. Theoretically, there may be three positions where the double bond may exist as well as *E* and *Z* isomers. The presence of the C2 methine at 3.38-3.34 ppm indicates that the enol form is either **116*a*** or **116*b***, where the geometry of the double bond is not defined. The ^{13}C NMR spectrum (Figure 2.5) revealed signals at 193.1, 193, 190.9 and 190.7 ppm indicating the presence of two significant enol tautomers. The peak at 170.9 ppm was assigned to the ester carbonyl, whilst there were also two signals at 100.4 and 100.1 ppm, indicative of alkenes. Whether the alkene signals were attributable to two different double bond locations or geometries was not determined.

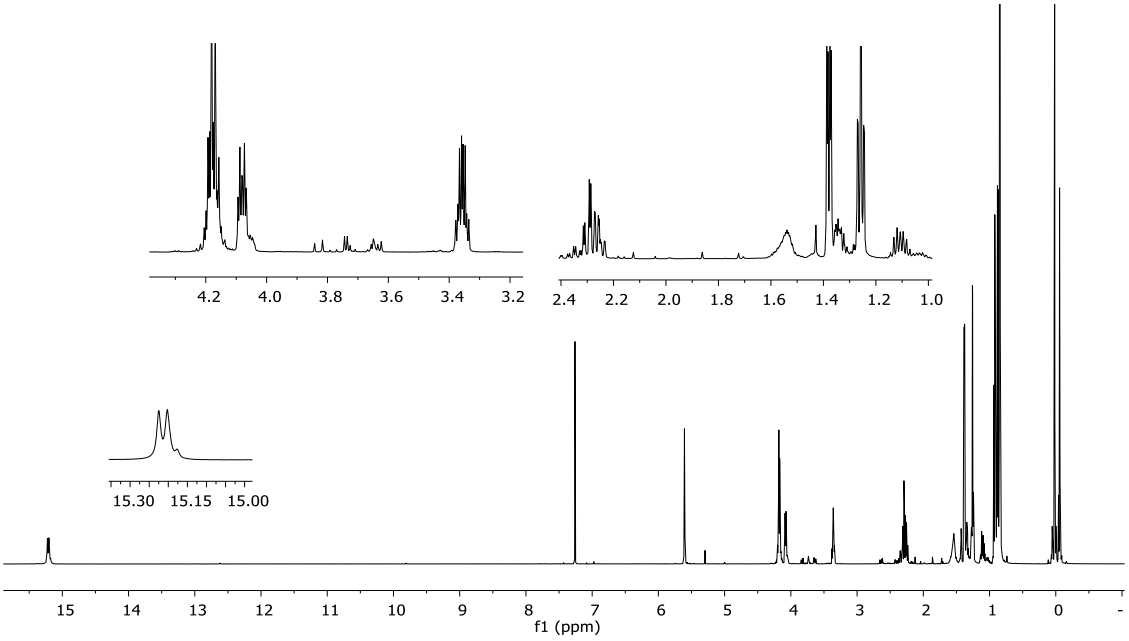


*Figure 2.4: ^{1}H NMR spectrum of β, δ-diketo ester **116***

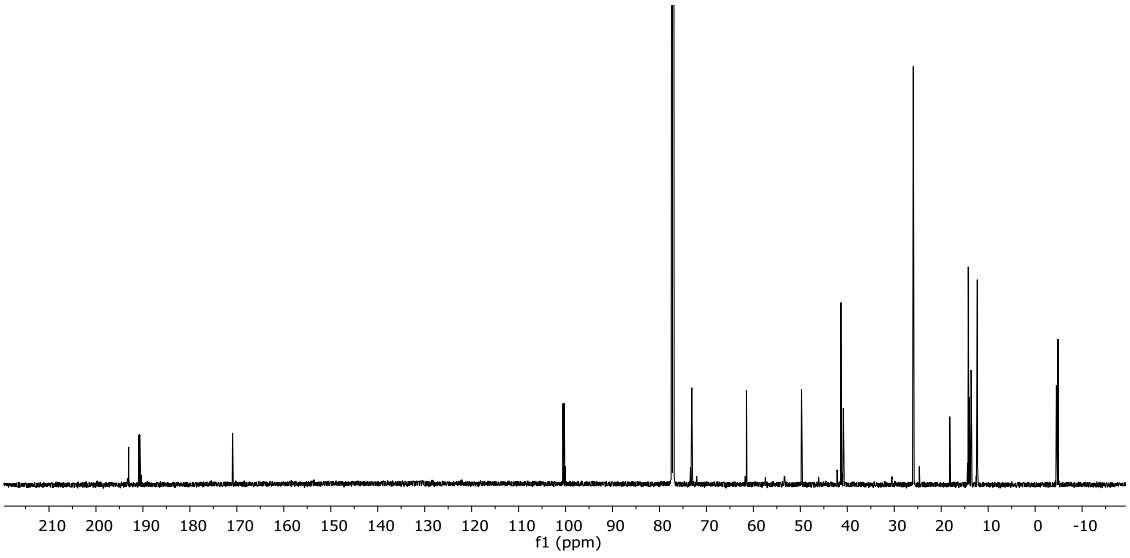


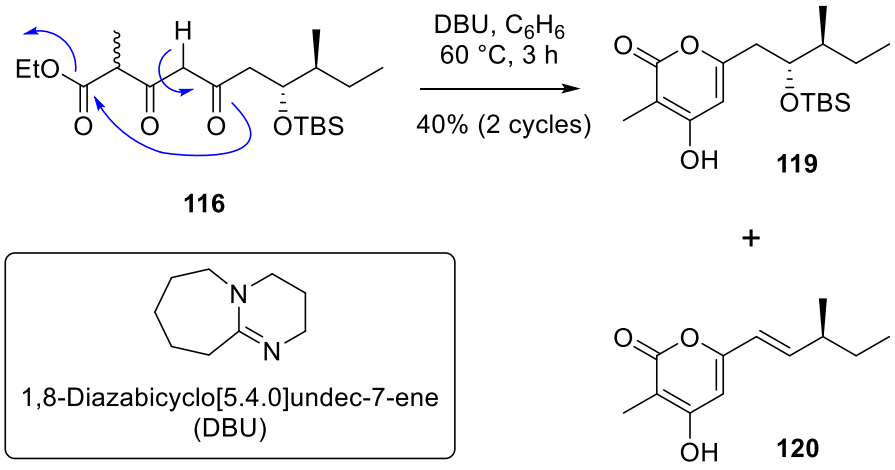
*Figure 2.5: ^{13}C NMR spectrum of β, δ-diketo ester **116***

2.5 Total Synthesis of ent-Phomapyrone B (**76**)

Previous work by the Perkins research group has established that DBU can be effective in mediating cyclisation.[53] However, in the synthesis of micropyrone and ascosalipyrone (Scheme 1.17), yields were between 25-45%. This was attributable to the α-methyl present, which under the cyclisation conditions epimerised. Therefore modifications were made in which the temperature was lowered and reaction duration decreased leading to decreased formation of the unwanted side-products.

2.5.1 Cyclisation of the diketo ester **116**

Phomapyrone B did not possess an α-methyl substituent so epimerisation was not a concern. However, during the cyclisation with DBU at 60 °C an unwanted β-elimination side-product was forming. Through TLC analysis, formation of pyrone **119** was initially observed, but with elevated temperatures and prolonged reaction times conversion of pyrone **119** to the elimination side-product **120** predominated (Scheme 2.15). The formation of side product **120** was mitigated by stopping the reaction after 3 hours, separating the products and re-subjecting the starting material to the cyclisation conditions. Pyrone **119** was obtained (ca. 40%, 60% brsm) in sufficient yield following the aforementioned reaction conditions.

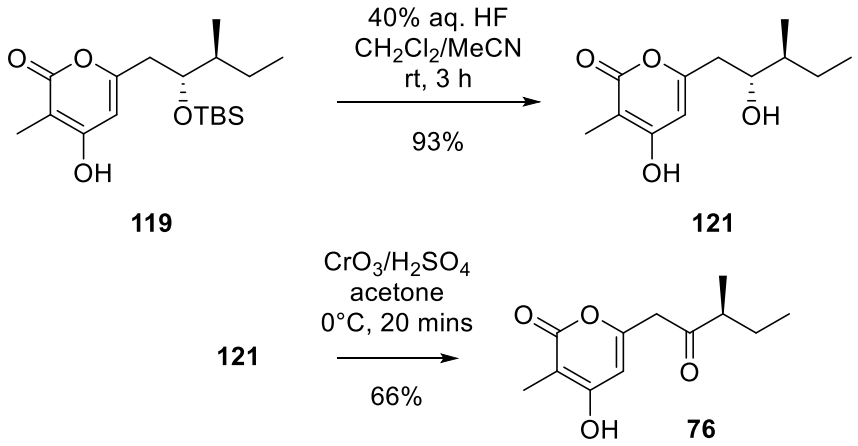


*Scheme 2.15: base-mediated cyclisation of enol **116a***

2.5.2 TBS deprotection and oxidation of C8

To complete the synthesis of compound **76**, the TBS ether **119** was deprotected using HF, affording the secondary alcohol **121** in 93% yield as white needles (Scheme 2.16). DMP oxidation in MeCN was attempted, but there was no observable product after two days. This was presumably due to solubility issues associated with pyrone **121**, which only dissolved in high polarity solvents such as DMSO, MeOH or acetone.

Considering the solubility issues, only Jones oxidation was amenable for oxidation to the corresponding ketone. The alcohol **121** was dissolved in acetone and titrated with Jones reagent until the orange colour was sustained. Following purification, compound **76** was obtained as white needles (Mp 118-121 °C) in 66% yield. Over prolonged storage, there was an apparent yellow discolouration of the previously white needles, although ^{1}H NMR analysis showed no significant impurities.



*Scheme 2.16: total synthesis of compound **76***

Figure 2.6 shows the ^{1}H NMR spectrum obtained for compound **76**. The broad singlet at 9.71 ppm is due to the acidic proton of the hydroxyl at C4, whilst the singlet at 6.2 ppm is due to H5. The peak at 3.62 ppm was assigned as the two H7 protons, which have no neighbouring ^{1}H nuclei. The methine proton at C9 appeared at 2.57 ppm (1h, ddq). The singlet at 1.93 is due to C13, whilst the two signals at 1.7 (1H, d. quin.) and 1.42 ppm (1H, d. quin.) are due to the two diastereotopic protons at C10 coupling with H9 and also H11. The ^{1}H NMR data (Table 2.2) is almost identical to the literature data[12] with the only discrepancy being due to the acidic proton from the pyrone hydroxyl at C4. This is to be expected as the acidic nature means the proton is exchangeable. All other chemical shift values are in good agreement with the literature values.

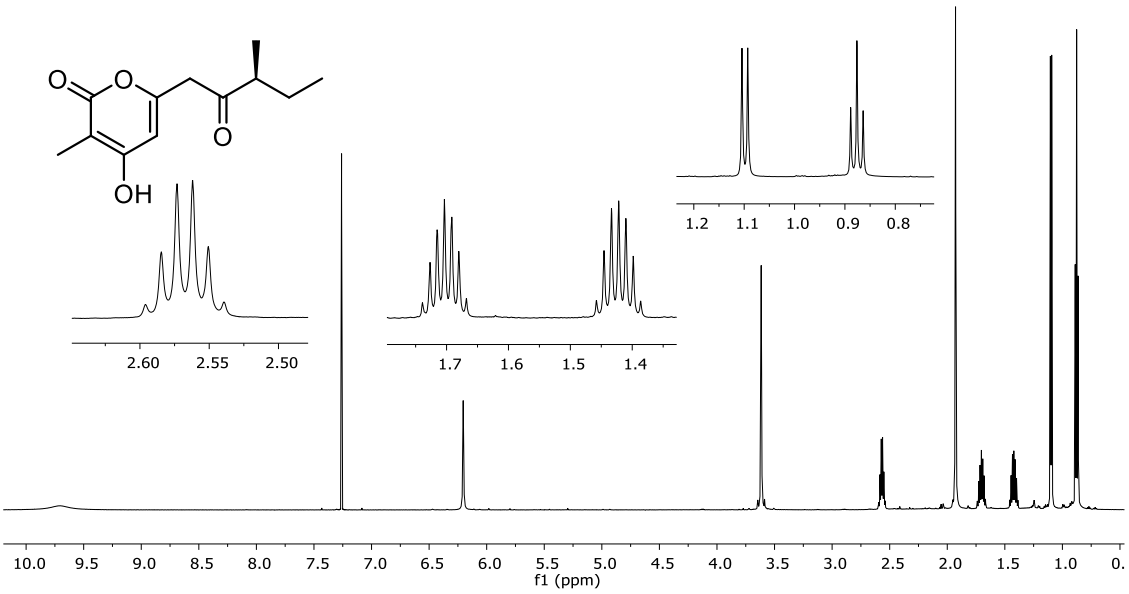


*Figure 2.6: ^{1}H NMR spectrum of compound **76***

*Table 2.2: ^{1}H NMR comparison for the synthesised compound **76** and phomapyrone B (**76**)*[12]

Proton #	**Phomapyrone B (76)** 500 MHz - δ ppm (J in Hz)	**Compound 76** 600 MHz - δ ppm (J in Hz)	**Difference**
OH	7.83 (br. s)	9.71 (br. s.)	1.88
5	6.07 (s)	6.2 (s)	0.13
7	3.58 (AB q., 18)	3.62 (AB q., 17.7)	0.04
9	2.56 (ddq, 6.8)	2.57 (ddq, 6.8)	0.01
10	1.7 (m)	1.7 (dquin, 7.1, 14.2)	0
10	1.42 (m)	1.42 (dquin, 7.2 14.2)	0
11	0.87 (t, 7.5)	0.88 (t, 7.4)	0.01
12	1.07 (d, 6.8)	1.1 (d, 6.9)	0.03
13	1.92 (s)	1.93 (s)	0.01

Analysis of the ^{13}C NMR spectrum (Figure 2.7) of compound **76** reveals that there is a ketone present (208.2 ppm) as well as three carbon environments indicative of carbonyls or enol tautomers (166.6, 164.4 and 155.6 ppm). There are also an additional two signals at 103.1 and 99.7 ppm indicative of alkenes. The signal at 208.2 ppm was

therefore assigned as C8, whilst 166.6, 164.4 and 155.6 ppm were attributable to C2, C4 and C6. The two alkene signals were therefore assigned as C3 and C5.

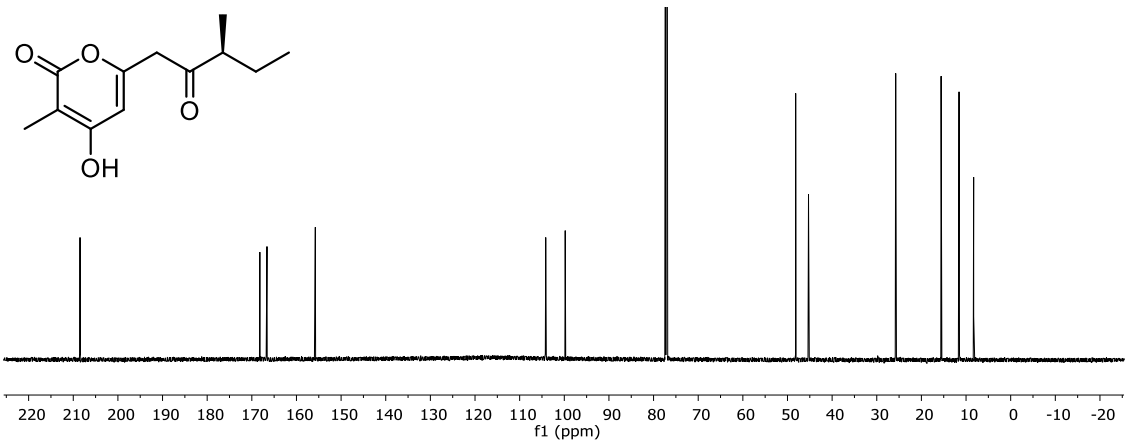


*Figure 2.7: ^{13}C NMR spectrum of compound **76***

Comparison of the ^{13}C NMR chemical shift values of compound **76** with that of natural phomapyrone B reveals that most of the chemical shift values are in good agreement (Table 2.3). However, there are a few minor discrepancies that were observed. C2 (Δ 2.21 ppm), C4 (Δ 1.61 ppm) and C5 (Δ 1.06 ppm) have differences that are all greater than 1 ppm and therefore can be considered significant. However, since each of these carbons is associated with the pyrone ring, and signals from enol carbons and their adjacent carbons fluctuate with changes in acidity, it may be expected that variations in the acidity of deuterated solvents used will lead to discrepancies in the chemical shifts reported. Considering that all other ^{13}C NMR signals are in good agreement with the literature values (Δ ≤ 0.3 ppm), this indicates that compound **76** has the same carbon skeleton as natural phomapyrone B (**76**).

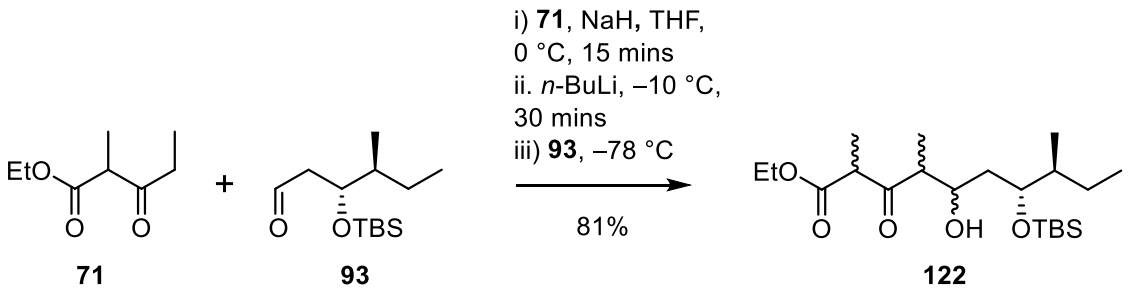
HRESIMS analysis of compound **76** reveals that the molecular ion observed (m/z 247.0944) corresponds to a molecular ion from $C_{12}H_{16}O_4Na^+$ (calcd. m/z 247.0946). Comparison of the measured specific rotation of $[\alpha]^{20}_D$ +18 (*c* 0.95 in $CHCl_3$) to the reported literature value for the initial isolation in 1994 by Pedras; $[\alpha]^{20}_D$ −18.6 (*c* 0.14 in $CHCl_3$) reveals that compound **76** is the (*S*)-enantiomer of phomapyrone B (**76**). These results conclusively assigned the carbon skeleton and stereochemistry of the natural product as (*R*)-phomapyrone B.

*Table 2.3: ^{13}C NMR comparison for compound **76** and phomapyrone B (**76**)*[12]

Carbon #	**phomapyrone B** 125.8 MHz - (δ ppm)	**Compound 76** 150 MHz - (δ ppm)	**Difference**
2	164.4	166.61	2.21
3	99.7	99.79	0.09
4	166.6	168.21	1.61
5	103.1	104.16	1.06
6	155.6	155.78	0.18
7	45.1	45.29	0.19
8	208.2	208.5	0.3
9	48.2	48.16	-0.04
10	25.6	25.75	0.15
11	11.5	11.56	0.06
12	15.5	15.58	0.08
13	8.1	8.29	0.19

*2.6 Total Synthesis of Paecilopyrone A (**78**)*

Using the same methodology that was previously used for compound **76**, the retrosynthetic analysis revealed that the methyl substituent at C5 of the pyrone ring could be installed through use of β-keto ester **71** as a nucleophile (Scheme 2.1). Addition of **71** to a vigorously stirred suspension of NaH in THF at 0 °C afforded deprotonation of the more acidic methine proton, with subsequent addition of *n*-butyl lithium at −10 °C affording the bisenolate (Scheme 2.17). The reaction mixture was cooled to −78 °C and the common aldehyde fragment **93** was added *via* cannulation. The δ-hydroxy β-keto ester **122** was isolated as a complex mixture of isomers along with residual β-keto ester **71**, which was removed under high vacuum before column chromatography.



*Scheme 2.17: synthesis of the δ-hydroxy β-keto ester **122***

Analysis of the ^{13}C NMR spectrum (Figure 2.8) revealed 105 observable peaks. Considering the chemical formula is $C_{21}H_{42}O_5Si$, with the three uncontrolled stereocenters there are eight potential isomers. A HRESIMS was obtained for the complex mixture of isomers, with the observed m/z of 425.2683 in agreement with the calculated value of 425.2699 m/z.

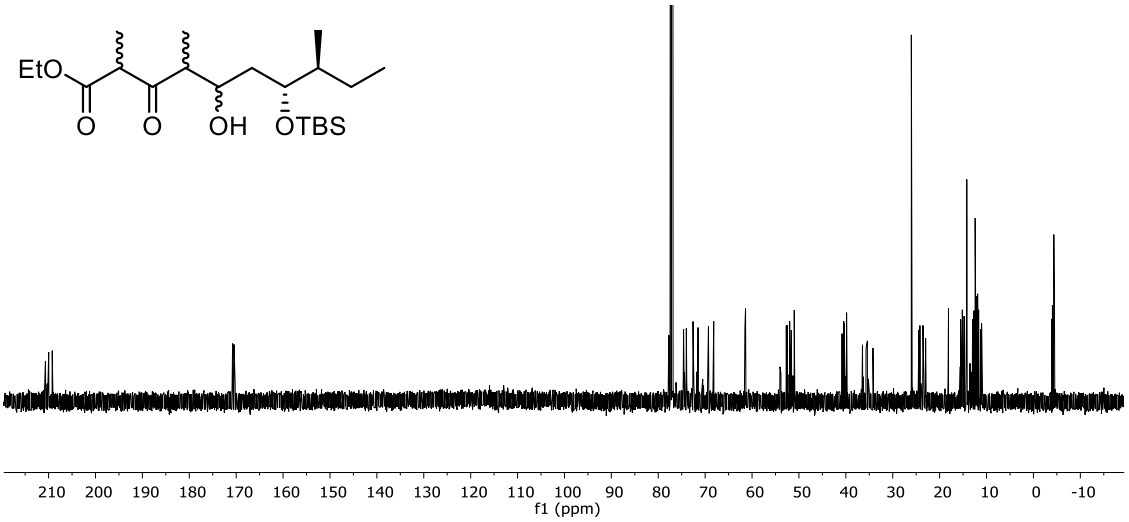
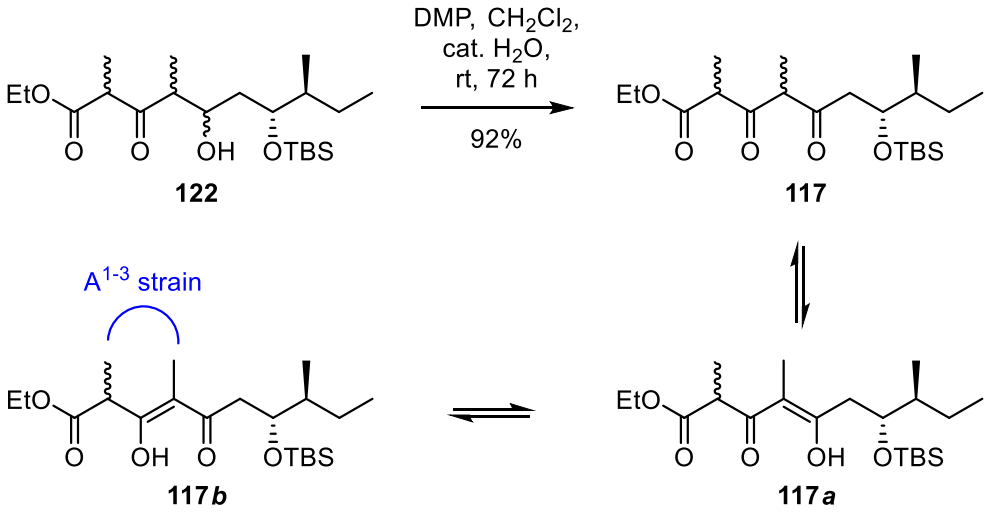


*Figure 2.8: ^{13}C NMR spectrum of δ-hydroxy β-keto ester **122***

*2.6.1 Dess-Martin periodinane oxidation of alcohol **122***

The inseparable mixture of isomers was subjected to oxidation with Dess-Martin Periodinane (Scheme 2.18). The inclusion of a methyl substituent at C4 resulted in a significantly slower oxidation rate compared to the C4 hydrogen analogue **118**. The β, δ-diketo ester **117** was obtained in high yield (92%) as a colourless oil. Based on analysis of the ^{1}H NMR spectrum, tricarbonyl **117** only existed partially as the enol tautomer as indicated by the sharp singlet observed at 1.91 ppm (1.29H). This peak was attributable to the vinylic methyl of either enol tautomer **117*a*** or **117*b***, with the integration indicating that in solution; ~40% existed as the enol tautomers. The lower

percentage of enol tautomer **117*b*** present in solution indicated that perhaps unfavourable A^{1-3} strain was responsible.



*Scheme 2.18: Oxidation of the δ-hydroxy β-keto ester **122** and tautomerism*

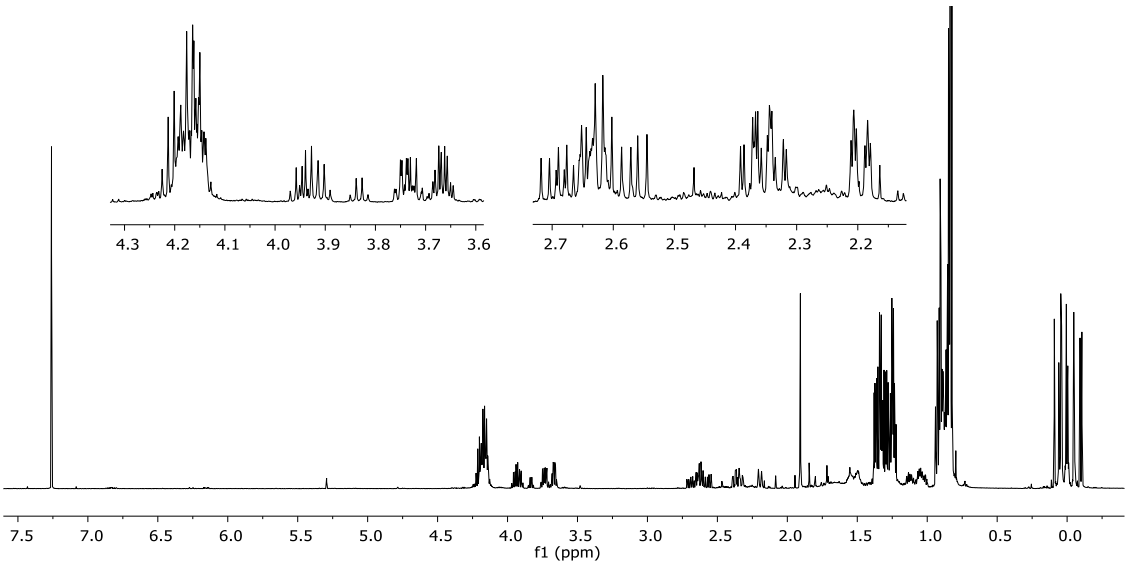
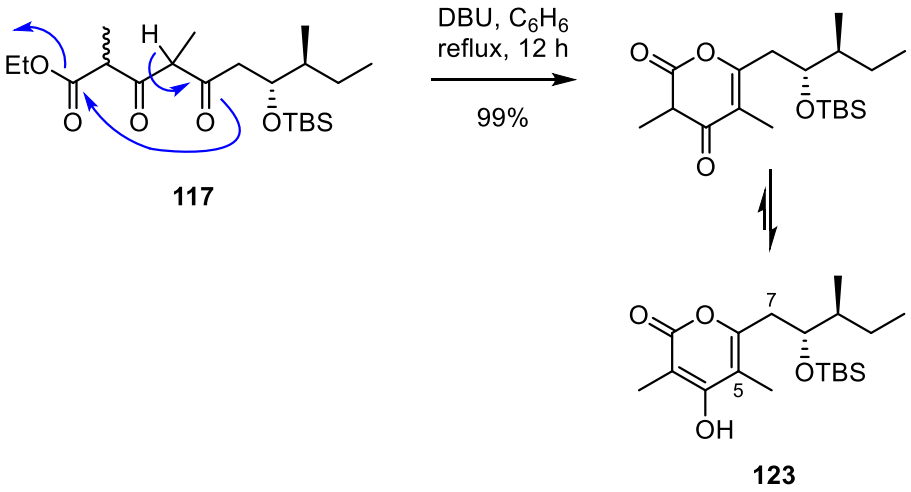


*Figure 2.9: ^{1}H NMR spectrum of β, δ-diketo ester **117***

*2.6.2 Cyclisation of diketo ester **117***

With the β, δ-diketo ester **117** in hand, the next step in the synthesis was the cyclisation of the linear precursor to produce the pyrone ring. Treatment of the ester **117** in benzene with DBU and heating at reflux overnight afforded the pyrone **123** in almost quantitative yield (99%) as white needles (Scheme 2.19). The melting point was observed at a range of 108-111 °C, whilst the specific rotation was recorded as +163.6 (0.94 in $CHCl_3$).

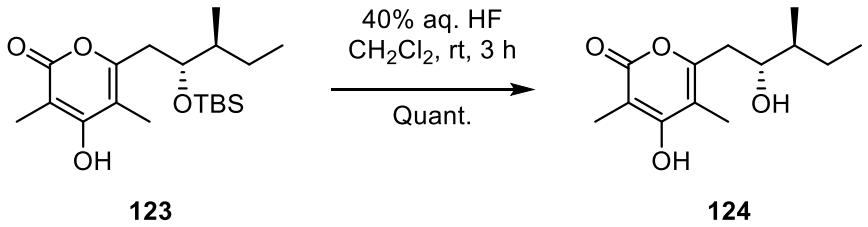


*Scheme 2.19: Synthesis of TBS pyrone **123***

This result supports earlier claims made by C. Gregg about the stability of the pyrone during cyclisation.[53] During the synthesis of ascosalipyrone (**66**), a significant degree of epimerisation at C7 occurred, whilst micropyrone (**65**) was synthesised without any epimerisation (Scheme 1.17). This was rationalised by consideration of the allylic strain that may be present in the pyrone for micropyrone (**65**) where C5 possessed a methyl substituent. In terms of explaining the decreased propensity for E1cB elimination of pyrone **123**, the methyl substituent at C5 may eclipse the C7 hydrogen anti-periplanar to the silyloxy substituent, thereby prohibiting its abstraction by base.

2.6.3 TBS deprotection and oxidation of C8

With construction of the pyrone ring accomplished in high yield, the remaining steps in the synthesis were attempted. Hydrofluoric acid was added to the TBS protected pyrone **123** (Scheme 2.20). Following purification, the deprotected pyrone **124** was obtained as an amorphous white solid, which upon NMR analysis (Figure 2.10), was deemed sufficiently pure.



*Scheme 2.20: Synthesis of β-hydroxy pyrone **124***

Analysis of the ^{1}H NMR spectrum (DMSO-*d6*) revealed hydroxyl protons at 5.67 ppm. The integration for these protons was ~8H, indicating that there was also water present, with the downfield shift presumably due to hydrogen bonding between pyrone **124** and H_2O. The resonance at 3.6 ppm (1H, ddd) was assigned to the oxymethine proton. The signal observed at 2.5 ppm integrated for 2H but the coupling constants could not be determined due to overlap with the residual DMSO peak.

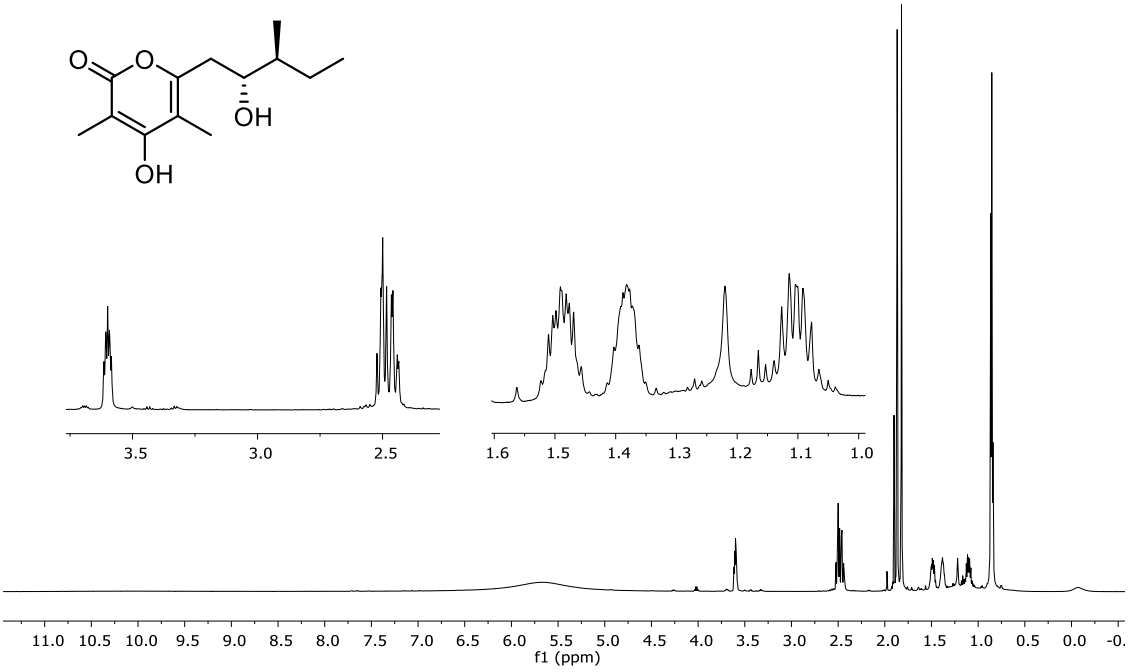
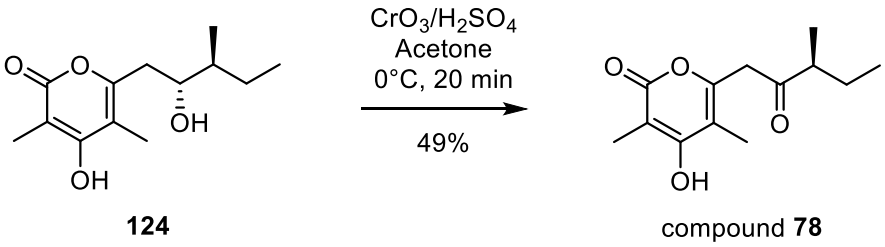


*Figure 2.10: ^{1}H NMR spectrum of pyrone **124** (DMSO)*

Titration of Jones reagent to the deprotected pyrone **124** afforded compound **78** in 49% yield (Scheme 2.21). Analysis of the ^{1}H NMR spectrum (Figure 2.11) revealed that the oxidation was successful, with the disappearance of the signal at 3.6 ppm corresponding to the oxymethine proton. The signal corresponding to the protons *alpha* to the pyrone ring were shifted from 2.5 ppm to 3.67 ppm.



124 compound **78**

*Scheme 2.21: Synthesis of compound **78***

Comparison of the ^{1}H NMR spectra reveals just how similar *ent*-phomapyrone B (**76**) and compound **78** really are (Figure 2.11). The only difference between the two structures is the methyl substituent at C5 for compound **78**. Consequently, the NMR spectra are almost identical, with the only differences appearing at 6.20 ppm for *ent*-phomapyrone B (**76**). This proton was assigned as the vinylic proton at C5. Conversely, compound **78** had two methyl singlets at 1.89 and 1.96 ppm respectively, whilst *ent*-phomapyrone B (**76**) possessed one vinylic methyl substituent at 1.93 ppm. The remarkable similarities between the two spectra are not too surprising considering that Jung *et al.* compared the spectra of paecilopyrone A (**76**) and micropyrone (**65**) to determine the position of methyl substitution.[63]

Analysis of the ^{13}C NMR spectrum of compound **78** revealed that there was a ketone present at 208.1 ppm. The signals at 165.4, 164.1 and 151.8 ppm were attributable to C2, C4 and C6. The two signals at 109.7 and 99.4 ppm were assigned as the two substituted alkenes.

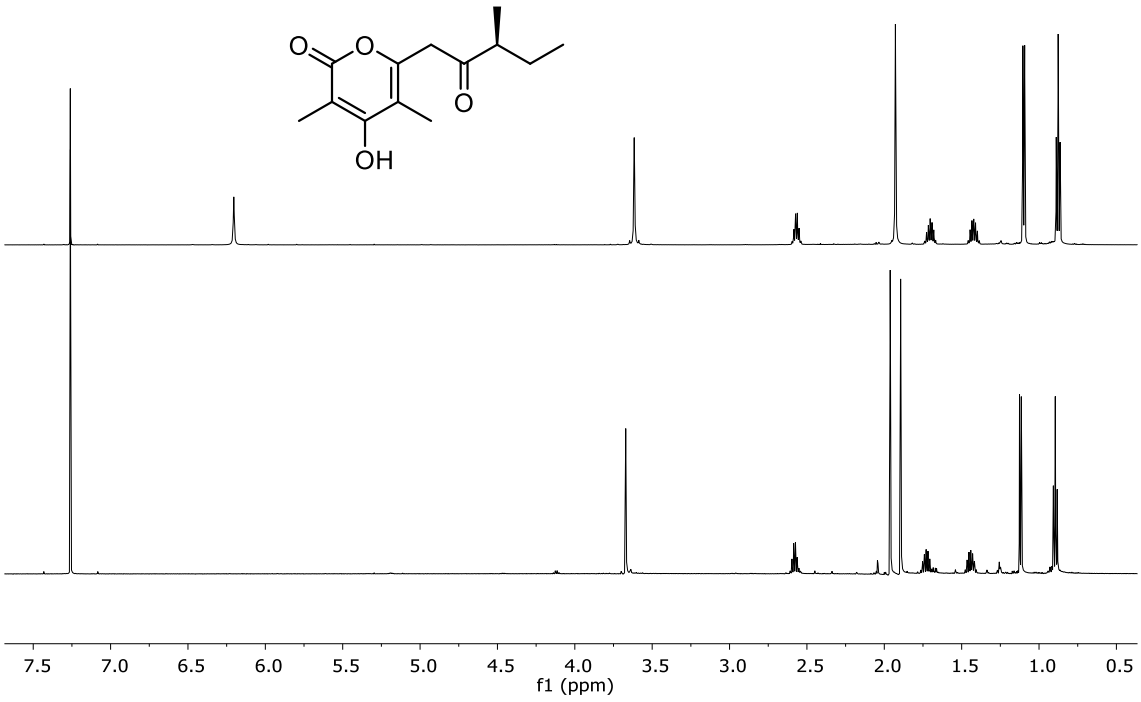


*Figure 2.11: Comparison of ent-phomapyrone B (**76**) (top) and compound **78** (bottom)*

The HRESIMS obtained for compound **78** indicated a molecular ion of 261.1108 m/z corresponding to $C_{13}H_{18}O_4Na^+$, which is in good agreement with the calculated value of 261.1103 m/z. The specific rotation of $[\alpha]^{20}_{D}$ +16° (*c* 0.25 in MeOH) was similar to that reported for the initial isolation of $[\alpha]^{26}_{D}$ +28° (*c* 0.12 in MeOH).[63] This indicates that

compound **78** has the same stereochemistry at C9 as paecilopyrone A (**78**). Considering C9 in compound **78** originated from the chiral starting material (*S*)-2-methylbutan-1-ol, the stereochemistry at this position is fixed. The similarity in optical rotation between compound **78** and natural paecilopyrone A (**78**) indicates that compound **78** is the correct enantiomer, and therefore elucidation of stereochemistry for the natural paecilopyrone A (**78**) as (9*S*)-paecilopyrone A (**78**).

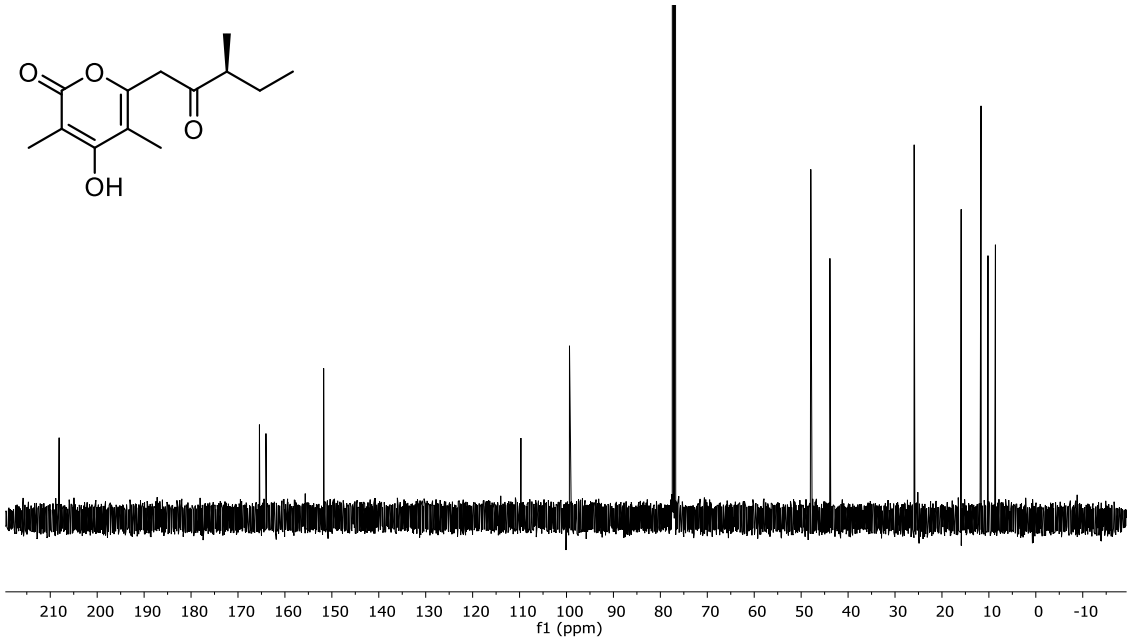


*Figure 2.12: ^{13}C NMR spectrum of paecilopyrone A (**78**) ($CDCl_3$)*

2.7 Conclusions

This chapter detailed the synthetic efforts towards phomapyrone B (**76**) and paecilopyrone A (**78**). Nucleophilic displacement of amides and thioamides was attempted utilising the dianion formed from β-keto esters. Synthesis of pyrones through alkylation of dioxinones was also attempted; however low yields and issues with reproducibility led to the abandonment of this methodology. Instead, dianion addition to the common aldehyde fragment **93** followed by oxidation and subsequent cyclisation afforded the prerequisite pyrone moieties.

The stereoselective synthesis of common aldehyde fragment **93** was achieved in 4 steps using acetate aldol methodology with the known chiral *N*-acetyl thiazolidinethione **108**. By using (*S*)-2-methyl butan-1-ol as a starting material, the stereochemistry at C9 was controlled, allowing for the synthesis of a single enantiomer of each natural product.

Ent-phomapyrone B (**76**) was obtained in 9 steps and 11% overall yield, whilst paecilopyrone A (**78**) was obtained in 22% yield over 9 steps. The structural similarities between micropyrone (**65**), ascosalipyrone (**66**), phomapyrone B (**76**) and paecilopyrone A (**78**) indicate that the marked increase in yield when C5 is a methyl substituent may be due to a similar steric interaction.

Chapter 3
Isolation, Biological Activity and Synthesis of Serrulatane Natural Products

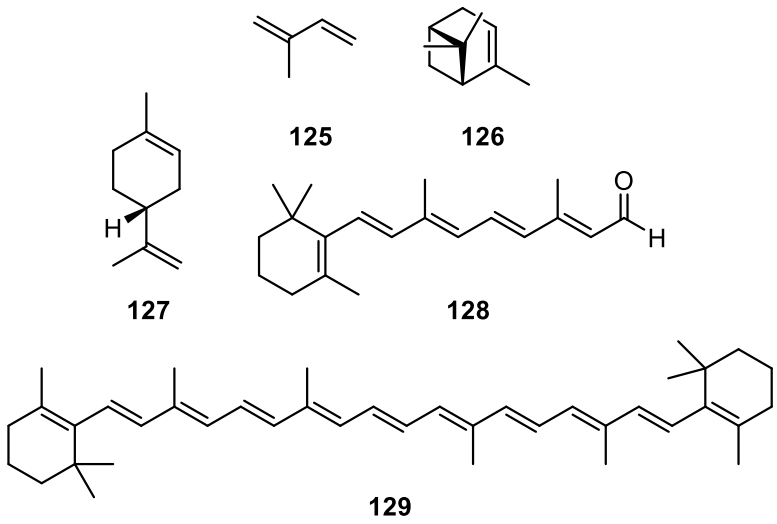
Chapter 3 Summary

Chapter 3 introduces the terpene natural products and discusses the many different classes, isolation, biosynthesis as well as biological activities. Literature examples detailing total synthesis of these natural products are given, with particular emphasis on the calamenene and serrulatane natural products. Development of synthetic methodology for preparation of the 8, 19-dihydroxy calamenene core and serrulatane prenyl tail by the Perkins research group is discussed, which underpins the work conducted in chapter 4.

3.1 Biosynthesis of Terpene Natural Products

The term terpene refers to a large group of primary and secondary metabolites that are biosynthesised predominantly by plants. All terpenes are derived from functionalised forms of isoprene (**125**), a five carbon building block, with the class of terpene defined by the number of condensed isoprene units.[79,80] For example, there are hemiterpenes (C5), monoterpenes (C10), sesquiterpenes (C15), diterpenes (C20), sesterterpenes (C25) and triterpenes (C30). Whilst the term terpene refers to the hydrocarbon, natural products that have undergone a skeletal rearrangement or other functionalisation including oxidation are commonly referred to as terpenoids or isoprenoids.

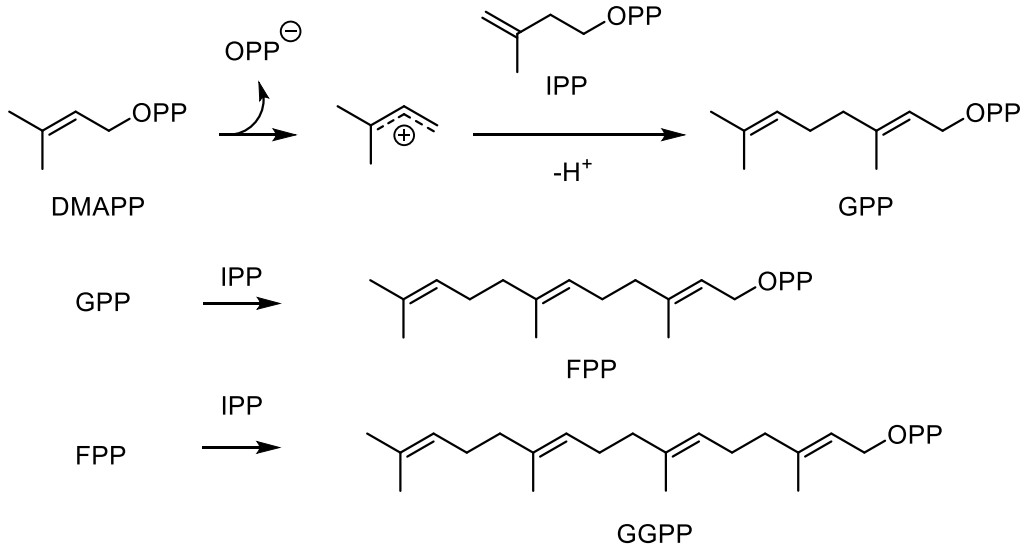
Two common monoterpenoids are α-pinene (**126**) and *D*-limonene (**127**) (Scheme 3.1). Pinene is one of the most common isolated from plants giving a distinctive pine odour, whilst limonene is found in the rinds of citrus fruits and is the principle constituent responsible for the lemon-orange aroma. The diterpenoid retinal (**128**) is critical for vision in animals, whilst the carotenoids are tetraterpenes and include β-carotene (**129**), which performs an essential role in photosynthesis within plants.[79]



Scheme 3.1: The C5 building block isoprene (125) and common terpenoids

The biosynthesis of terpene natural products arises through the condensation of dimethylallyl pyrophosphate (DPP) and isopentyl pyrophosphate (IPP), two C_5 subunits that produce the C_{10} terpene geranyl pyrophosphate (GPP) (Scheme 3.2).[79] Formation of a carbocation that then adds to an electron rich carbon of the double bond in IPP is catalysed by enzymes called prenyltransferases.[80] Condensation of GPP with another IPP molecule results in formation of the C_{15} terpene farnesyl pyrophosphate (FPP), with

repetition of this process resulting in formation of the C_{20} terpene, geranylgeranyl pyrophosphate (GGPP). Additionally, the tail-tail condensation of FPP results in the formation of squalene, a C_{30} triterpene critical to sterol synthesis.

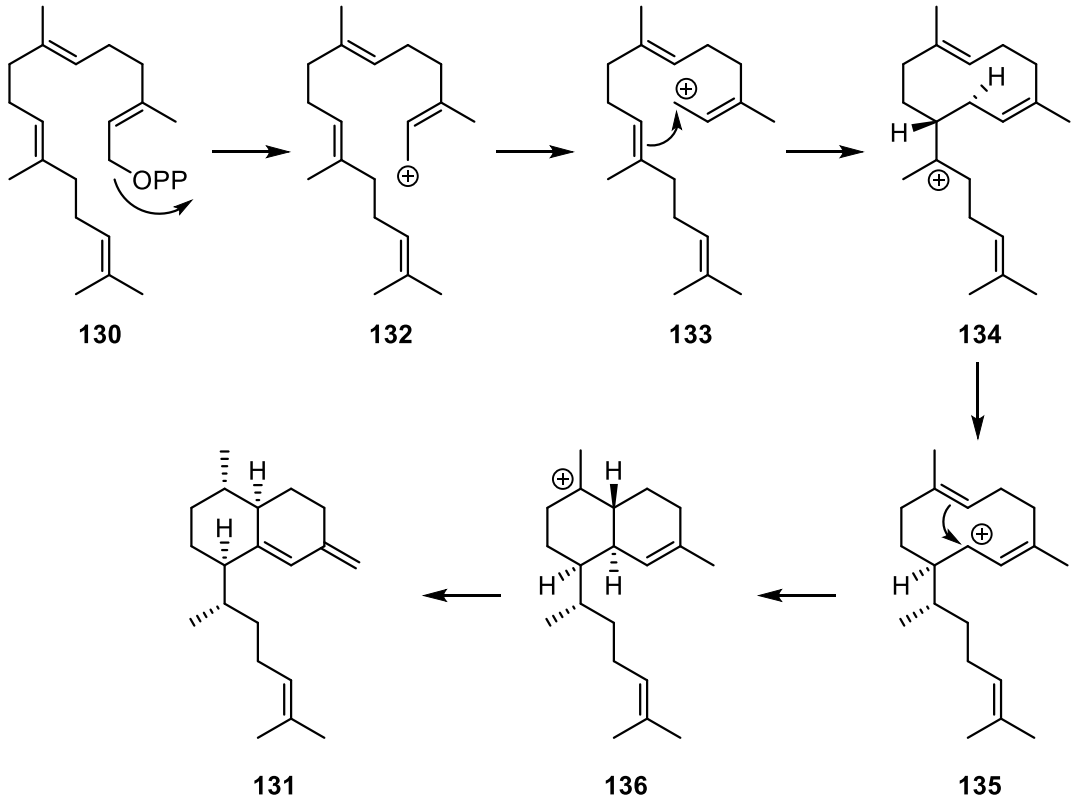


Scheme 3.2: Biosynthesis of C_5-C_{20} terpenes from condensation of DMAPP and IPP[79]

Aside from prenyl transferases that catalyse the polymerisation of a growing isoprene chain, terpene cyclases are also involved in the biosynthesis of terpene natural products. They are categorised based on the chain length of the terpene that they can accommodate, as well as the general structure of the terpene synthesised. For example, the C_{10} terpene GPP is cyclised by monoterpene cyclases, C_{15} terpenes are cyclised by sesquiterpene cyclases and GGPP fragments are cyclised by diterpene cyclases.

In terms of forming the carbocation, there are two possible mechanisms that have been observed biosynthetically. The first is similar to that observed with the prenyl transferases, whereby a carbocation is formed through ionisation due to loss of the pyrophosphate group. The second involves a proton-addition mechanism for formation of the cation.[80] Although both groups of enzymes facilitate addition of a cationic species to an electron-rich double bond, the prenyltransferase enzymes involve intermolecular additions whilst the cyclases promote intramolecular cyclisation of a cationic intermediate. Different cyclase enzymes are also capable of turning the same terpene into markedly different natural products that increase in diversity with increasing chain lengths.

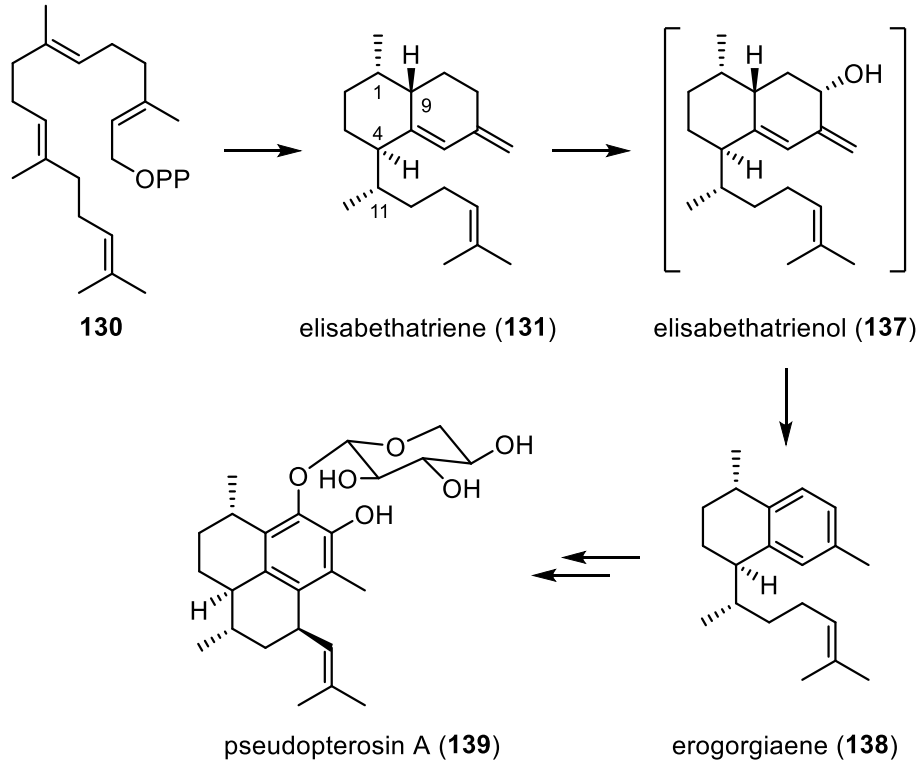
Radiolabelled feeding studies by Kerr *et al.*[81] have shown that when a cell-free preparation of *P. elisabethae* was incubated with radiolabelled geranylgeranyl pyrophosphate **130**, elisabethatriene (**131**) was observed as a secondary metabolite (Scheme 3.3). Mechanistically, loss of the pyrophosphate group would result in formation of carbocation **132**, which following isomerisation to the *Z* olefin **133**, could undergo a cyclisation to form the 10-membered ring **134**. Subsequent hydride shifts at C10 and C4 would afford the bicyclic allylic cation **135**, which following a second ring closure and abstraction of the proton at C19 of **136**, would lead to elisabethatriene (**131**).[81,82]



*Scheme 3.3 Proposed biosynthesis of elisabethatriene (**131**) from GGPP*[83]

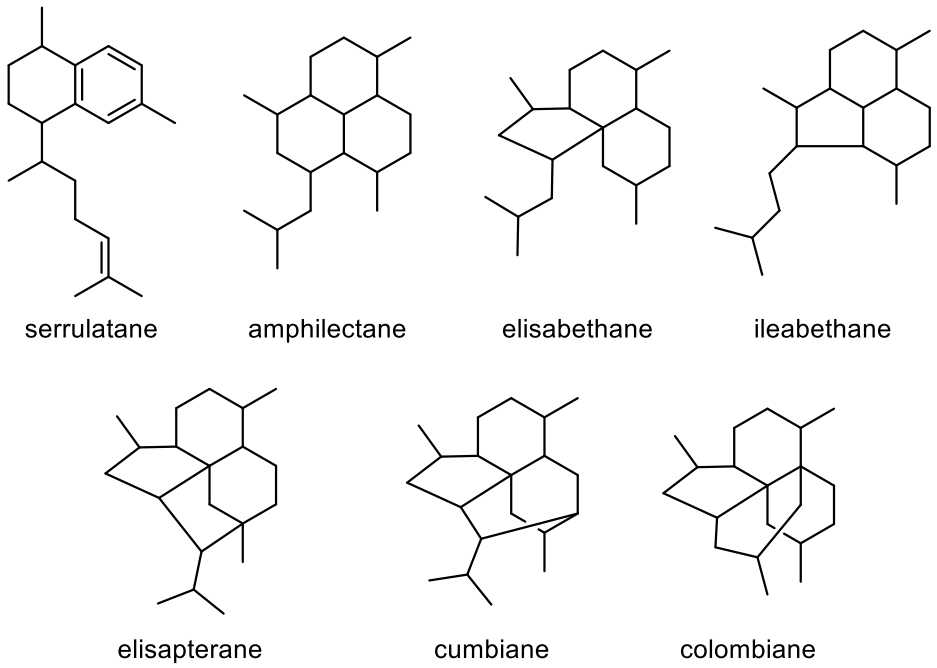
Because of their recent isolation of elisabethatrienol (**137**), an intermediate in pseudopterosin biosynthesis, Fujimoto *et al.* proposed that the stereochemistry of elisabethatriene (**131**) needed to be revised (Scheme 3.4).[83] Elisabethatrienol (**137**) was found to possess the 1*S*, 4*R*, 9*S*, 11*S* configuration based on detailed nuclear Overhauser effect (NOE) experiments.[84] Considering elisabethatrienol (**137**) was biosynthetically linked to elisabethatriene (**131**) and the same stereochemical mechanism was presumably operating for both, Fujimoto rationalised that the previously reported

1*S*, 4*R*, 9*R*, 11*S* configuration for elisabethatriene (**131**) should be amended to the 1*S*, 4*R*, 9*S*, 11*S* configuration. They supported this through the synthesis of 1*S*, 4*R*, 9*R*, 11*S* elisabethatriene and compared the NMR spectra for the synthesised material to that of the natural product. They found that the NMR spectra did not match; reinforcing their claim for the reassignment of stereochemistry.



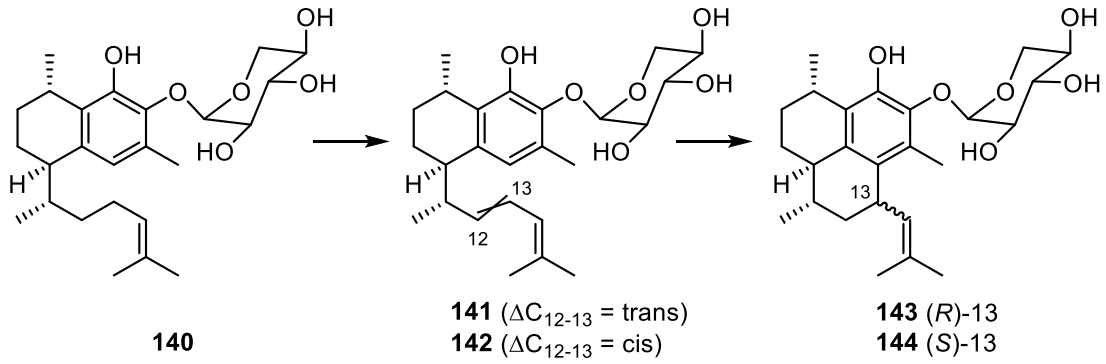
Scheme 3.4: Proposed biosynthesis of the pseudopterosins

Kerr *et al.*[81] were also able to show that elisabethatriene (**131**) is converted to erogorgiaene (**138**) and pseudopterosin A (**139**) (Scheme 3.4). Furthermore, the serrulatane skeleton has been implicated as a putative precursor to a diverse range of structurally related diterpene natural products (Scheme 3.5).[82] In particular, secondary metabolites from *Pseudopterogorgia elisabethae* have been isolated containing the amphilectane skeleton, being derived from the serrulatane skeleton through disconnection between C5 and C13. The elisabethane natural products differ in that they possess a C10-C13 carbon bond producing a five membered C ring. The ileabethanes are again subtly different in that they possess a C5-C12 bond producing a five membered C ring.[85] The elisapterane, cumbiane and colombiane skeletons all appear to be derived from different cyclisation modes of the elisabethane skeleton.



Scheme 3.5: Common carbon frameworks from Pseudopterogorgia elisabethae[82]

The biosynthesis of compounds belonging to these representative classes is more complicated than it might first appear. In further studies conducted by Kerr,[86] the serrulatane seco-pseudopterosin (**140**) was co-isolated with the pseudopterosins (Scheme 3.6). This led Kerr *et al.* to propose that they must be functionalised in a manner that would allow for formation of a carbon-carbon bond between the aromatic ring and C13. Further analysis of the mid-polarity extracts from *P. elisabethae* identified two new compounds named amphilectosins A (**141**) and B (**142**). They were identified as derivatives of the seco-pseudopterosins, containing a double bond between C12-C13. They differed in the geometry of the double bond, with amphilectosin A (**141**) possessing *trans* double bond geometry, whilst amphilectosin B (**142**) possessed the *cis* double bond geometry. Incubation studies by Kerr revealed that amphilectosin A (**141**) gave rise to pseudopterosin Y (**143**), whilst amphilectosin B (**142**) gave rise exclusively to pseudopterosin F (**144**).[81] It was therefore determined that the double bond geometry was responsible for the stereochemistry at C13 of the psuodopterosins, with amphilectosins identified as intermediates in pseudopterosin biosynthesis.



Scheme 3.6: Incubation studies by Kerr with Pseudopterogorgia elisabethae[86]

3.2 Isolation and Biological Activities of Serrulatane Diterpenes

The genus *Eremophila* consists typically of plant species that are woody shrubs and trees, with most producing attractive flowers or foliage. They were initially classified as part of the small family Myoporaceae, which consisted of *Eremophila*, *Myoporum* and *Bontia*.[87] The species of this family are largely found in Australia, although some species of *Myoporum* have been found in China, Japan and islands of the Indian and Pacific Oceans. *Bontia* however, is a monotypic genus that is found only in the West Indies.[88] More recently, *Eremophila* has been reclassified as belonging to the family *Scrophulariaceae.*[89,90]

Due to the semi-arid to arid climates in which they are found, *Eremophila* species often produce waxy resins comprising up to 20% of the dry weight of the plant on their leaves. Extraction of the leaf material with an organic solvent has led to the isolation of a variety of secondary metabolites, with lipids, flavones and terpenes the most common constituents.[87,89] Amongst the most prolific terpenes isolated from *Eremophila* species are the serrulatanes, which are C_{20} diterpenes biosynthesised from geranylgeranyl pyrophosphate. The location of these secondary metabolites in leaf cuticles indicates that they may serve a biological role in protection of the plant from grazing herbivores, as antimicrobial agents or possess insecticidal properties for defence of the plant.

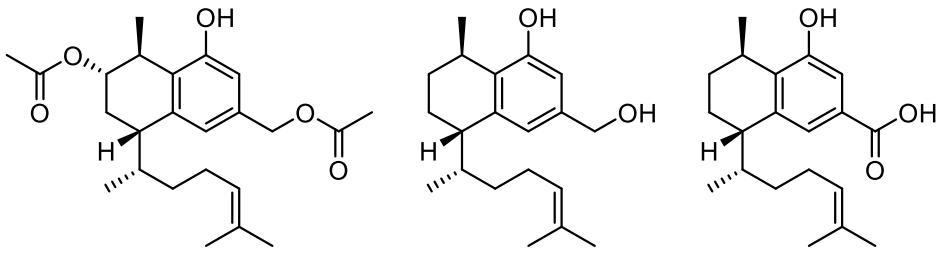
Whilst there are at least 260 reported species within the *Eremophila* genus, relatively few have been explored for pharmaceutically relevant metabolites. This is in part because of the difficulty in acquiring large quantities of plant material and the remote locations in which many of the species grow. Rather than investigate all 260 species for bioactive constituents, isolation chemists can take an ethnopharmacological approach, where they consider the species reportedly used in traditional medicines by Aboriginal

Australians. Extracts from *E. sturtii* have been used by indigenous Australians in the Northern Territory to wash sores and cuts, whilst also being used in New South Wales for the treatment of skin infections.[91] *E. duttonii* has been reportedly used for the topical treatment of minor wounds as well as a gargle for sore throats.[92] There have been a number of other reported uses for *Eremophila* species such as the treatment of aches and pains as well as general well-being. All of the above ailments suggest that some *Eremophila* species may possess chemical constituents with either antimicrobial or anti-inflammatory activity.

Using this methodology, Ndi *et al.* investigated the activity of 72 *Eremophila* species against streptococci and staphylococci.[93] They found that a number of these species possess antibacterial activity against gram positive bacteria, but have no clinically significant activity against gram-negative bacteria. In general, they were also found to have higher activity against Streptococcus species (16 to 62 µg/mL) than *Staphylococcus aureus* (62 to 250 µg/mL). Based on the MIC values for the isolates, the 15 most active extracts were tested for activity against 68 clinical isolates of mMRSA, with *E. drummondii*, *E. linearis*, *E. serrulata*, *E. acrida*, *E. neglecta* and *E. virens* all inhibiting growth of the majority of clinical isolates below 62.5 µg/mL.[93]

Following on from their initial studies, Ndi *et al.* isolated three serrulatane diterpenes (**145**-**147**) as well as the previously isolated biflorin from the endemic Australian plant *Eremophila neglecta* in 2007 (Scheme 3.7).[94] Following bioassay-directed fractionation of the ether extract using a broth microdilution assay, the three new serrulatane diterpenes were characterised using 1D and 2D NMR spectroscopy, FTIR and high resolution mass spectrometry. The diacetate **145** had no reported biological activity, whilst 8,19-dihydroxyserrulat-14-ene (**146**) and 8-hydroxyserrulat-14-en-19-oic acid (**147**) showed high antimicrobial activity against a range of gram-positive bacteria.

Because the two natural products that we are interested in were never given a trivial name, for the purposes of referral during the remainder of this thesis, abbreviations used previously by Lu and Griesser *et al.* will be used.[95,96] 8,19-dihydroxyserrulat-14-ene (**146**) will be referred to as EN3 (**146**), whilst 8-hydroxyserrulat-14-en-19-oic acid (**147**) will be referred to as EN4 (**147**) as they were the third and fourth metabolites isolated from *Eremophila neglecta* respectively.[94]



145 EN3 (**146**) EN4 (**147**)

Scheme 3.7: serrulatane natural products from Eremophila neglecta[94]

With the biological activity of EN3 and EN4 in mind, Semple *et al*. were interested in the potential application of EN3 and EN4 as antimicrobial agents. Particular interest was given to EN4 due to the carboxylic acid functionality at C19 which could be easily appended to surfaces through functionalisation. In a recent publication, they investigated the bacterial biofilm dispersion and anti-inflammatory activity of EN4 against *S. epidermidis* and *S. aureus* biofilms.[97] The efficacy of EN4 (**147**) was compared to the known antiseptic chlorhexidine and the antibiotic levofloxacin.

In order to investigate the biofilm breakup activity, biofilms were established for 3, 6, 12 and 24 hours (Figure 3.1). The biofilms were then incubated with the corresponding antimicrobial for 20 hours at 37 °C, after which time the growth was stopped and the biofilms stained with safranin. The results indicate that after 12 hours, EN4 shows superior biofilm-removing activity compared to levofloxacin, but worse activity following 24 hours of biofilm formation. The authors suggest that the diminished activity observed at 24 hours may be attributable to the complex matrix developed during maturation of the biofilm,[98] with EN4 unable to penetrate the biofilm as efficiently as chlorhexidine or levofloxacin.

Semple *et al.* also raise an interesting point with respect to the MIC values reported for the respective agents. They note that the MIC value for Levofloxacin (0.66 μM) against planktonic populations of *S. epidermidis* is significantly lower than that of EN4 (**147**) (82 μM). Considering these values, it would be reasonable to expect that Levofloxacin would have superior activity, but EN4 was shown to have increased activity up to 12 hours of biofilm pre-establishment. These results suggest that MIC values against planktonic populations do not always translate to the same activity against a biofilm from the same organism.[97]

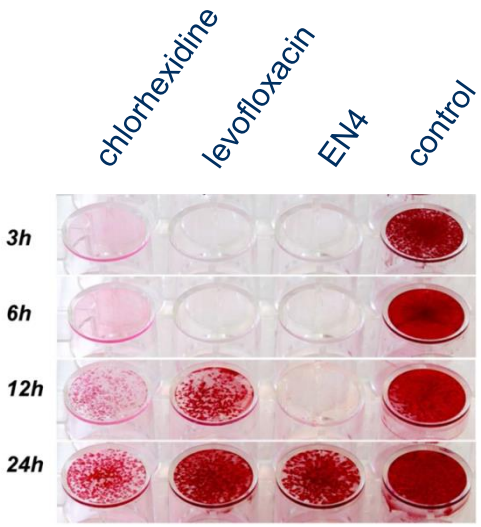
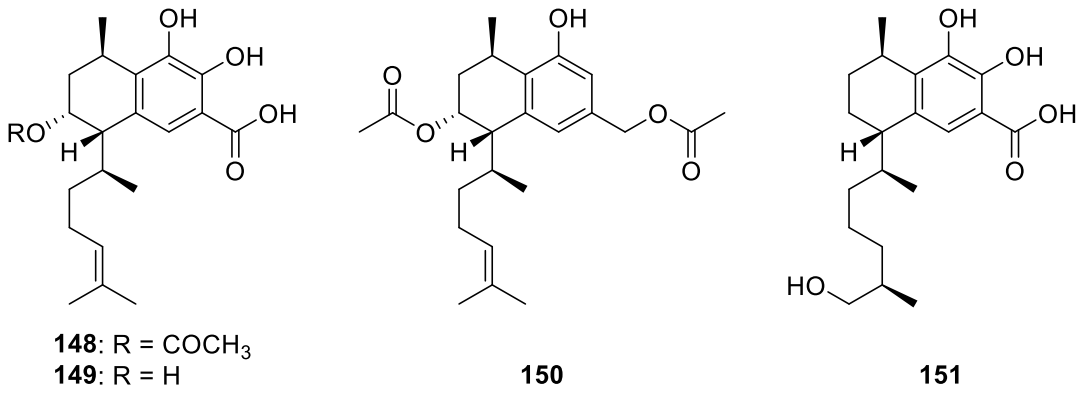


Figure 3.1: Safranin-stained-developed S. epidermidis (ATCC 35984) biofilms with antimicrobial treatments vs. control by Semple et al.[97]

Three structurally related serrulatane natural products (**148-150**), along with the previously isolated verbascoside and jaceosidin were isolated from the aerial parts of the Australian plant *Eremophila microtheca* in 2013 (Scheme 3.8).[99] They each possess the core serrulatane scaffold, with differing substitution patterns. The same prenyl hydrocarbon side chain with conserved *S, S* stereochemistry at C4 and C11 is present, whilst there are also varying oxidation patterns on the aromatic ring. The stereochemistry at C4 and C11 was determined to be the same as **151**, which was previously reported by Croft *et al.* from *E. drummondii* in 1981.[100]

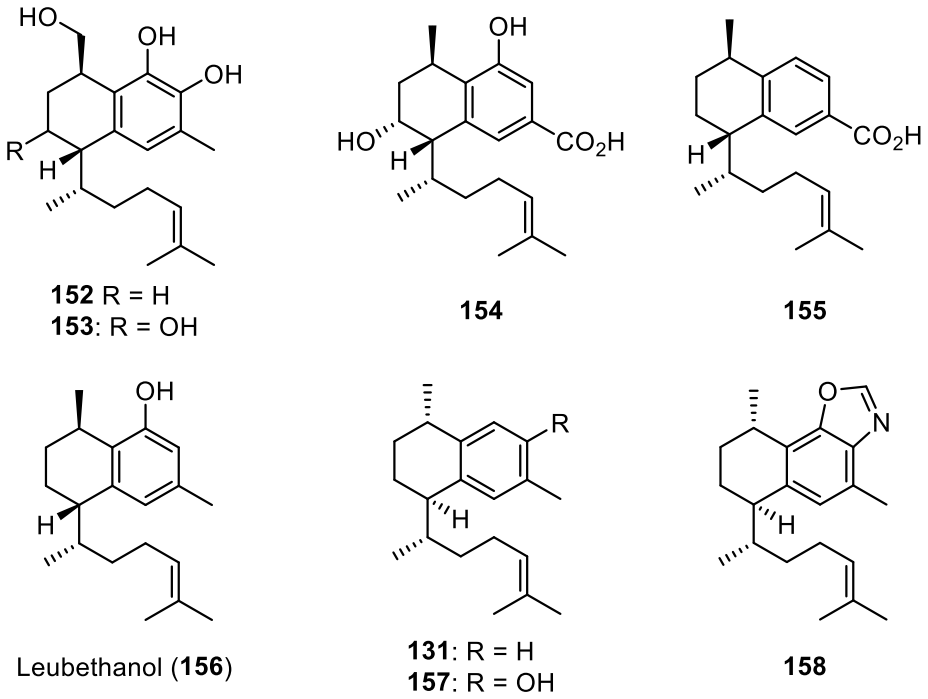


Scheme 3.8: Serrulatane natural products isolated from E. microtheca and E. drummondii

In addition to the serrulatanes isolated from *E. drummondii* and *E. neglecta*, serrulatane diterpenes have also been isolated from *E. sturtii* and *E. duttonii*. Extracts from each of these species have antibacterial activity against Gram-positive bacteria. This led Smith *et al.* to examine the extracts from *E. duttonii*, leading to the isolation of two serrulatane

diterpenes (**152-153**), which had been previously reported in 1993 by Massy-Westropp and co-workers (Scheme 3.9).[92,101] Furthermore, Jamie *et al.* isolated 3,8-dihydroxyserrulatic acid (**154**) and serrulatic acid (**155**) following bioassay-guided fractionation of the leaf extracts from *E. sturtii.*[91]

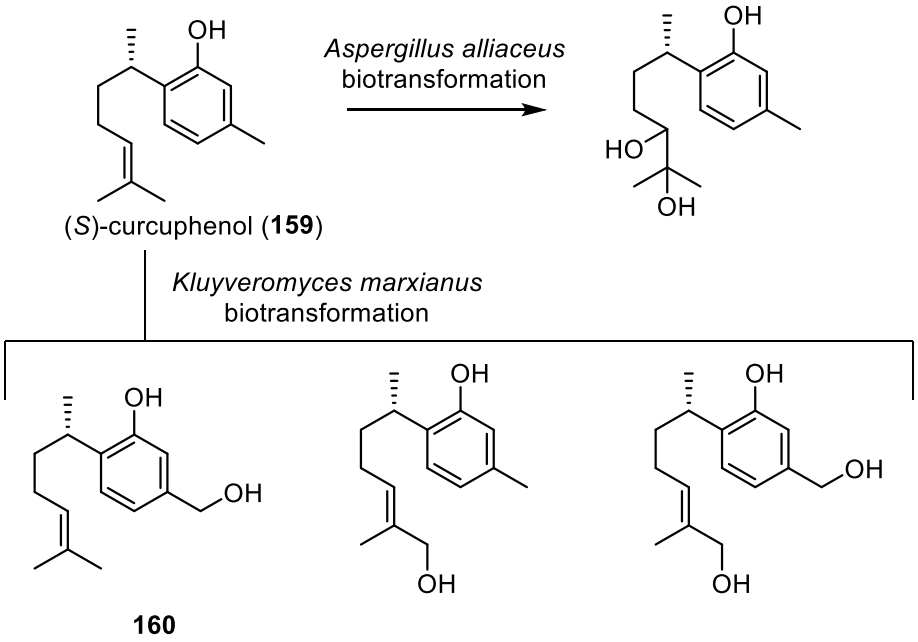
Natural products possessing the serrulatane scaffold are not restricted to the *Eremophila* genus. In 2011, Leubethanol (**156**) was isolated from the root bark extract of *Leucophyllum frutescens* by Waksman and co-workers.[102] Leubethanol (**156**) possessed activity against multi-drug resistant strains of virulent *Mycobacterium tuberculosis*. Erogorgiaene (**131**), 7-hydroxyerogorgiaene (**157**) and seco-pseudopteroxazole (**158**) were isolated from the West Indian gorgonian octocoral *Pseudopterogorgia elisabethae.*[103] Interestingly, 7-hydroxyerogorgiaene (**157**) may be derived biosynthetically from elisabethatrienol (**137**), the proposed intermediate in pseudopterosin and erogorgiaene (**131**) biosynthesis (Scheme 3.4). All three compounds were assessed for their inhibition of *Mycobacterium tuberculosis*, with erogorgiaene (**131**) and 7-hydroxyerogorgiaene (**157**) showing the highest activity (12.5 μg/mL and 6.25 μg/mL respectively). The activities, not surprisingly, were comparable to the structurally similar leubethanol (**156**).



Scheme 3.9: Serrulatane natural products isolated from marine and terrestrial organisms

3.3 Structure-Activity-Relationship (SAR) Studies

A number of studies have probed the pharmacophore of sesquiterpene and diterpene natural products. One particular example involves (*S*)-curcuphenol (**159**). In order to examine the SAR, Hamann *et al.* incubated (*S*)-curcuphenol (**159**) with *Kluyveromyces marxianus* var. *lactis* (ATCC 2628) and *Aspergillus alliaceus* (NRRL 315) which resulted in a number of oxygenated metabolites (Scheme 3.10).[104] The metabolites were screened for antimicrobial properties as well as antimalarial activity, with (*S*)-curcuphenol (**159**) and the benzylic oxidised derivative **160** identified as the most active constituents. The results indicated that oxidation at the benzylic position was tolerated, but oxidation of the side chain led to diminished activity.



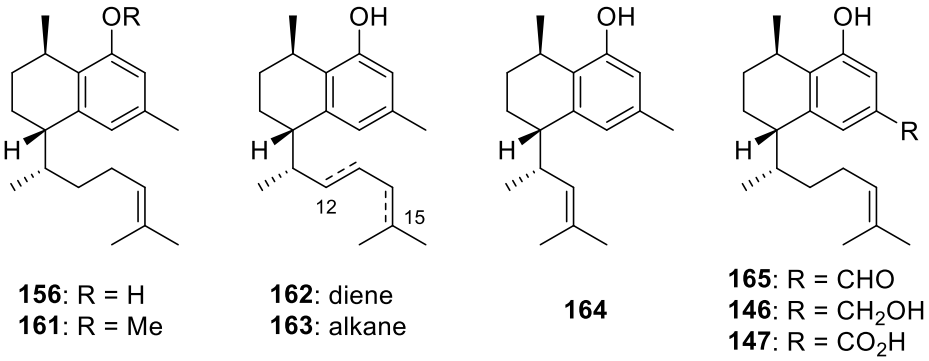
*Scheme 3.10: Hamann's biotransformations of (S)-curcuphenol (**159**)*[104]

In order to investigate the pharmacophore of the serrulatane skeleton, Lu synthesised leubethanol[105] as well as a series of analogues (Table 3.1). Having the phenol free as the hydroxyl was essential for biological activity, with protection as the methyl ether **161** resulting in a significant decrease (>230 μg/mL) compared to leubethanol (12 μg/mL). Incorporating an additional degree of unsaturation into the side chain resulted in a reduction in activity (**162**, >100 μg/mL), whilst full saturation of the side chain also resulted in less activity (**163**, 44.5 μg/mL). Interestingly, the short chain analogue **164**

had comparable activity to leubethanol (**156**), indicating that a chain length between 4-6 carbons long with one degree of unsaturation was preferable.

The synthetic analogue of EN3, termed EN3-CHO **165**, was synthesised by Lu through semi-synthesis from EN3.[96] For the limited number of clinical isolates tested, EN3-CHO **165** exhibited comparable biological activities to that of leubethanol (**156**). The activities of EN3 and EN4 were also determined by Ndi *et al*. against the same strains, with EN3 and EN4 having similar activities despite the additional functionality at C19.[94] These results indicate that substitution at the benzylic C19 position is well tolerated.

Table 3.1: Structures and biological activities of serrulatane diterpenes and synthetic analogues[94,96]



156: R = H
161: R = Me

162: diene
163: alkane

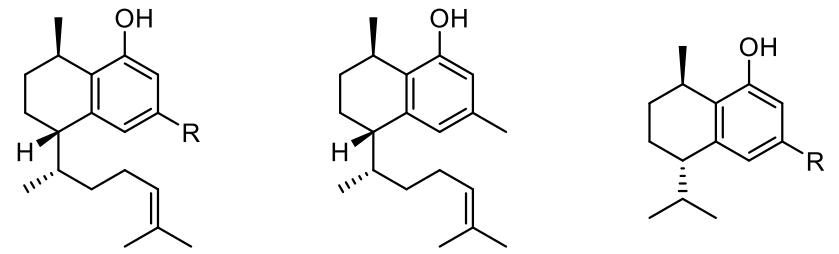
164

165: R = CHO
146: R = CH_2OH
147: R = CO_2H

	Minimum Inhibitory Concentration (μg/mL)							
Compound Number	**156**	**161**	**162**	**163**	**164**	**165**	**146**	**147**
S. aureus (ATCC 29213)	12	>230	>100	44.5	6	12.5	25.8	49.3
S. aureus (ATCC 25923)	6	>230	>100	44.5	6	12.5	25.8	49.3
S. aureus (ATCC 43300)	12	>230	NA	NA	NA	NA	NT	NT
S. epidermidis (ATCC 35984)	12	>230	>100	44.5	6	12.5	NT	NT
P. Aeruginosa (ATCC 27853)	NA	NA	>100	>100	>50	NA	NT	NT
E. Coli (ATCC 25922)	NA	NA	>100	>100	>50	NA	NT	NT
S. pneumoniae (ATCC 49619)	NT	NT	NT	NT	NT	NT	12.9	24.7
S. pyogenes (ATCC 10389)	NT	NT	NT	NT	NT	NT	12.9	24.7

In addition to the preliminary studies by Lu, Escarcena *et al.* have also investigated the antimycobacterial activity of leubethanol derivatives.[106,107] They found that hydrogenation of the side chain resulted in a loss of activity and cytotoxicity, whilst introduction of nitrogen or oxygen functionality to C14 and C15 also resulted in decreased activity. Alkylation of the phenol functionality resulted in complete loss of activity, even when glycosylated. Escarcena also investigated the effect of C7 substitution, with functionalisation at this position rationalised by the activity shown from the pseudopterosins that possess oxazole functionality at C7-C8. They observed that both the C7-NO_2 and C7-Br derivatives exhibited decreased activity.

Whilst EN3 (**146**) and EN4 (**147**) were novel compounds, each possessed the same serrulatane skeleton with varying oxidation states at C19. They were remarkably similar to the previously isolated leubethanol (**156**), leading Lu to hypothesise that leubethanol may be a synthetic precursor for the two benzylic-oxidised metabolites. Another structurally related class of natural products are the calamenenes. They are C_{15} sesquiterpenes, meaning they are biosynthesised through cationic cyclisation of farnesyl pyrophosphate as opposed to geranylgeranyl pyrophosphate. The structural similarities between the calamenenes (**166-167**) and the serrulatanes could make a good model system for synthesis of the tetrahydronaphthalene ring (Scheme 3.11). Developing synthetic methodology that would allow access to sufficient quantities of these natural products, as well as synthetic analogues, would therefore be beneficial.



146: R = CH_2OH
147: R = CO_2H

Leubethanol (**156**)

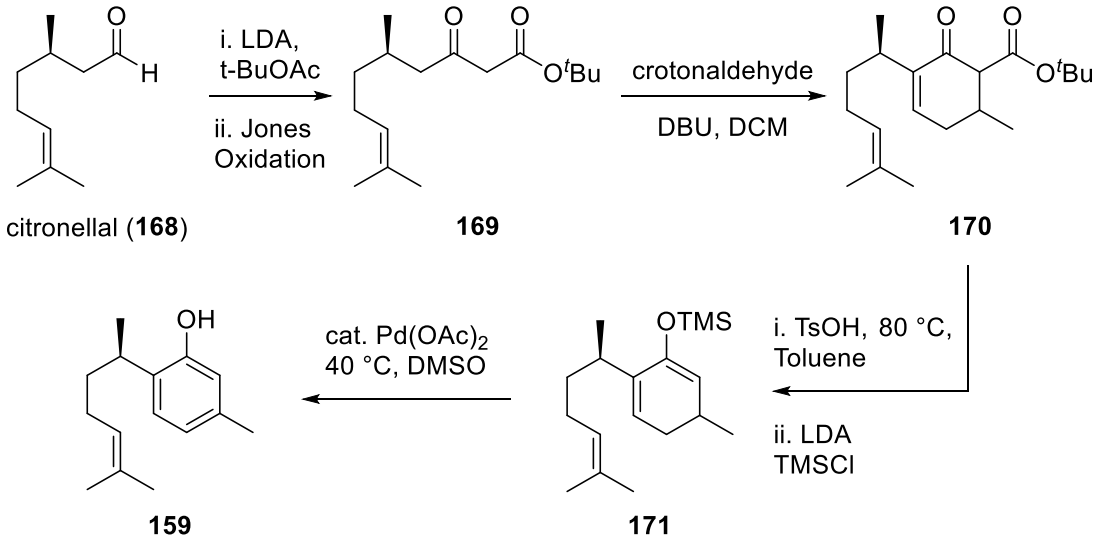
166: R = CH_2OH
167: R = CO_2H

Scheme 3.11: Structurally related serrulatane and calamenene natural products

3.4 Literature Syntheses of Terpene Natural Products

Curcuphenol (**159**) has been the subject of a number of total syntheses to date.[108–117] Due to its broad activity, it has proved a sought after natural product. Therefore,

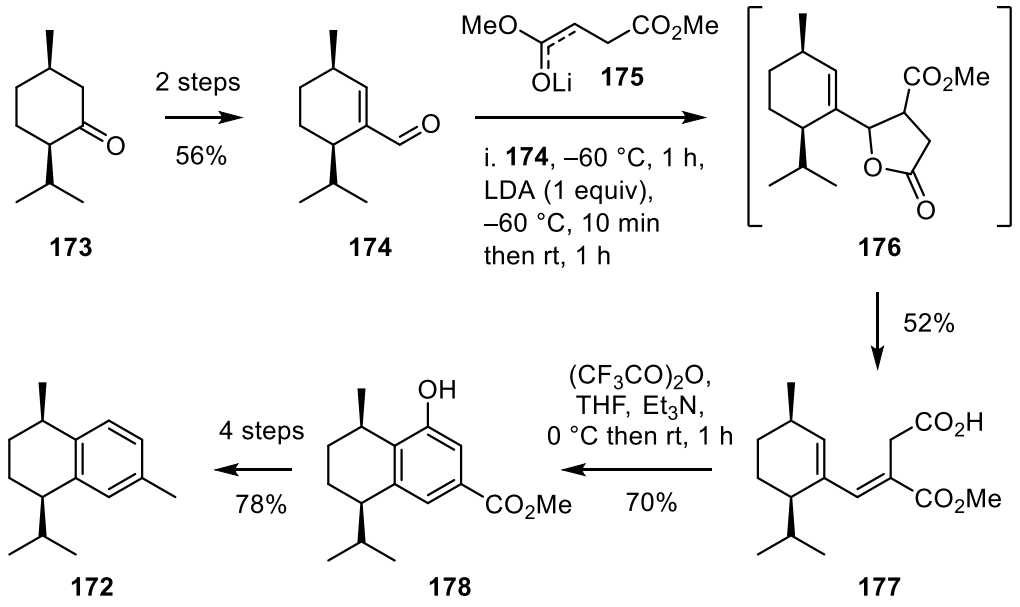
achieving total synthesis in a concise and scalable manner has been the subject of various articles. One particular example was reported in 2013 by Zhou and coworkers (Scheme 3.12).[108] Starting from citronellal (**168**), they formed the β-keto ester **169** through alkylation of the lithium enolate of tert-butyl acetate followed by Jones oxidation. They then performed a Michael-Aldol cascade to install the cyclehexenone functionality of *t*-butyl ester **170**. Subsequent removal of the tert-butyl group led to the corresponding unstable β-keto acid, which readily underwent decarboxylation. Formation of the OTMS diene **171** and subsequent aromatisation with palladium acetate afforded (*R*)-curcuphenol (***R*-159**) in 46% yield over 6 steps and two chromatographic purifications.



*Scheme 3.12: Feng's synthesis of (R)-Curcuphenol (**159**)*[108]

Aside from the bisabolane sesquiterpene curcuphenol, synthetic interest has also been shown towards the calamenenes. Serra and Fuganti synthesised calamenene (**172**) starting from the commercially available (−)-menthone (**173**) (Scheme 3.13).[118] The ketone **173** was converted into the tosylhydrazone, then treated with *n*-butyl lithium and *N*,*N*-dimethylformamide added to afford the corresponding enal **174** in 56% yield over two steps.[119] Addition of the enolate **175** afforded the intermediate **176**, which rearranged to the 3-(*E*)-dienoic acid **177** following addition of LDA at −60 °C. Dienoic acid **177** was obtained alongside an inseparable mixture of the 3-*Z* isomer and 2,5-hexadienic acids. The crude mixture of isomers was treated with TFAA at 0 °C and excess Et_3N, [120] affording phenol **178** in 70% yield as a single isomer since the (*Z*)-isomer could not undergo the annulation reaction. Serra and Fuganti were then able to

synthesise the calamenene (**172**) in 4 steps and 78% yield through removal of the oxygen-containing functional groups.

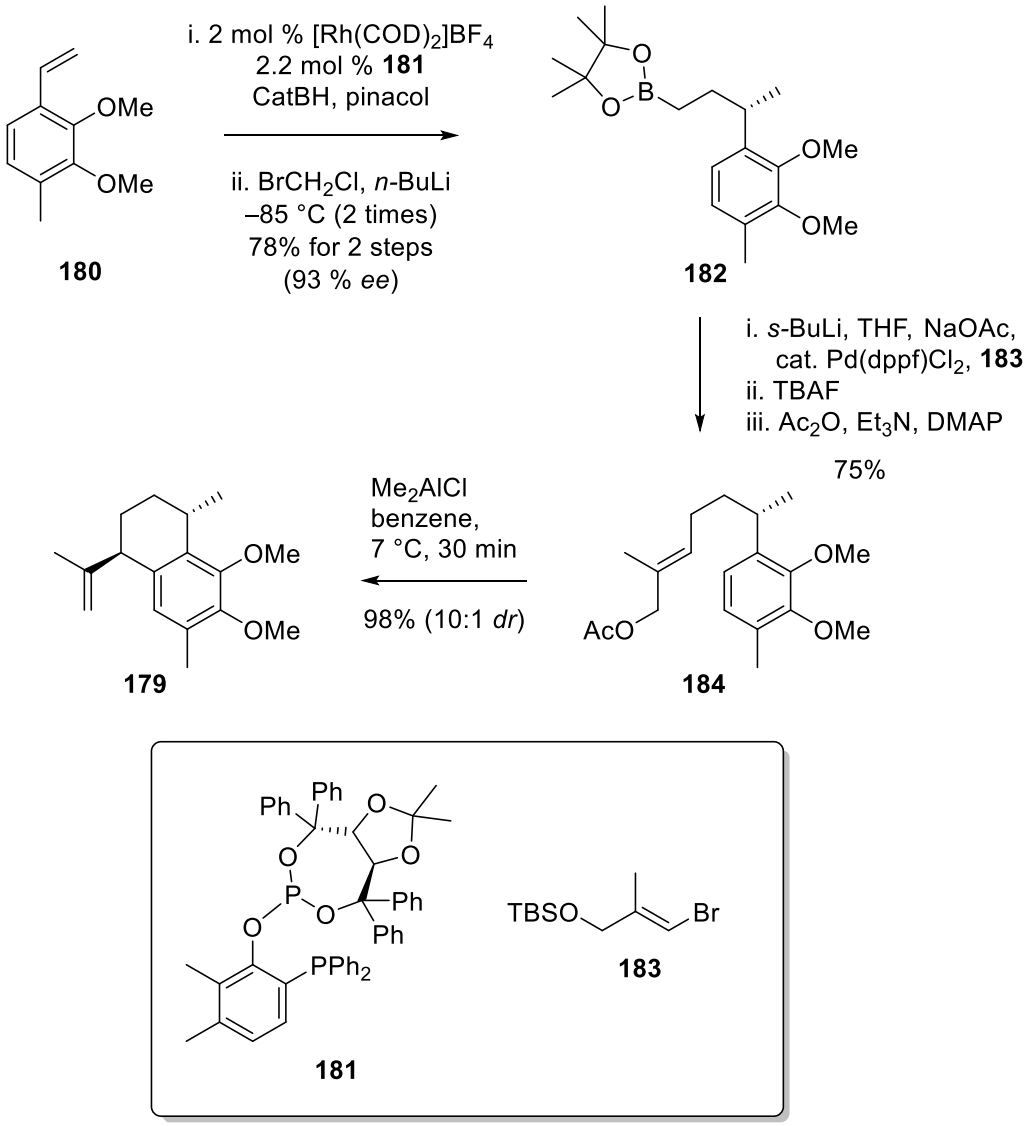


Scheme 3.13: Serra's synthesis of calamenene 172[118]

The previously described syntheses of curcuphenol (**159**) by Zhou[108] and calamenene (**172**) by Serra and Fuganti[118] are two representative examples of how bisabolane and calamenene natural products may be synthesised by first installing stereochemistry, then constructing the aromatic ring. This is a particularly advantageous sequence since both citronellal (**168**) and (−)-menthone (**173**) are commercially available and contain the prerequisite stereochemistries. They are C10 monoterpenes derived from two isoprene units. Consequently, all stereocenters are 'bought in' which negates the need for enantioselective synthesis or diastereoselective reactions involving chiral catalysts or auxiliaries.

The second commonly encountered approach towards terpene natural products involves starting with the aromatic ring, then installing the stereochemistry at the benzylic positions and building the alkyl chain. Schmalz *et al.* synthesised the trans-7,8-dimethoxycalamenene (**179**) starting from the commercially available 2,3-dimethoxytoluene **180** (Scheme 3.14).[121] They utilised an asymmetric hydroboration with catalyst **181** for installation of the benzylic stereocenter, followed by a double homologation for extension of the carbon chain. Suzuki cross coupling of **182** with vinyl bromide **183**, followed by TBS deprotection and subsequent O-acetylation afforded the allylic acetate **184** in 75% yield. The final step in their synthesis involved

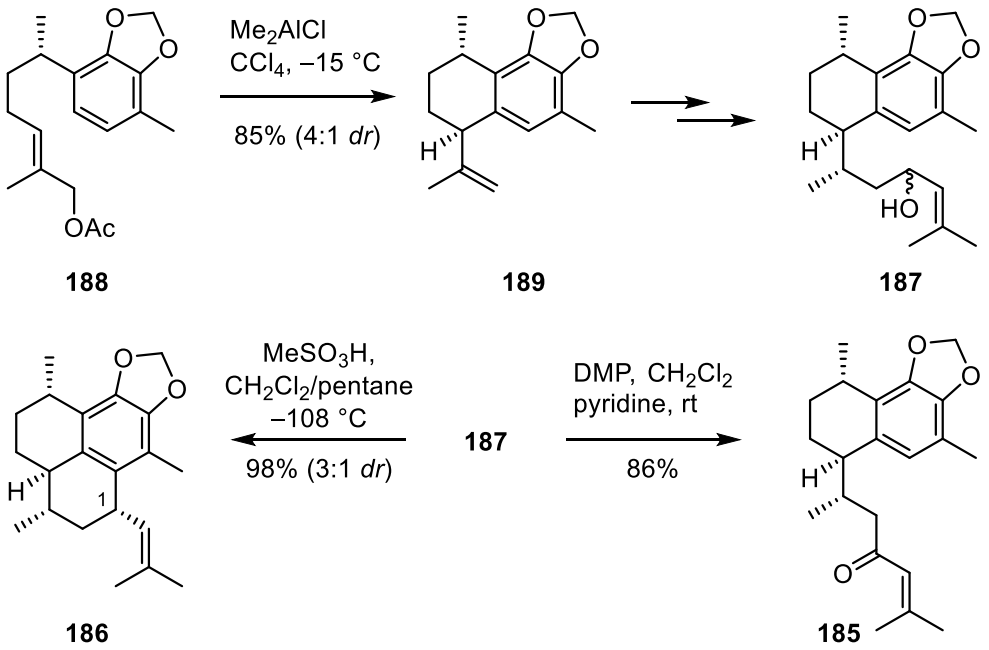
the cyclisation of **184** under aprotic conditions to afford the trans-7, 8-dimethoxycalamenene (**179**) in 57% yield over 6 linear steps.



*Scheme 3.14: Schmalz's synthesis of the trans-7,8-dimethoxycalamenene **179***[121]

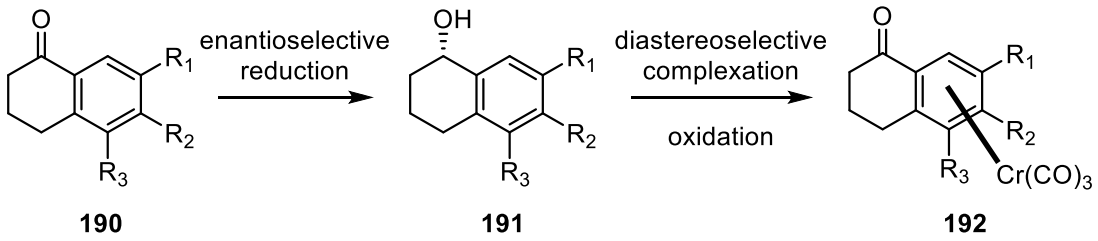
Schmalz *et al.* proposed that dimethoxy calamenene **179** could be a viable synthon for elaboration into a number of serrulatane and amphilectane type natural products. In 2012 they published the total synthesis of helioporins C (**185**) and E (**186**) from the calamenene synthon **187** (Scheme 3.15).[122] In an analogous fashion, the allylic acetate **188** was converted to the calamenene **189** through a cationic cyclisation under aprotic conditions with dimethylaluminium chloride. The cyclisation proceeded in 85% yield giving **189** in a 4:1 mixture of inseparable diastereomers. Elaboration of the side chain in 5 steps allowed for synthesis of the allylic alcohol **187**, which underwent oxidation

with DMP to afford helioporin C (**185**). Alternatively, the amphilectane natural product helioporin E (**186**) was accessed through a cationic cyclisation with $MeSO_3H$ (30 mol%) at low temperature giving helioporin E (**186**) as an inseparable 3:1 mixture of epimers at the C1 isobutenyl group.



Scheme 3.15: Total synthesis of helioporins C and E by Schmalz et al.[122]

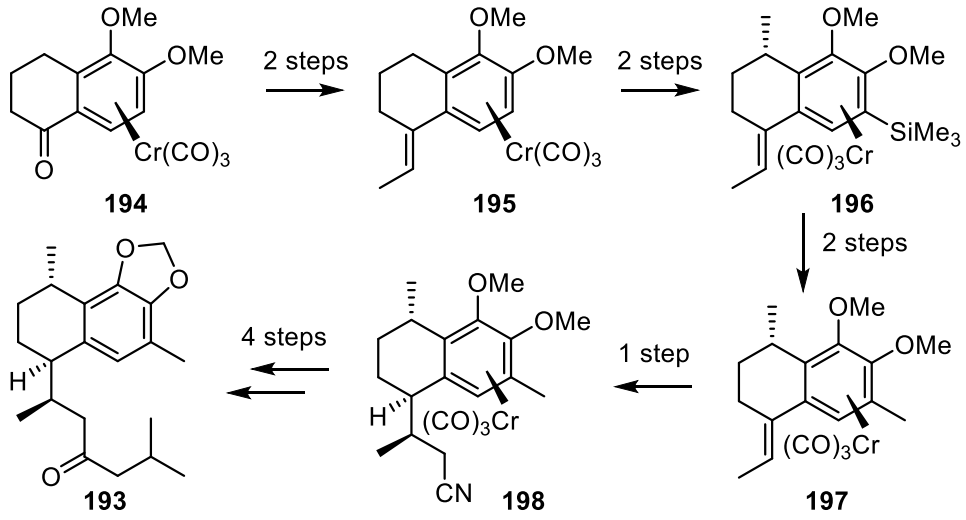
Another approach commonly encountered in the synthesis of diterpenes possessing the serrulatane and amphilectane skeletons involves the use of arene-$Cr(CO)_3$ complexes for installation of the benzylic stereocenters. Starting from l-tetralone **190**, a catalytic enantioselective reduction of the ketone to the benzylic alcohol **191** followed by diastereoselective complexation and subsequent oxidation affords the η^6-tricarbonylchromium complexes **192** in high enantiomeric purity (Scheme 3.16).[123]



Scheme 3.16: General procedure for preparation of arene-$Cr(CO)_3$ complexes (R_1, R_2 and R_3 = H or OMe)[123]

In the synthesis of 11-*epi*-helioporin B (**193**), Schmalz utilised the arene-$Cr(CO)_3$ complex **194** to install the prerequisite benzylic stereocenters (Scheme 3.17). Starting from ketone **194**, Grignard addition of vinylmagnesium chloride in the presence of $CeCl_3$ afforded the tertiary alcohol, which underwent a vinylogous ionic hydrogenation[124] in the presence of the Lewis acids Me_2AlCl and $EtAlCl_2$ to afford the olefin **195** in 67% yield over two steps. The most acidic position was protected as the trimethylsilane, with the benzylic position then deprotonated with *n*-butyl lithium and the enolate alkylated with methyl iodide to afford trimethylsilane **196** as a single diastereomer. The silane was removed with fluoride and the arene alkylated with methyl iodide to give methyl arene **197** in 85% yield over two steps. Schmalz then attempted to functionalise the side chain, using 2-lithioacetonitrile as a nucleophile. Interestingly, they observed that the major product **198** was obtained as a consequence of nucleophilic attack from the *endo* face of the complex, instead of the expected *exo* face.

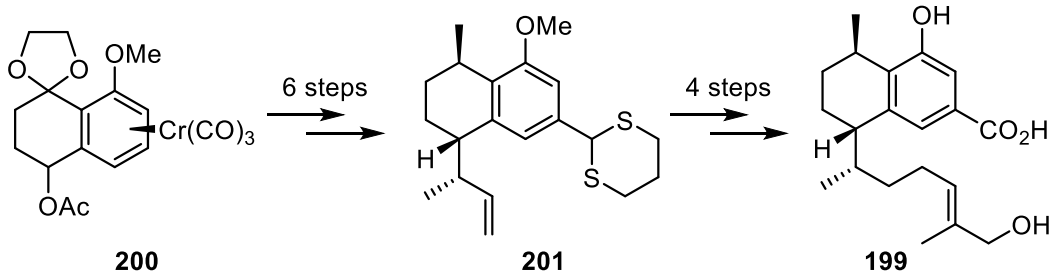
To finish the synthesis, the chromium complex was removed through oxidative decomplexation, followed by removal of the methyl ether functionality with lithium ethanethiolate. Protection as the benzodioxole was achieved with CH_2Cl_2 and caesium fluoride. The final step in the synthesis was the nucleophilic addition of isobutylmagnesium bromide to the nitrile, which upon aqueous work up afforded 11-*epi*-helioporin B (**193**).



*Scheme 3.17: Synthesis of 11-epi-helioporin B (**193**) by Dehmel and Schmalz*[125,126]

Dihydroxyserrulatic acid (**199**) was synthesised by Uemura *et al.* in 1991 utilising the arene-chromium complex **200** (Scheme 3.18). In order to install the carboxylic acid

functionality, 2-lithio-1,3-dithiane was used to perform a nucleophilic addition to the *meta* position, with the dithiane **201** later hydrolysed and then oxidised to the methyl ester.

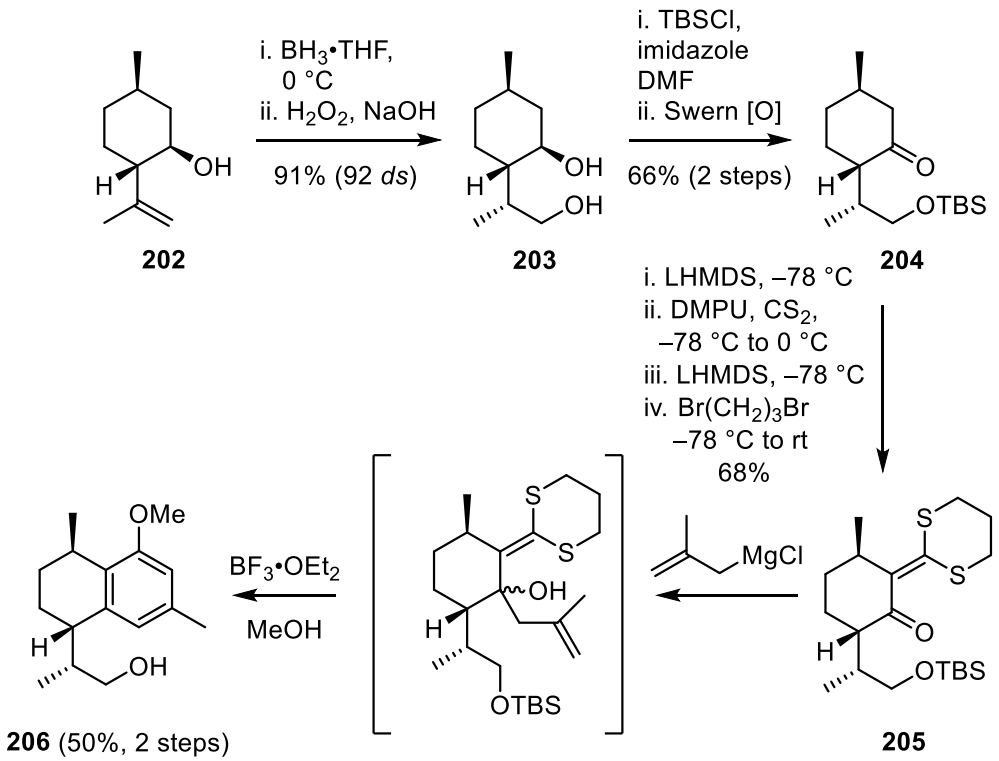


200 **201** **199**

Scheme 3.18: (±)-Dihydroxyserrulatic Acid by Uemura et al.[125]

3.5 Total Synthesis of Leubethanol

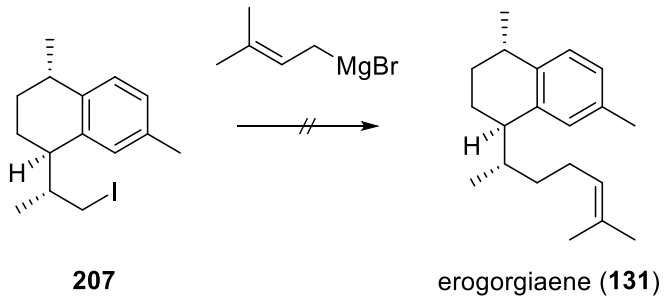
As mentioned earlier, our group has been interested in developing methodology applicable to the synthesis of the serrulatane diterpene class of natural products. In 2012, Lu's work culminated in the synthesis of leubethanol (**156**) (Scheme 3.19). Whilst leubethanol itself exhibited high levels of antimicrobial activity, synthesis of the analogous EN3 (**146**) and EN4 (**147**) natural products would afford a chemical handle at C19 that could be easily manipulated.



*Scheme 3.19: Lu's synthesis of methoxy-arene (**206**)*[105]

Lu's synthesis of leubethanol (**156**) began with a substrate directed diastereoselective hydroboration[105,127] of the commercially available (−)-isopulegol (**202**). It was rationalised that due to the stereochemistry of the C1 hydroxyl, hydroboration predominantly leads to production of diol **203** (92% *ds*). Selective protection of the primary alcohol as the TBS silyl ether was accomplished using 1 equivalent of TBSCl and imidazole in DMF. Oxidation using standard Swern oxidation conditions afforded the ketone **204**. Lu then subjected ketone **204** to an iterative deprotonation procedure whereby the enolate of **204** was initially formed with 1 equivalent of LiHMDS at −78 °C. DMPU was added followed by carbon disulphide according to a procedure by Kocienski.[128] Deprotonation of the resulting dithiol followed by alkylation with 1, 3-dibromopropane afforded α-oxoketene-S,S-acetal **205** in 68% yield as a yellow oil. The ketone **205** was treated with methallylmagnesium chloride, followed by boron trifluoride to give the methoxyarene **206** in 50% yield.

In previous literature syntheses of related natural products, the commercially available prenyl magnesium bromide has been used for chain assembly. However, one issue associated with allylic Grignard reagents is the propensity to undergo self-condensations, known commonly as Wurtz couplings.

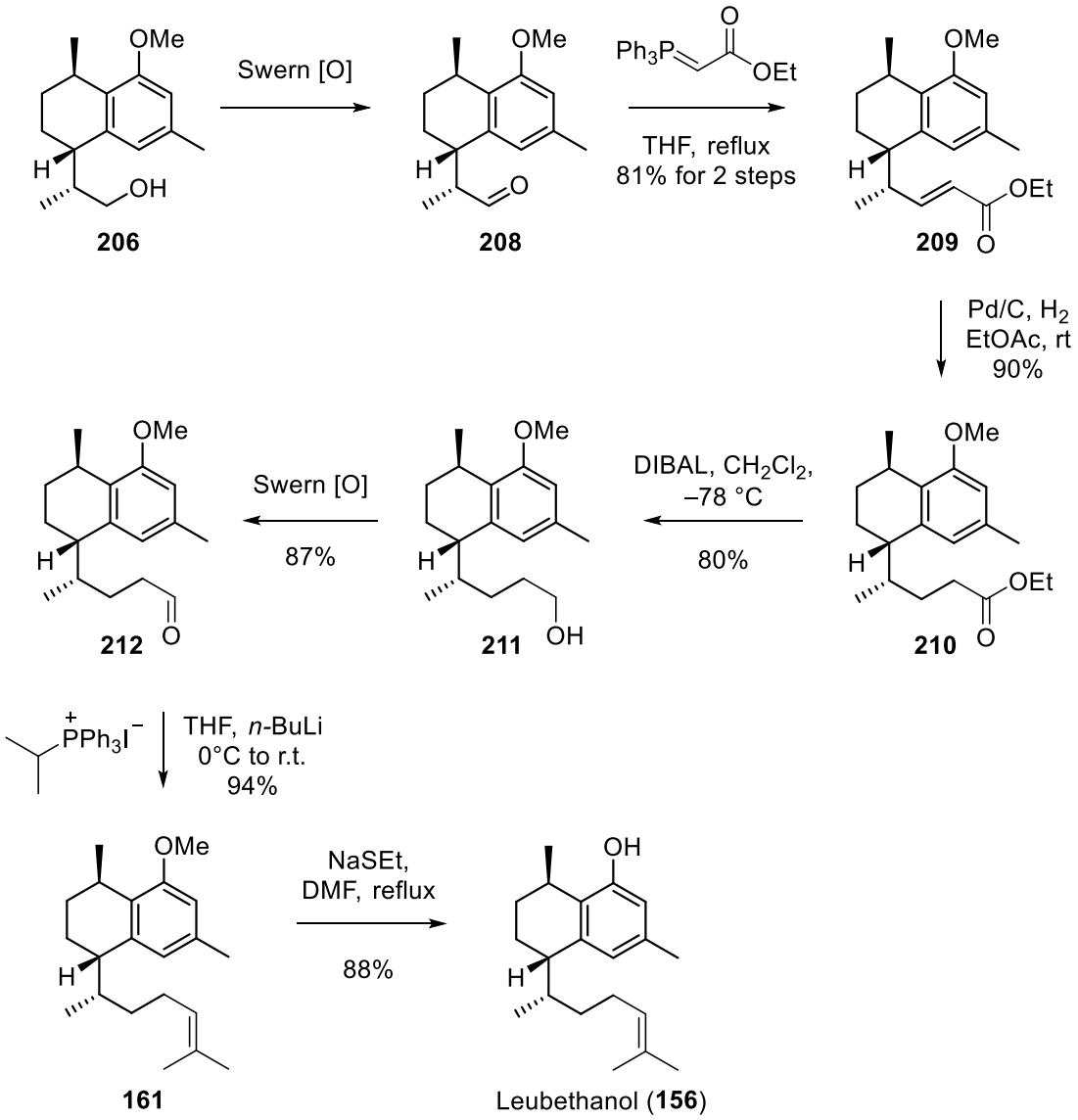


207 erogorgiaene (**131**)

Scheme 3.20: Yadav's attempted coupling with prenylmagnesium bromide[129]

In the total synthesis of erogorgiaene (**131**) by Yadav *et al.*[129] the addition of prenyl magnesium bromide to the halogenated side chain **207** was unsuccessful (Scheme 3.20). Instead a more conventional approach was used with the primary alcohol oxidised to the aldehyde. Subsequent Wittig chain extension, hydrogenation, reduction and another Wittig chain extension appended the prenyl moiety. This sequence of chemical transformations is relatively trivial and high yielding, and was therefore employed in the total synthesis of Leubethanol (Scheme 3.21).

In order to install the aliphatic side chain of leubethanol (**156**), alcohol **206** was first oxidised to the corresponding aldehyde **208** (Scheme 3.21). Wittig olefination with (carbethoxymethylene) triphenylphosphorane afforded the unsaturated ester **209**, which was subjected to hydrogenation conditions with Pd/C affording the saturated ester **210**. Reduction with diisobutyl aluminium hydride gave the aliphatic alcohol **211**, which was oxidised to aldehyde **212** with standard Swern oxidation conditions. Deprotonation of isopropyl-triphenylphosphonium iodide with *n*-butyl lithium at 0 °C formed the ylide, which underwent a Wittig olefination with aldehyde **212** to afford the prerequisite isoprenyl chain of **161**. The final step in Lu's synthesis was the deprotection of the methoxy protecting group through reflux with sodium ethane thiolate. Overall, Leubethanol (**156**) was synthesised in 7% yield over 13 steps from the commercially available (−)-isopulegol (**202**).

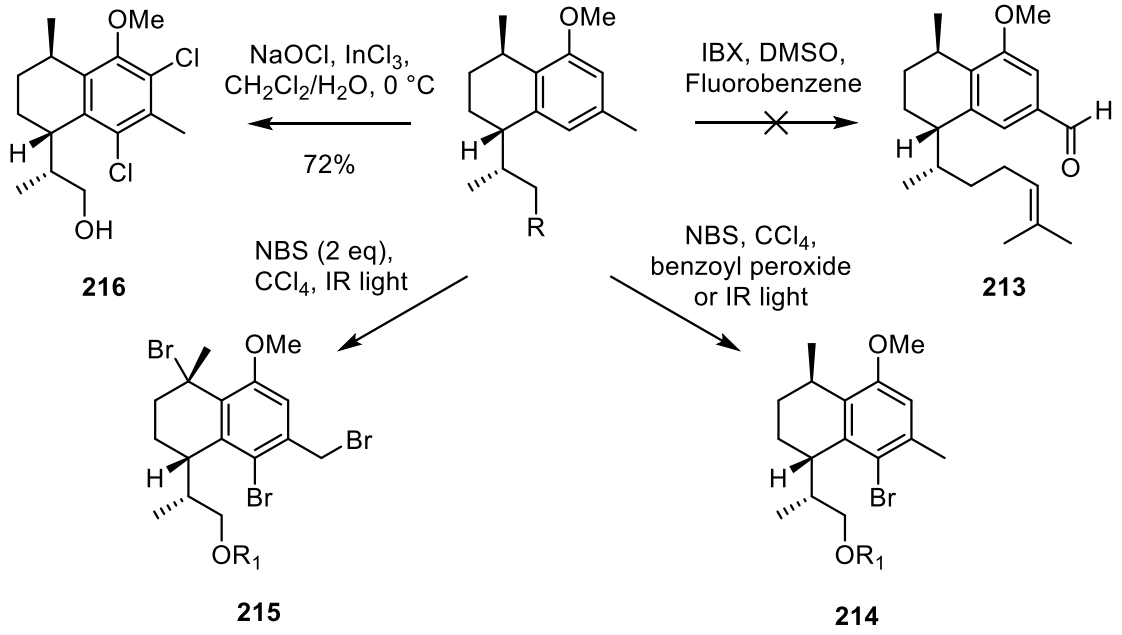


*Scheme 3.21: Lu's synthesis of Leubethanol (**156**)*[105]

3.6 Attempted Benzylic Functionalisation of Leubethanol

With the total synthesis of leubethanol (**156**) complete, Lu attempted the benzylic functionalisation of C19 for transformation into EN3 and EN4. There were two potential routes that were suggested for the synthesis of EN3 and EN4. The first involved the direct benzylic oxidation with an appropriate oxidant. Alternatively, the benzylic position may be functionalised and then converted into the required functionality. Based on methodology reported by K. C. Nicolaou,[130] the first reaction attempted was the benzylic oxidation utilising IBX as oxidant (Scheme 3.22). Methoxy ether **161** was dissolved in a mixture of fluorobenzene/DMSO and IBX (3 equivalents)

added. The reaction mixture was heated at reflux for 5-18 hours but aldehyde **213** was not observed, whilst increasing the equivalents of IBX resulted in decomposition of the starting material.



Scheme 3.22: Lu's attempted functionalisation of the benzylic position[96]

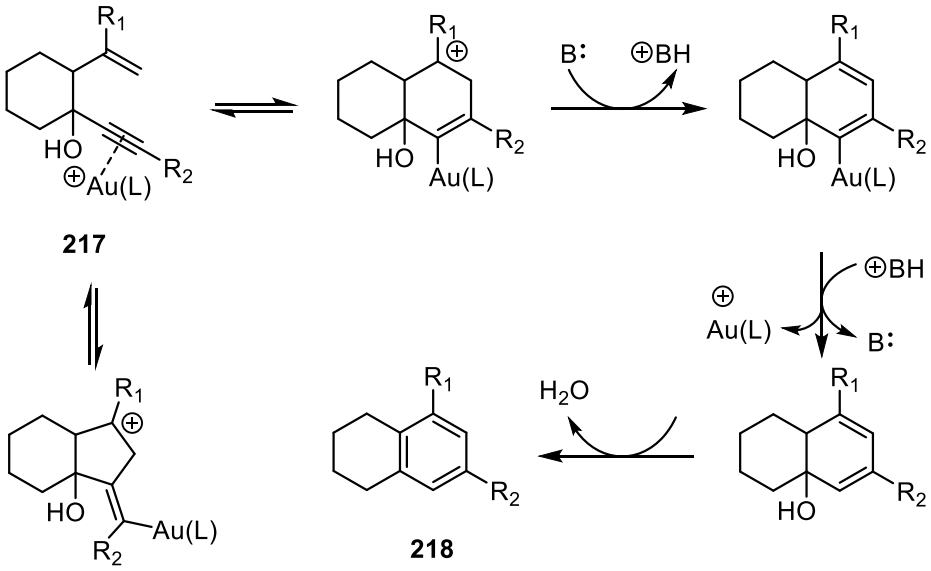
Considering oxidation of C19 was unsuccessful, Lu then attempted a benzylic bromination using *N*-bromosuccinimide (NBS) as brominating agent. Free-radical bromination was first attempted using benzoyl peroxide as a radical initiator[131] and carbon tetrachloride as solvent. Instead of observing benzylic bromination, only bromination of the aromatic ring was observed. Aryl bromide **214** was characterised based on the indicative mass obtained (*m/z* = 349.0779, $C_{16}H_{23}BrNaO_2$) as well as characteristic 1D and 2D NMR spectra, in particular the disappearance of a signal corresponding to an aromatic hydrogen. Further attempts at bromination were conducted using methodology by Gruter *et al.*,[132] where the reaction mixture was irradiated with IR light. NBS was limited to 0.5 equivalents, but the only product observed was the same bromination product **214**. When an excess of NBS was used (2 equivalents), Lu observed formation of the tri-brominated adduct **215**. Lu rationalised that the propensity for nuclear bromination to occur was in part due to the electron donating effect of the methoxy substituent. Derivatisation to the trifluoroacetoxy-arene and the acetoxy-arene was accomplished in 3 steps, with the same conditions for bromination with benzoyl peroxide or infrared light tested. Unfortunately, in each

circumstance only starting materials were observed. The aromatic bromination was suppressed but no products corresponding to benzylic bromination were observed.

With attempts at benzylic bromination proving fruitless, Lu then attempted a benzylic chlorination reaction using sodium hypochlorite and indium(III) chloride at 0 °C in a mixture of CH_2Cl_2 and water.[133] However, the only product obtained was the dichlorinated product **216**, obtained from reaction with the *in situ* generated electrophilic chlorine. Further attempts at benzylic functionalisation were abandoned; instead attention was turned to incorporation of the prerequisite benzylic functionality prior to aromatic ring construction.

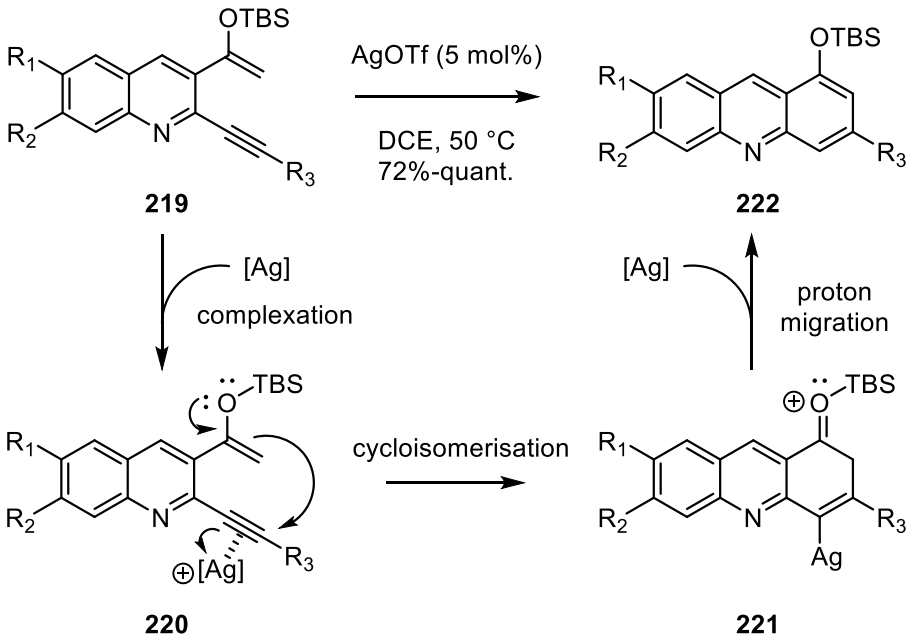
3.7 6-endo-dig Cyclisation of 3-Hydroxy-1 ,5-enynes

Barriault *et al.* reported that the 6-*endo-dig* cyclisation catalysed by gold(I) complexes of 3-hydroxy-1 ,5-enynes **217** afforded the corresponding tetrahydronaphthalenes **218** in good yields (Scheme 3.23).[134,135] The best yields were obtained when the R_1 substituent was either a methyl or phenyl group. When R_1 and R_2 were hydrogen atoms, only 10% yield was observed. When the R_1 substituent was changed to an ethoxy group, only a 12% yield was observed alongside decomposition. Similarly for the R_2 position, the best yields were obtained when the substituent was an aromatic or methyl group, with hydrogen tolerated at this position when R_1 was a substituent other than hydrogen or ethoxy.



Scheme 3.23: Proposed mechanism for the 6-endo-dig cyclisation by Barriault et al.[134]

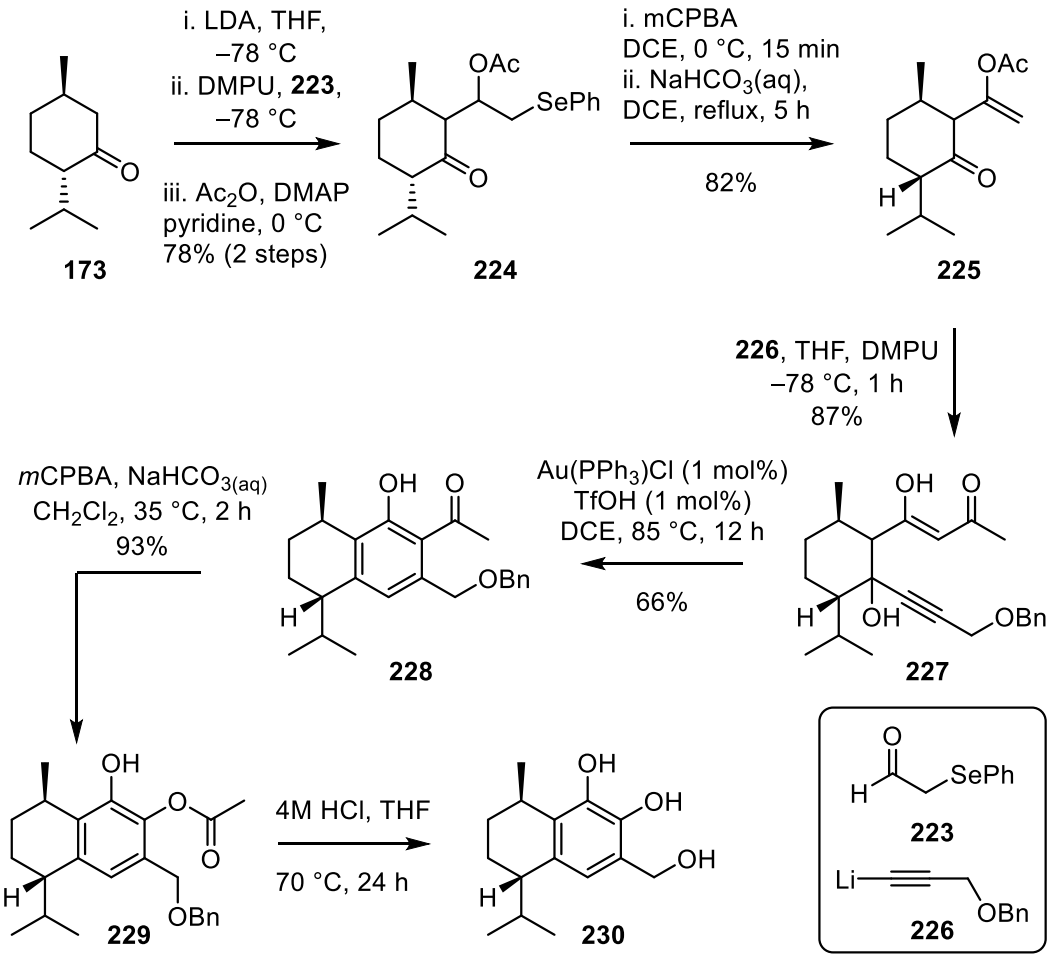
Although the yields were low when R_1 was an alkoxy substituent using gold(I) catalysts, Belmont *et al.* have reported the use of activated gold(I) catalysts such as $AuPPh_3SbF_6$ as well as silver(I) catalysts for the ene-yne cycloisomerisation of quinolines **219** (Scheme 3.24).[136,137] Starting from the silyl enol ether **219**, complexation of the silver cation with the alkyne results in intermediate **220**, which following an ene-yne cycloisomerisation affords intermediate **221**. Finally, proton migration and regeneration of the catalyst leads to the acridine **222**. The use of silver salts afforded the aromatic compounds in upwards of 72% yields after just 1 hour at 50 °C in 1, 2-dichloroethane. In contrast, the simple gold complex $AuCl_3$ afforded just 12% yield after 50 °C overnight, whilst refluxing overnight with $Au(PPh_3)Cl$ resulted in no discernible product.



Scheme 3.24: Belmont's silver(I) catalysed ene-yne cycloisomerisation[136]

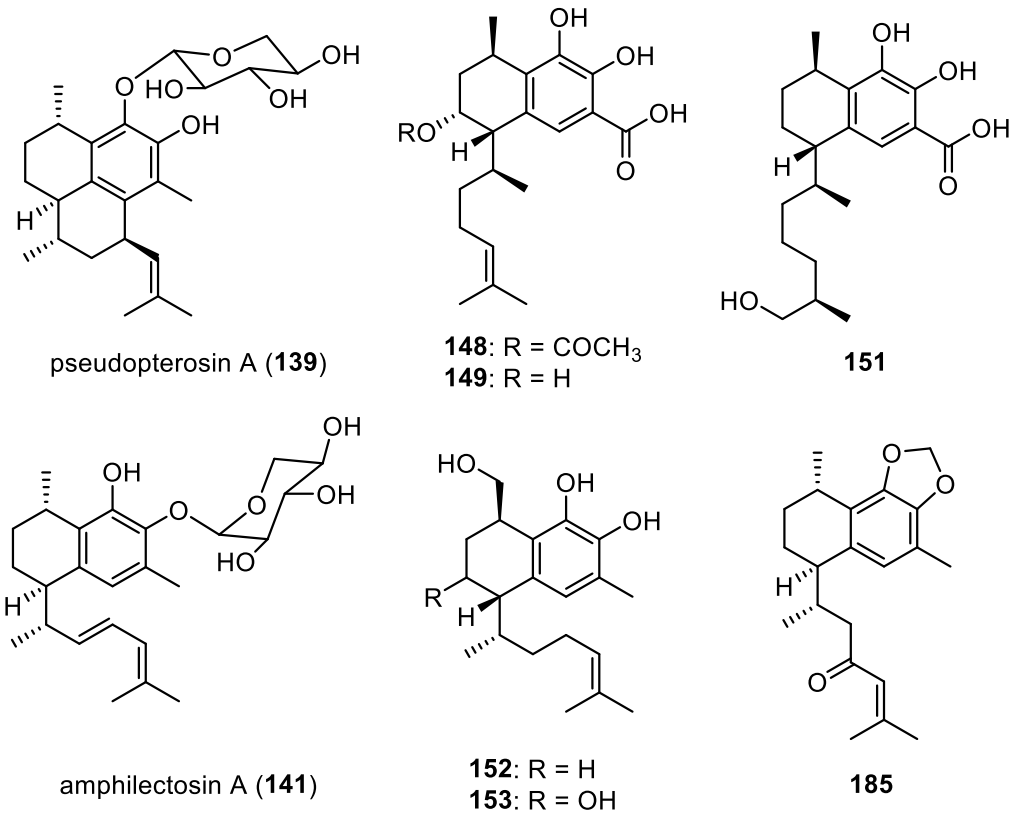
3.8 Total Synthesis of the 8-Hydroxycalamenenes by March

Considering the promising results reported by Belmont and Barriault, March[138] investigated the aromatic ring construction using the 8-hydroxy-calamenenes as a model system for serrulatane synthesis. March began investigations with an LDA aldol between the commercially available (−)-menthone (**173**) and phenylselenoacetaldehyde (**223**) (Scheme 3.25). The hydroxyselenide was protected as the acetate derivative **224**, which was oxidised to the selenoxide with *m*CPBA and eliminated affording the enol acetate **225**. Upon treatment with the lithium acetylide **226**, the acetate rearranged giving enol-acetone **227**. Although unfortunate that the enol ether underwent this rearrangement, a number of *ortho-di*phenol natural products have been reported in the literature (Scheme 3.26).[81,86,92,99–101]



Scheme 3.25: March's synthesis of ortho-diphenols[138]

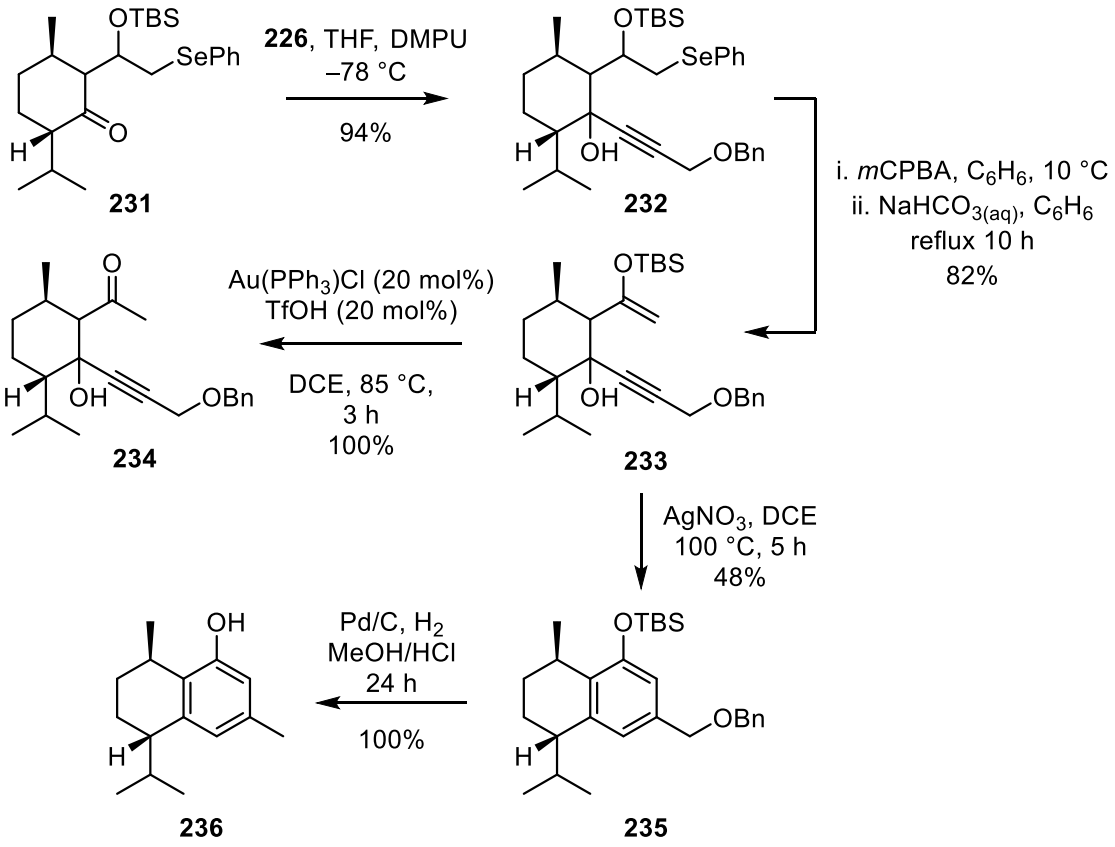
Because enol-acetone **227** was an unusual substrate for 6-*endo-dig* cyclisation, March initially attempted the conditions published by Barriault and co-workers.[134] Treatment of enol **227** with Au(PPh$_3$)Cl (1 mol%) and TfOH (1 mol%) in DCE heated at reflux resulted in formation of the aromatic ketone **228**. Bayer-Villager oxidation with *m*CPBA afforded the aromatic ester **229**. The ester and benzyl groups were hydrolysed, albeit with inconsistent yields to afford the *ortho*-diphenol **230**. March rationalised that although unoptimised, this could be applied to the synthesis of a variety of *ortho*-diphenol natural products.



Scheme 3.26: Natural products possessing ortho-diphenol functionality

Having shown the effectiveness of this method towards *ortho*-diphenols, March then revised the synthetic sequence as well as the protecting group strategy to circumvent the enol-acetate rearrangement. The lithium acetylide **226** was successfully added to the TBS protected phenylselenide **231**, with the 3-hydroxy alkyne **232** then eliminated to afford the enol ether **233** (Scheme 3.27). Unfortunately, subsequent treatment with $Au(PPh_3)Cl$ resulted in the hydrolysis of the TBS protecting group to give ketone **234** in quantitative yield.

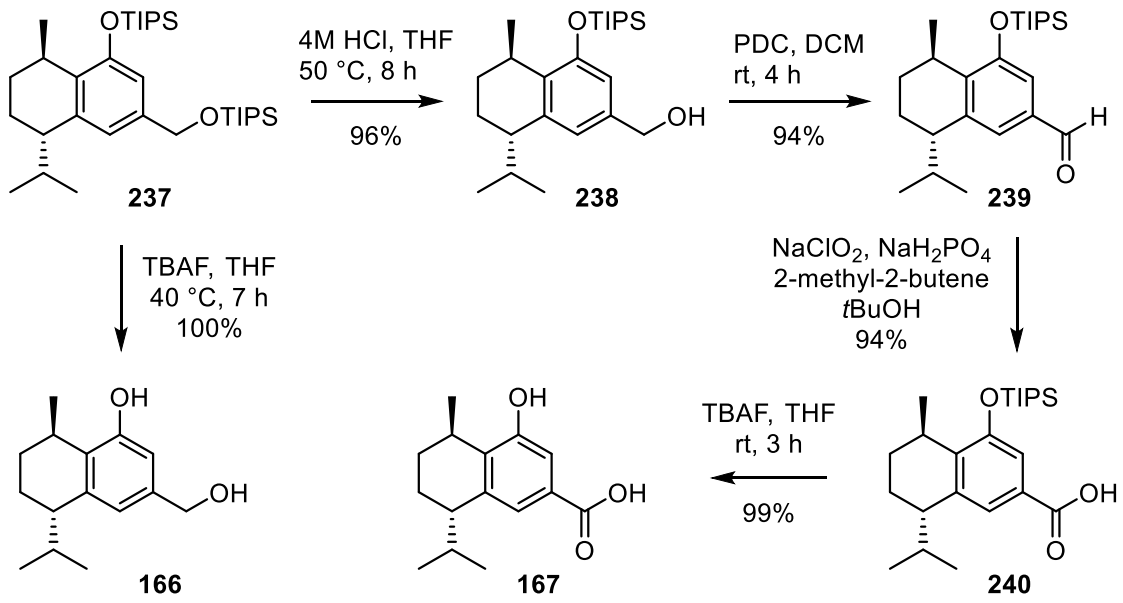
The hydrolysis of the enol ether was attributed to either protecting group stability or the reaction conditions, and in particular the use of $Au(PPh_3)Cl$ as catalyst. Extensive screening of other transition metals and conditions identified silver nitrate as an efficient catalyst for the 6-*endo-dig* cyclisation of 3-hydroxy-1, 5-enynes. Under the optimised conditions, enyne **233** was heated at reflux in DCE for five hours in darkness, affording the protected calamenene **235** in 48% yield.



*Scheme 3.27: March's synthesis of deoxy-calamenene **236***

Attempted benzyl deprotection through hydrogenolysis resulted in formation of deoxy-calamenene **236**. Considering the previous difficulties that were encountered during benzyl deprotection of the *ortho*-diphenols, March devised an alternate protecting group strategy allowing for the orthogonal deprotection of the benzyloxy position. Following the same synthetic methodology, the bis-TIPS calamenene **237** was synthesised efficiently from (−)-menthone (**173**). Calamenene **237** was then used as a precursor for construction of the two natural products (Scheme 3.28).

Treatment of **237** with TBAF for 7 hours at 40 °C allowed for universal deprotection and synthesis of **166** in quantitative yield. In order to synthesise the carboxylic acid, March adapted the synthesis by selectively deprotecting the benzylic silyl ether with 4M HCl to give alcohol **238**. Subsequent oxidation with PDC afforded the aldehyde **239**, with Pinnick oxidation affording carboxylic acid **240**. The final step in the synthesis was the deprotection of the remaining silyl ether by addition of TBAF. Overall, the carboxylic acid **167** was obtained in 84% from the bis-silyl precursor **237**.



*Scheme 3.28: March's total synthesis of calamenenes **166** and **167***

The combination of methodology applicable to synthesis of leubethanol and the 8-hydroxycalamenenes could provide a viable route to EN3 and EN4. In an analogous fashion to leubethanol (**156**), the use of (−)-isopulegol (**202**) could establish the C1, C4 and C11 stereocenters early in the synthesis. The silver catalysed en-yne cycloisomerisation is applicable to the formation of the the 8, 19-dihydroxy calamenene core with introduction of the desired C19 functional groups. The prenyl side chain could be extended in a similar manner to leubethanol. In the upcoming chapter, the synthetic methodology developed during these studies will thus be applied to the total synthesis of EN3 (**146**) and EN4 (**147**).

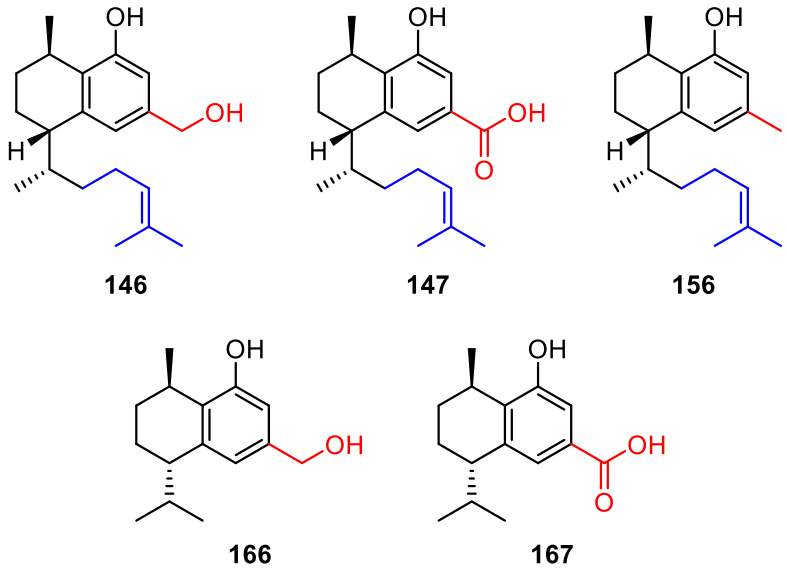
Chapter 4
Total Synthesis of EN3 and EN4

Chapter 4 Summary

This chapter details the first total synthesis and stereochemical elucidation of EN3 (**146**) and EN4 (**147**). The stereochemistry was introduced early in the synthesis using (−)-isopulegol as a starting material. Key steps included lithium acetylide addition and silver catalysed ene-yne cycloisomerisation. EN3 was synthesised in 17 steps and 5% yield, whilst EN4 was accessed in 17 steps and 3.8% yield. The stereochemistry of the natural products was determined as 1*R*, 4*S*, 11*S* through comparison of the optical rotations and NMR data with reported literature values.

4.1 Retrosynthetic Analysis of EN3 and EN4

As discussed in chapter 3, EN3 and EN4 are structurally similar to leubethanol (**156**) as well as the 8-hydroxycalamenenes (**166-167**) (Scheme 4.1). They differ in the oxidation state at the benzylic C19 position (highlighted in red) as well as the presence of the prenyl tail (highlighted in blue). For leubethanol (**156**), C19 is a methyl substituent, whilst EN3 and EN4 possess hydroxyl and carboxylic acid functional groups respectively. The C19 substitution pattern of the two calamenenes (**166** and **167**) is identical to that of EN3 and EN4, with the only difference being the presence of the prenyl tail.

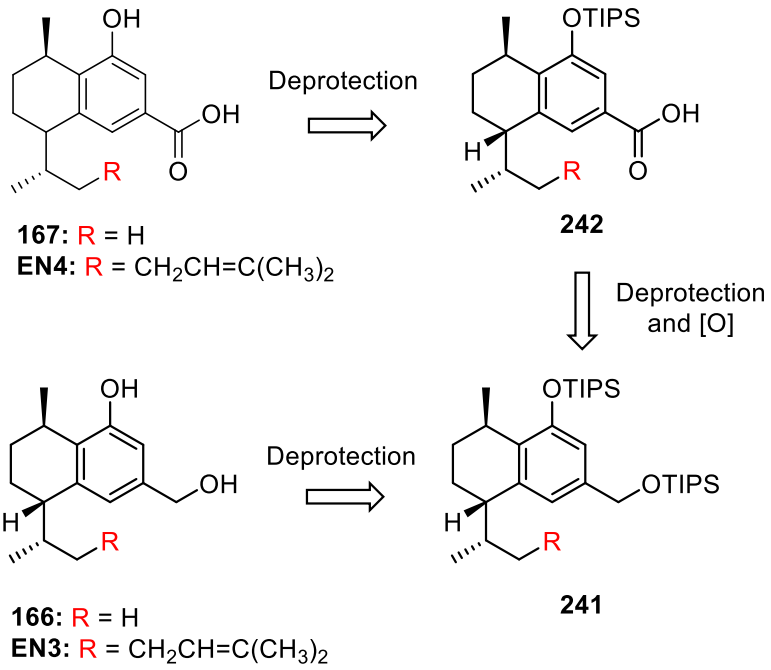


Scheme 4.1: serrulatane and calamenene natural products

Retrosynthetically, EN3 and EN4 may be accessed through a combination of the approaches used for leubethanol[105] and the calamenenes.[138] By employing isopulegol as a starting material, the stereochemistry at C1, C4 and C11 may be installed early in the synthesis. Furthermore, the aromatic ring may be installed using a silver catalysed ene-yne cycloisomerisation.

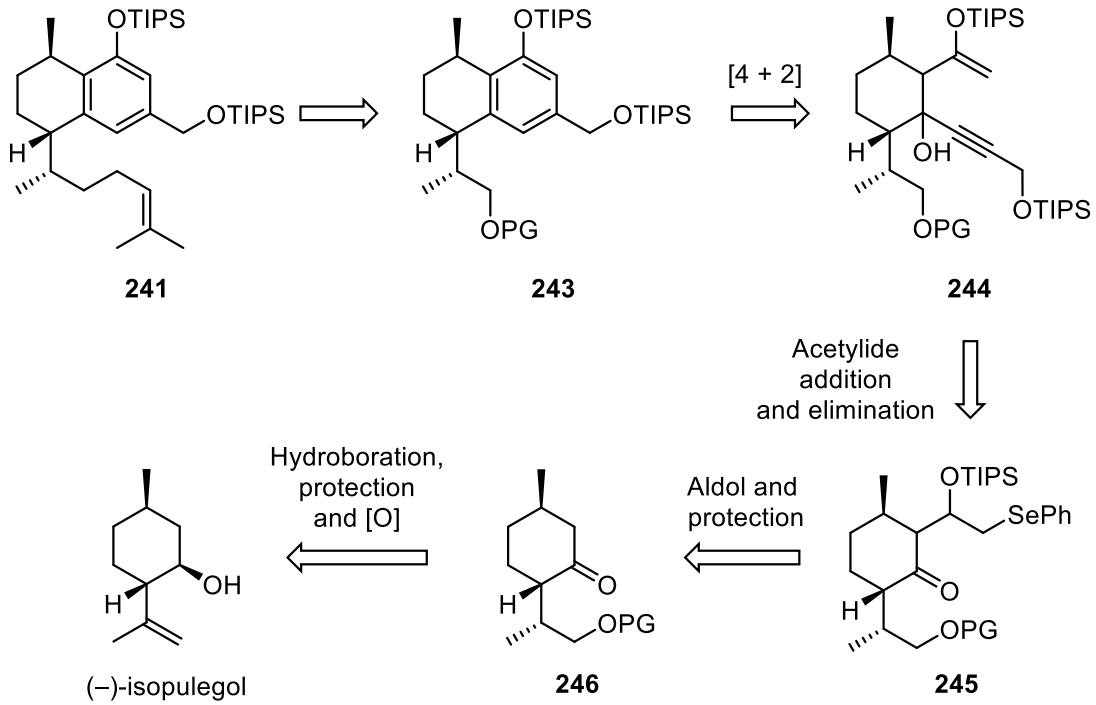
During the synthesis of the 8-hydroxycalamenenes, March investigated deprotection/oxidation strategies necessary to access both natural products from a common bis-silyl synthon.[138] The studies indicated that the C19 hydroxyl substituted calamenene **166** was easily accessed through a double deprotection, whilst the carboxylic acid **167** required a lengthier deprotection/oxidation sequence. This was necessary due to the instability of the free phenol to oxidation. Based on these results, it

was theorised that EN3 may be accessed in one step from the bis-silyl synthon **241** (Scheme 4.2). EN4 would require the selective desilylation of the primary TIPS ether followed by oxidation to carboxylic acid **242** and deprotection. Synthesis of EN4 would be possible in 4 steps from the bis-silyl synthon **241**.



*Scheme 4.2: Retrosynthetic analysis of EN3 and EN4 from synthon **241***

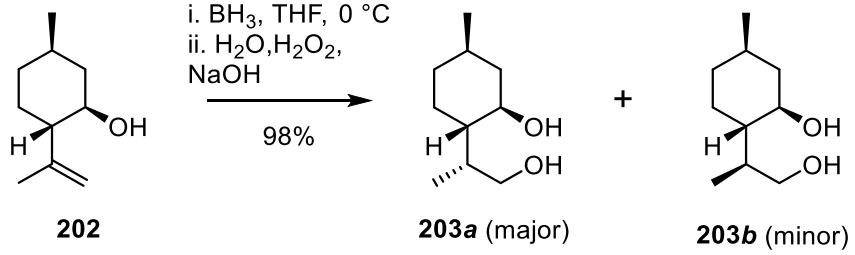
Although the substituted 8-hydroxycalamenenes contain the tetrahydronaphthalene core characteristic of the serrulatanes, they differ in that the prenyl chain is absent. For EN3 and EN4, the retrosynthesis must also address the installation of this group. The bis-silyl synthon **241** could be synthesised from protected alcohol **243** through an oxidation/chain extension sequence. tetrahydronaphthalene **243** could be synthesised through benzannulation of enyne **244**, which in turn may be formed through selenoxide elimination and acetylide addition to ketone **245** (Scheme 4.3). Ketone **245** may be synthesised through TIPS protection of the corresponding β-hydroxy ketone obtained from aldol addition with protected ketone **246** and phenylselenoacetaldehyde. Ketone **246** could be obtained in three steps from the commercially available (−)-isopulegol (**202**) in a similar manner to leubethanol.



*Scheme 4.3: Retrosynthetic analysis of bis-silyl synthon **241***

*4.2 Synthesis of Benzyl Ketone **248***

Synthetic studies towards EN3 and EN4 began with the substrate-directed hydroboration of (−)-isopulegol (**202**) (Scheme 4.4). Coordination of the secondary hydroxyl group at C1 with the borane, followed by subsequent addition to the alkene resulted in hydroboration occurring predominantly from one side of the alkene. This result was in accordance with the literature, with the hydroboration of isopulegol known to produce the 1*R*, 2*S*, 5*R*, 7*R* stereochemistry of diol **203*a***.[83,105,127]



*Scheme 4.4: Stereoselective hydroboration of (−)-isopulegol (**202**)*

Reaction progress was determined by disappearance of the two vinyl protons from (−)-isopulegol and appearance of two diastereotopic protons at 3.66 and 3.60 ppm corresponding to the newly created oxymethylene functionality. The ^{1}H NMR spectrum

revealed that following recrystallisation from hot cyclohexane, the major diastereomer **203*a*** was obtained in a ratio of 11.5:1 with the minor diastereomer **203*b***. This was supported by the ^{13}C NMR spectrum (Figure 4.1), which showed 10 carbon signals from the major diastereomer **203*a***. Trace signals at 71.8, 66.4 and 48.9 ppm are indicative of the minor diastereomer **203*b***. Due to the similarities in R_f, complete separation of the diastereomers was not achieved. Instead, separation at a later step could be possible.

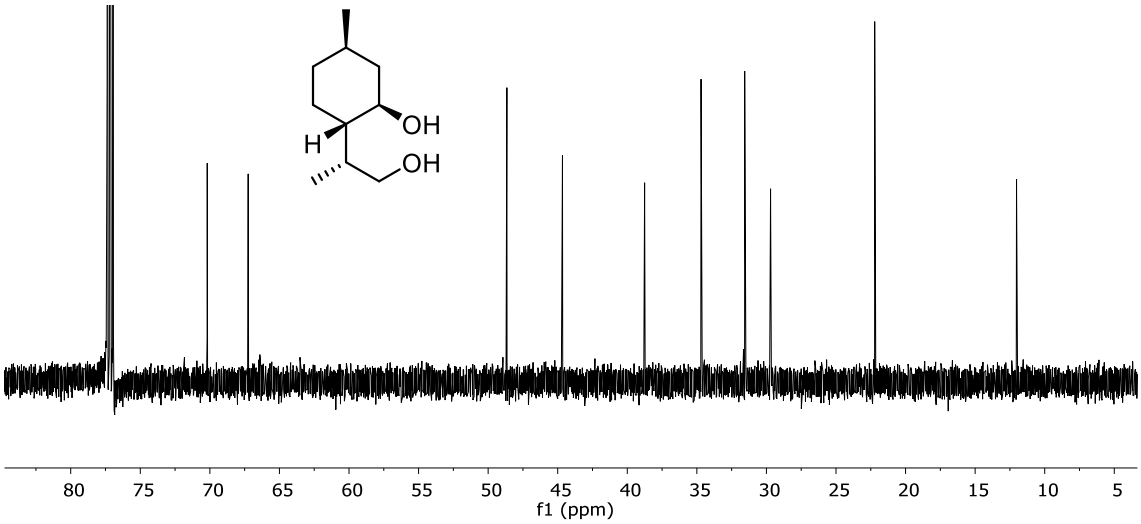
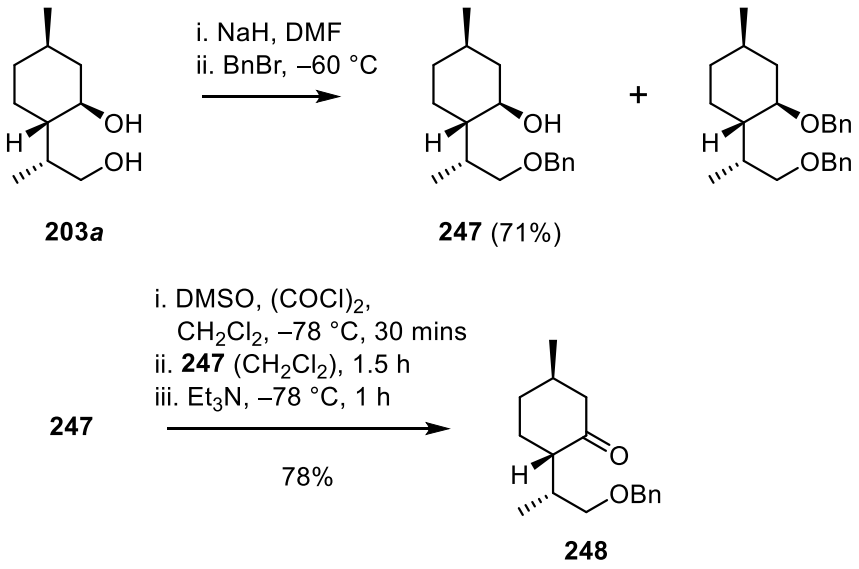


*Figure 4.1: ^{13}C NMR spectrum of diol **203a** (150 MHz, $CDCl_3$)*

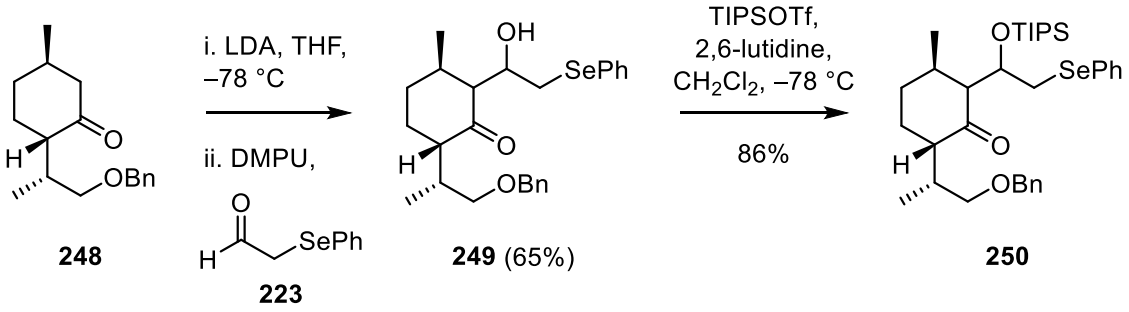
Treatment of diol **203*a*** with sodium hydride and benzyl bromide in DMF at −60 °C gave a mixture of the primary mono-benzylated product **247** as well as a small amount of the di-benzylated side-product (Scheme 4.5). Fortunately, protection of the minor diastereomer **203*b*** from the previous step enabled separation by column chromatography at this point. Swern oxidation of the secondary alcohol afforded ketone **248** in 78% yield. Since ketone **248** was known, the NMR spectra obtained were compared to the literature and were in good agreement.[127]



*Scheme 4.5: Synthesis of benzyl-protected ketone **248***

4.3 Installation of the C8 and C19 Oxygen Functionality

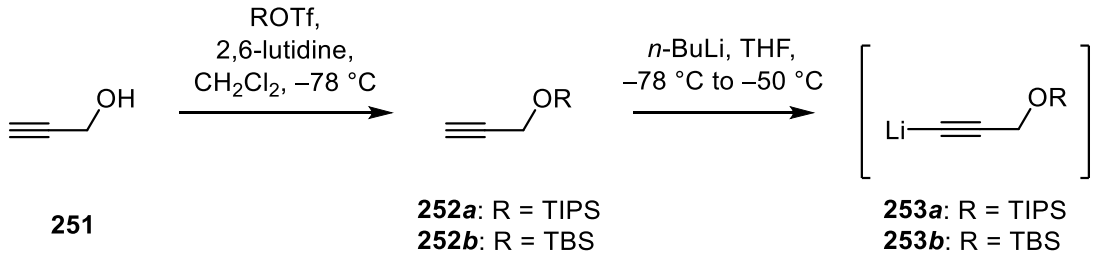
The proposed retrosynthesis required a substrate with hydroxyl functionality that could be converted to the silyl enol ether. To this end, the aldol reaction between ketone **248** and phenylselenoacetaldehyde (**223**) was performed (Scheme 4.6). LDA was prepared *in situ* by the deprotonation of diisopropylamine with *n*-butyl lithium. Ketone **248** was added *via* cannulation at −78 °C and the enolate aged for 1.5 hours. DMPU was added prior to the addition of phenylselenoacetaldehyde (**223**), with the solution stirred at −78 °C until TLC showed consumption of starting materials. The reaction proceeded smoothly, affording hydroxyselenide **249** in good yield and as a single diastereomer, although the stereochemistry was not determined. The hydroxyl functionality was protected, with the silyl ether **250** obtained in 86% yield.



*Scheme 4.6: Synthesis of the triisopropylsilyl ether **250***

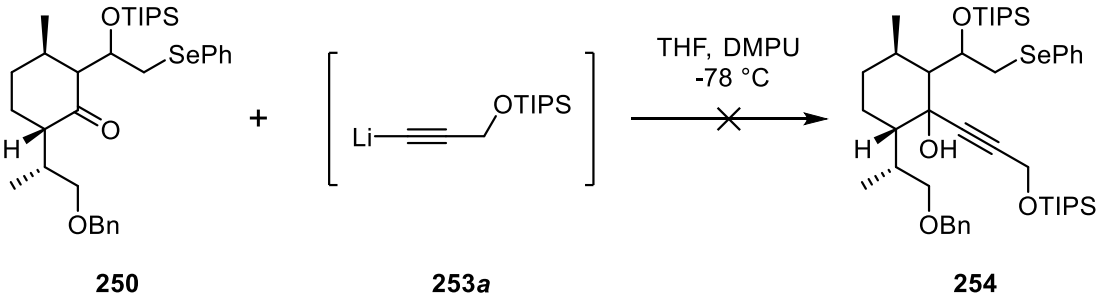
4.3.1 Attempted lithium acetylide addition to ketone *250*

Having successfully introduced the oxygen functionality corresponding to the phenol at C8 of the natural products, introduction of the C19 functionality was attempted *via* lithium acetylide addition. Propargyl alcohol **251** was protected as the known triisopropylsilyl ether **252*a*** in quantitative yield (Scheme 4.7).



*Scheme 4.7: Formation of lithium acetylides **253a** and **253b***

The alkyne was deprotonated with *n*-butyl lithium affording the lithium acetylide **253*a***. Addition of the previously prepared ketone **250** afforded no discernible change in R_f after 3 hours (Scheme 4.8). Comparison of the crude ^{1}H NMR spectrum to the ^{1}H NMR spectra of the starting materials revealed that no reaction had occurred. A number of alternate reaction conditions were trialled including the addition of DMPU but in each case alkyne **254** was not observed.

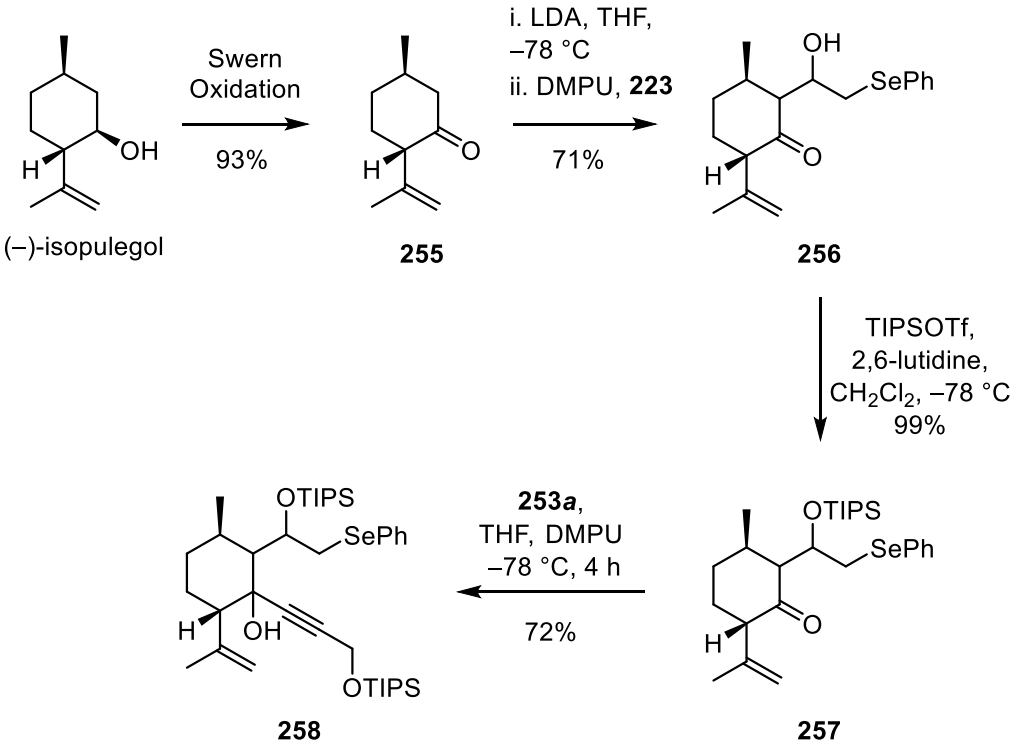


*Scheme 4.8: Attempted lithium acetylide addition to ketone **250***

4.3.2 Model lithium acetylide addition

At this stage it was determined that the cause for the poor reactivity could be the benzyl ether functionality. To test this theory, the substrate for acetylide addition was simplified. (−)-isopulegol (**202**) was oxidised to (−)-isopulegone (**255**) in high yield (Scheme 4.9). Deprotonation with LDA followed by addition of phenylselenoacetaldehyde (**223**) afforded the diastereomerically pure hydroxyselenide **256**, which was protected as the silyl ether **257** in 70% yield over two steps. Addition of

lithium acetylide **253*a*** to the phenylselenide **257** afforded 3-hydroxy alkyne **258** in 72% yield and as a mixture of diastereomers. This result suggests that the lithium acetylide **253*a*** does form, and that the poor reactivity of phenylselenide **250** is attributable to the benzyl ether side chain.

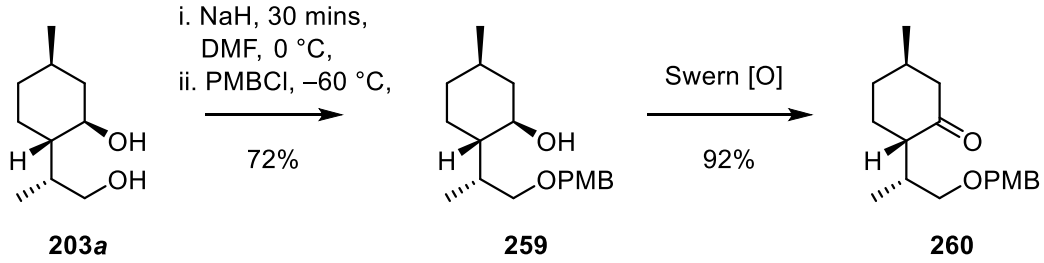


*Scheme 4.9: Synthesis of model 3-hydroxy alkyne **258***

Although lithium acetylide addition to the simplified substrate was successful, the poor reactivity of benzyl ether **250** meant that an alternative substrate was required. Whilst the poor reactivity could be attributable to the side chain itself, changing the protecting group could potentially lead to a different outcome during lithium acetylide addition. Considering the synthetic strategy had two silyl protecting groups in place, the 4-methoxybenzyl (PMB) protecting group was investigated. PMB groups exhibit different chemical reactivity to the benzyl group and therefore different modes of deprotection. In particular, they can be removed through single electron transfer oxidation with an oxidant such as DDQ. The different chemical behaviour of this protecting group could allow for orthogonal deprotection and would be less likely to result in chemoselectivity issues. This was seen as advantageous considering the issues associated with benzyl deprotection during the calamenene synthesis (Scheme 3.27).

4.3.3 Introduction of the PMB protecting group

Following the same synthetic sequence as before, diol **203*a*** was protected as the primary PMB ether **259** in good yield (Scheme 4.10). Column chromatography afforded separation of ether **259** from the small quantity of bis-PMB ether and a protected analogue of minor diastereomer **203*b***. Swern oxidation afforded the ketone **260**, which was obtained in 65% yield over three steps from (−)-isopulegol.

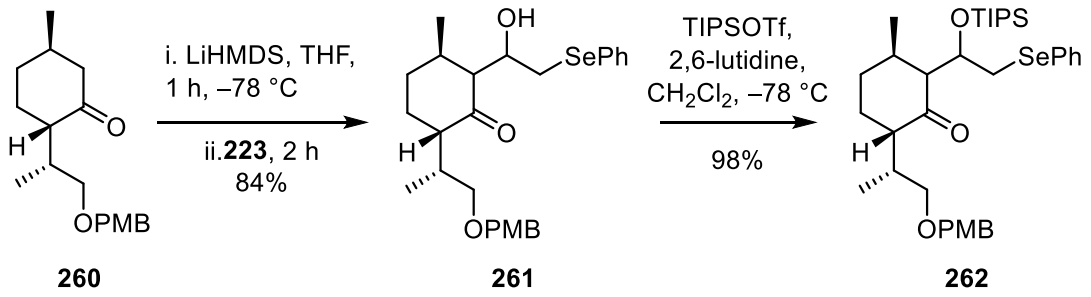


*Scheme 4.10: Synthesis of the PMB-protected ketone **260***

4.3.4 Synthesis of the silyloxy selenide **262**

Ketone **260** was subjected to the aforementioned aldol conditions with LDA as base. Even with a number of experimental conditions trialled, the best yield obtained was 40%, with return of the starting ketone **260** (~40%). Recovery of the phenylselenoacetaldehyde (**223**) was not possible, since the aldehyde decomposed during the reaction or purification.

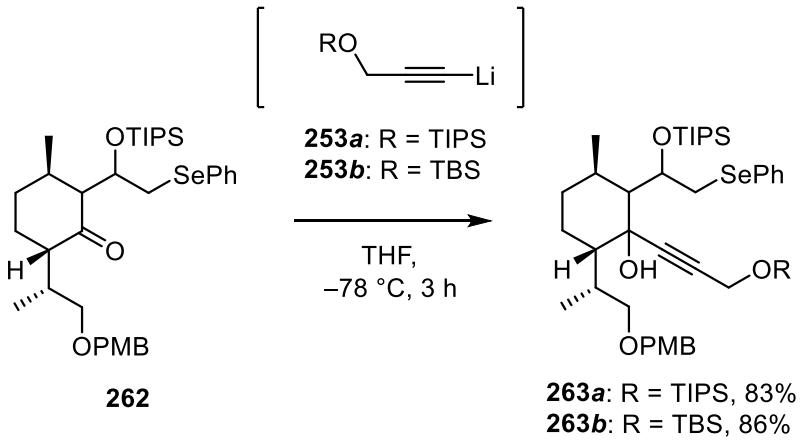
Considering the poor yield and reproducibility, LiHMDS was trialled as an alternative base. Treatment of ketone **260** with LiHMDS (0.2M) resulted in poor conversion with recovery of mainly starting materials. Increasing the concentration to 0.5M afforded the desired hydroxyselenide **261** in an excellent 84% yield (Scheme 4.11). The ^{1}H NMR indicated the presence of only one diastereomer, as did the ^{13}C NMR spectrum that contained an expected 22 carbon signals. Protection as the triisopropylsilyl ether **262** proceeded almost quantitatively (98% yield).



*Scheme 4.11: Synthesis of silyloxy selenide **262***

*4.3.5 Lithium acetylide addition to ketone **262***

With the protected phenylselenide **262** in hand, the next step was the addition of lithium acetylide **253**. A large excess (4 equivalents) of alkyne was used, due to difficulties encountered during chromatography of the model 3-hydroxy alkyne **258**. The TIPS and TBS alkynes (**252*a*** and **252*b***) were deprotonated with freshly titrated *n*-butyl lithium, and phenylselenide **262** added (Scheme 4.12). ^{1}H NMR analysis of the crude reaction mixtures revealed that there were no observable starting materials.



*Scheme 4.12: Lithium acetylide addition to ketone **262***

Where the model study with ketone **257** resulted in a mixture of diastereomers, addition of lithium acetylide **253*b*** to ketone **262** resulted in one distinguishable diastereomer based on analysis of the ^{1}H NMR spectrum (Figure 4.2). The multiplets at 7.52 ppm and 7.07 ppm were attributable to the protons on the aromatic ring attached to selenium, whilst the two signals at 7.25 ppm and 6.85 ppm were assigned as the aromatic protons of the PMB protecting group. There were two apparent AB quartets at 4.49 ppm and also at 4.18 ppm. The AB quartet at 4.49 ppm was attributed to the oxymethylene of the 4-methoxybenzyl group, due to the HMBC correlations with the aromatic protons. The

AB quartet at 4.18 ppm exhibited HMBC correlations to the two carbon signals at 89.1 and 84.4 ppm, identifying it as the oxymethylene *alpha* to the alkyne. The methylene protons *alpha* to selenium at 3.94-3.88 and 3.09 ppm were easily identifiable by their HMQC correlation to the carbon signal at 32.8 ppm. This is characteristic of the carbon-selenium bond, and allowed for discrimination of these diastereotopic protons from the oxymethylene protons. The COSY correlations between the protons at 3.94-3.88 and 3.09 ppm and the proton at 4.94 ppm allowed for its identification as the methine proton *alpha* to the TIPS ether. The singlet observed at 5.42 ppm showed no HMQC correlation and was therefore assigned as the hydroxyl proton. Finally, the molecular ion of 839.3977 m/z was obtained corresponding to $C_{44}H_{72}O_5Si_2(80)SeNa^+$, further supporting the assignment of the structure as alkyne **263*b***.

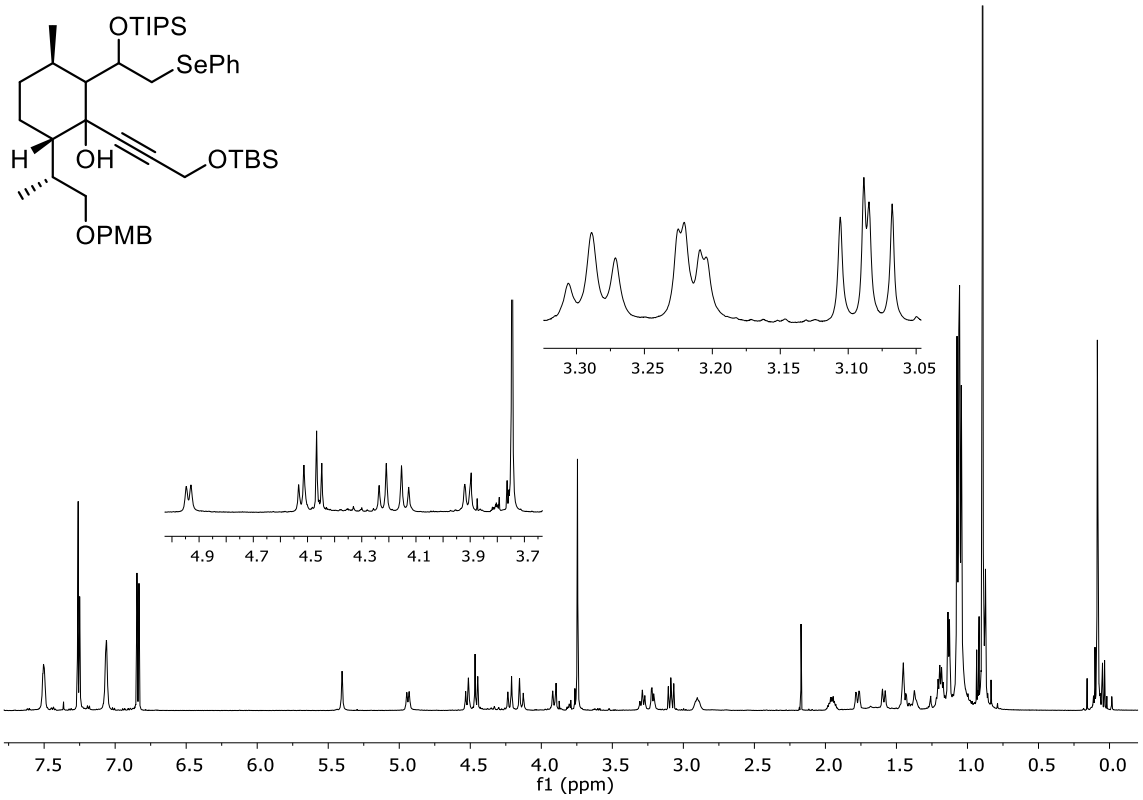


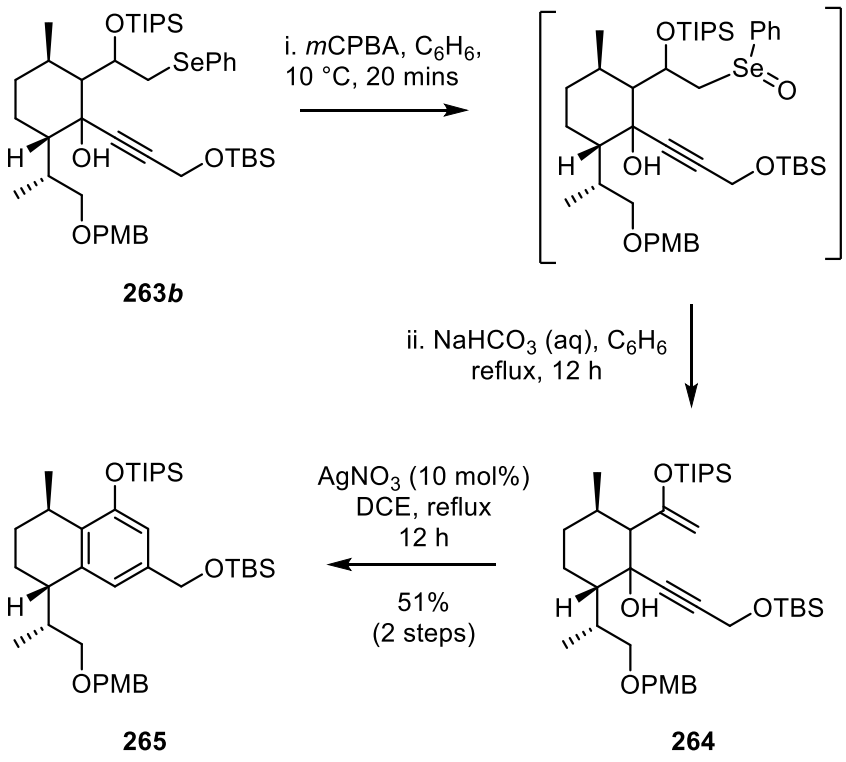
*Figure 4.2: ^{1}H NMR spectrum of alkyne **263b***

The addition of the commonly used polar aprotic solvent DMPU as co-solvent was necessary during the synthesis of the 8-hydroxycalamenenes (Scheme 3.28) and the model study with (−)-isopulegone (**255**). However, the reaction of PMB ketone **262** with lithium acetylide **253*b*** proceeded smoothly without DMPU. The increased reactivity of PMB ketone **262** compared to the analogous benzyl ketone **250** could be due to the different electronics of the 4-methoxybenzyl protecting group. Ketone **262**

could adopt a less-hindered conformation, allowing nucleophilic attack of the lithium acetylide at the C1 carbonyl. Additionally, the oxygen atoms of the 4-methoxybenzyl group may chelate the lithium ion, which could result in a different conformation or increased nucleophilicity of the lithium acetylide.

4.4 Investigation of the Annulation Reaction

With the silyloxy selenide and 3-hydroxy alkyne functionality installed successfully, elimination of the phenylselenide needed to occur in order to form the silyl enol ether. Phenylselenide **263*b*** was first treated with *m*-chloroperbenzoic acid (Scheme 4.13) in anhydrous benzene for 20 minutes at 10 °C.[139] A saturated aqueous solution of $NaHCO_3$ was added, with the intermediate selenoxide heated at reflux overnight in the biphasic mixture. The harsh conditions enabled the unfavourable elimination towards oxygen, producing the silyl enol ether **264**.



*Scheme 4.13: Synthesis of the silyl enol ether **264** and arene **265***

Enyne **264** was dissolved in DCE and the resulting solution heated to reflux. A catalytic amount of $AgNO_3$ (10 mol%) was added and the solution heated at reflux in darkness for 12 hours. Following column chromatography, arene **265** was isolated as a colourless

oil. Interestingly, comparable yields were obtained for the benzannulation reaction when the crude enyne was used.

Analysis of the ^{1}H NMR spectrum (Figure 4.3) revealed two signals at 6.68 and 6.60 ppm corresponding to the protons of the newly established aromatic ring. There was a sharp singlet at 4.61 ppm corresponding to the benzylic methylene protons *alpha* to the primary TBS ether. The diastereotopic protons *alpha* to the OPMB functional group appeared at 3.31 and 3.24 ppm, whilst the benzylic methine protons were apparent at 3.20-3.14 ppm and 2.71 ppm. The remainder of the ^{1}H NMR spectrum corresponding to the cyclohexyl ring was similar to that of the starting material.

The ^{13}C NMR spectrum (Figure 4.3) also contained diagnostic peaks. The signals previously observed at 89.1 and 84.4 ppm corresponding to the alkyne were absent. There were 10 carbon signals attributable to the two aromatic rings, whilst there were also three signals at 74.0, 72.7 and 65.1 ppm corresponding to oxymethylene carbons. The HRESIMS of 663.4226 m/z was obtained corresponding to a molecular ion of $C_{38}H_{64}O_4Si_2Na^+$, confirming the structure of tetrahydronaphthalene **265**.

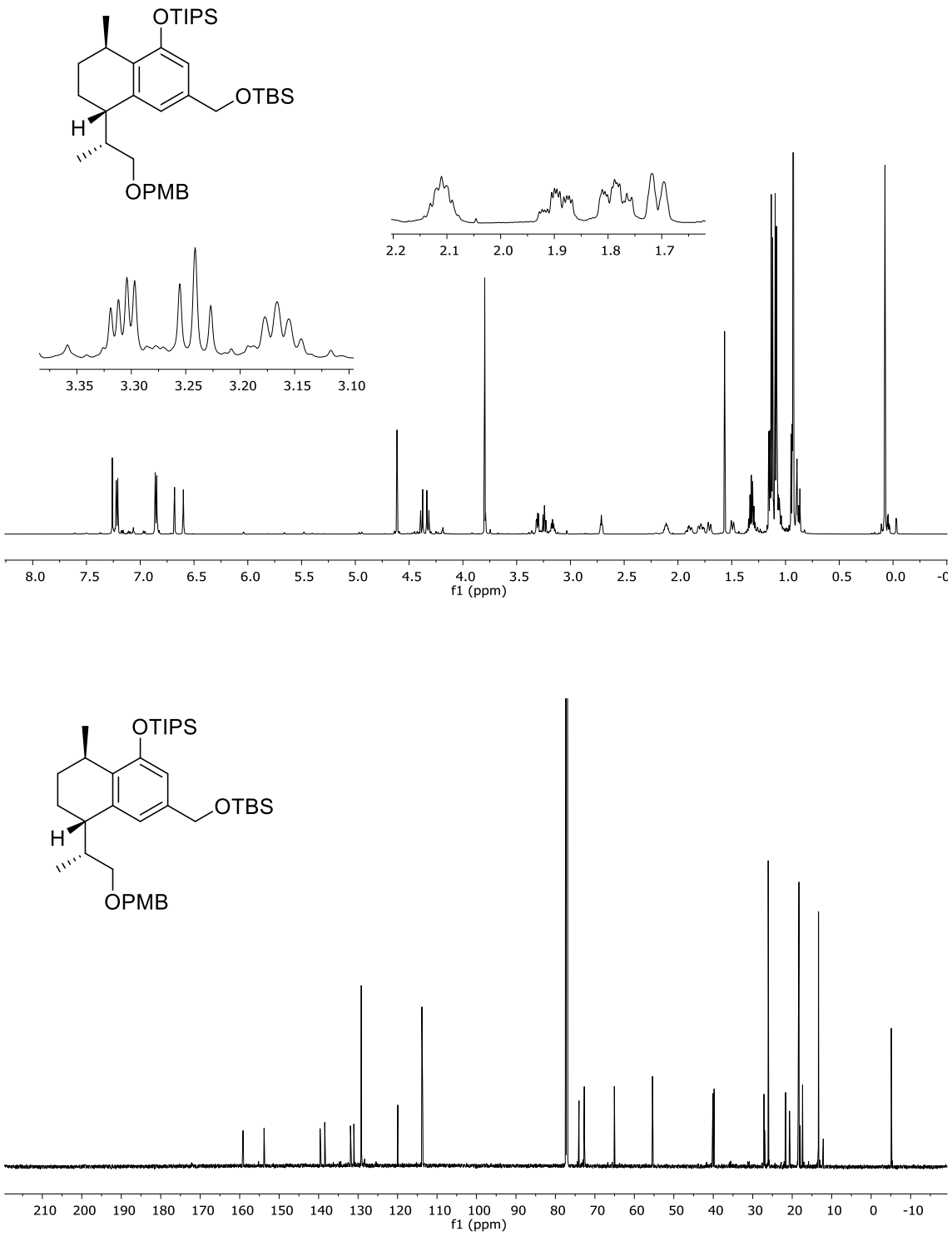
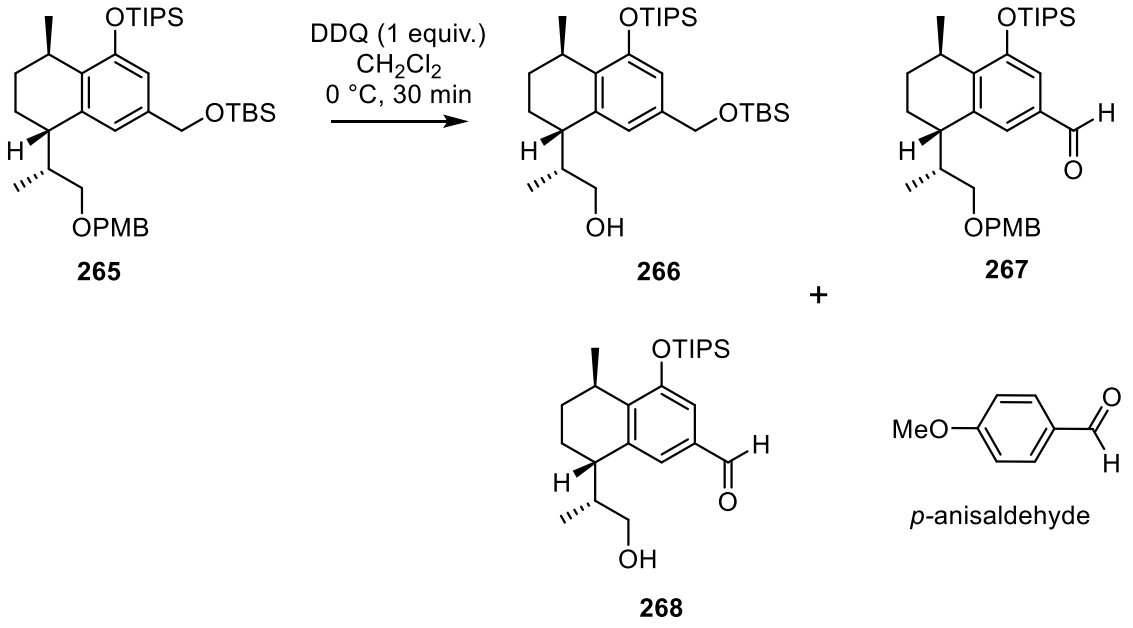


*Figure 4.3: ^{1}H and ^{13}C NMR spectrum of arene **265***

4.5 4-Methoxybenzyl Protecting Group Removal

With tetrahydronaphthalene **265** synthesised, installation of the prenyl side chain was attempted. The first step in this process was the removal of the 4-methoxy benzyl (PMB) protecting group. Once the free alcohol was obtained, oxidation of C12 to the aldehyde would allow for elaboration of the side chain. However, when arene **265** was treated with 1.1 equivalents of DDQ, a complex mixture of products was observed (Scheme 4.14). Column chromatography afforded four major fractions. Two were the expected *p*-anisaldehyde and primary alcohol **266** resulting from PMB deprotection, whilst the two other products were side-products attributed to chemoselectivity issues.



*Scheme 4.14: DDQ oxidation of PMB ether **265***

The structure for aldehyde **268**, and in particular, the location of the aldehyde was determined by 1D and 2D NMR spectroscopy. The most useful information obtained was from the ^{1}H NMR spectrum (Figure 4.4). There was one signal present at 9.85 ppm, indicating the presence of an aldehyde. There was no observable coupling for the aldehyde proton, indicating no adjacent ^{1}H nuclei. This indicated that the benzylic C13 position had been oxidised. The proton signals at 3.55 and 3.48 ppm were characteristic of diastereotopic oxymethylene protons. They exhibited a COSY correlation to one proton at 2.06 ppm, which in turn had a correlation to the methyl doublet at 0.97 ppm and the triplet observed at 2.84 ppm. These protons were therefore assigned to the side chain, with the signal at 2.84 ppm due to the C4 benzylic methine. The proton at 3.28

ppm appeared as a pentet, and exhibited COSY correlations with the multiplet at 1.87-1.83 ppm, the multiplet at 1.60-1.58 ppm and also the methyl doublet at 1.18 ppm. This was attributed to the C1 benzylic methine position.

Considering that C13 aldehyde **267** was isolated in conjunction with recovered starting material, this suggested the regioselective SET oxidation of PMB ether **265** was not possible. Instead, the deprotection of the 4-methoxybenzyl group using non-oxidative conditions was investigated.

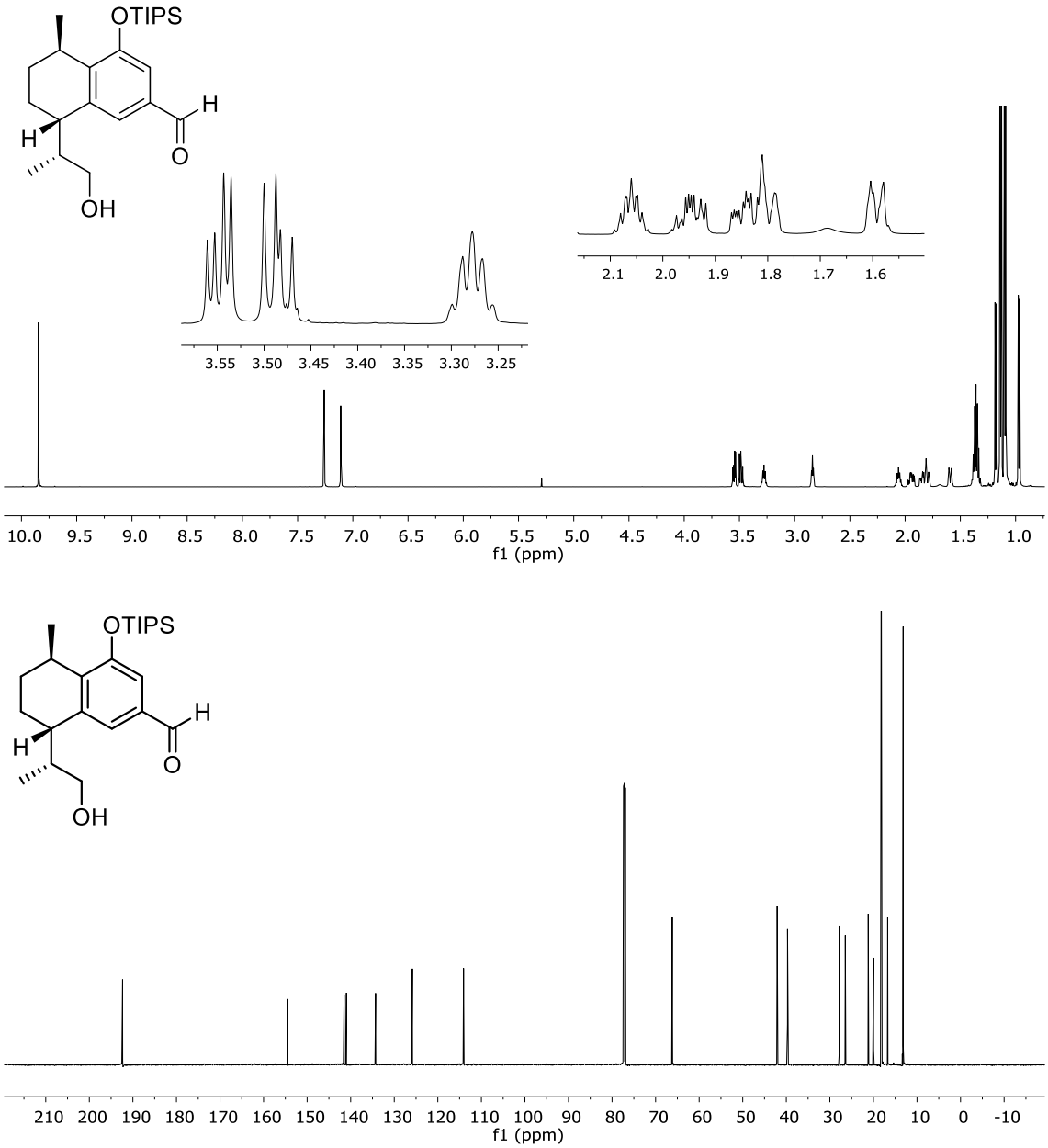
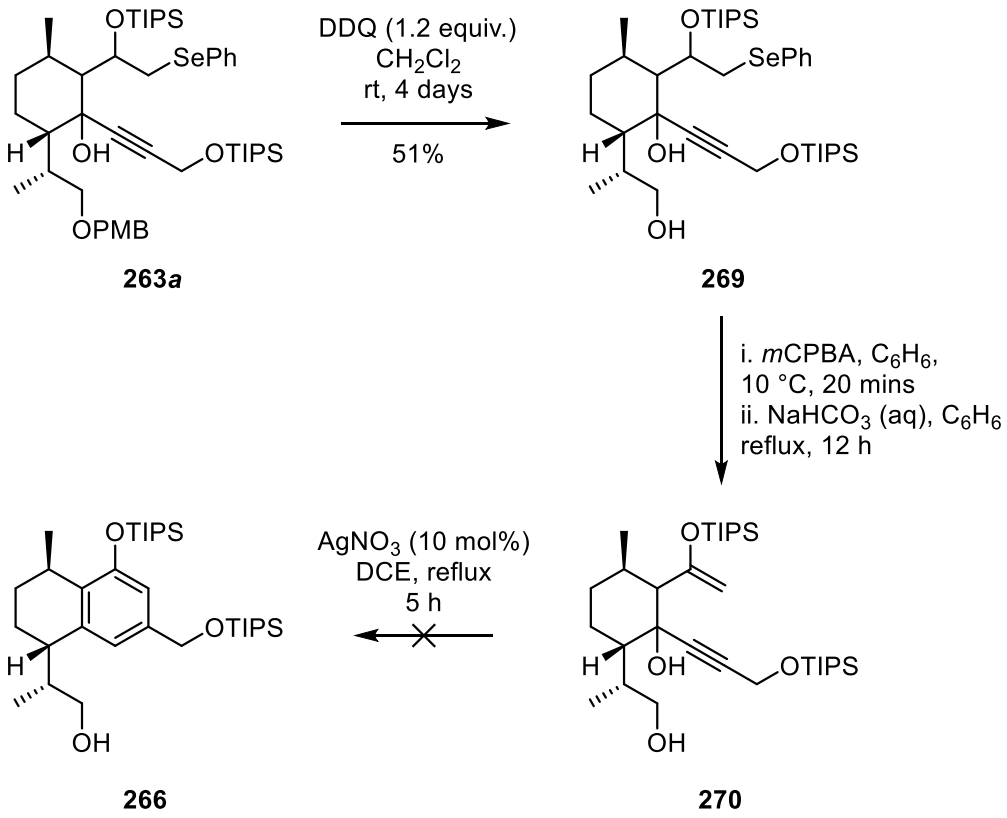


*Figure 4.4: ^{1}H and ^{13}C NMR spectrum of aldehyde **268***

4.5.1 Alternative protecting group removal strategies

A number of deprotection methods have been reported that do not rely on SET oxidation of the PMB group. The non-oxidative conditions include use of Lewis acids such as silver salts[140], triflic acid[141] and $POCl_3$.[142] These conditions were trialled, but in each case only starting materials or complex mixtures of products were obtained. As an alternative strategy, removal of the protecting group prior to ene-yne cyclosimerisation was attempted to provide access to the hydroxy-serrulatane **266**.

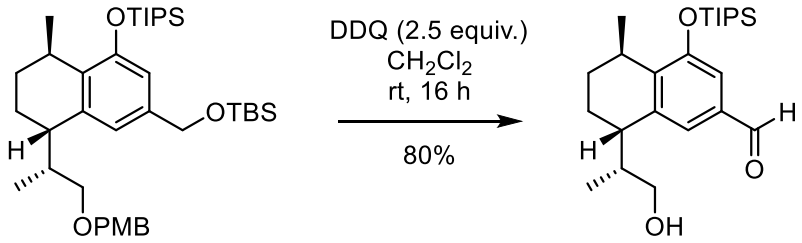
Starting from alkyne **263*a***, treatment with DDQ in CH_2Cl_2 for 4 days at room temperature afforded the primary alcohol **269** in 51% yield as a colourless oil (Scheme 4.15). The phenylselenide was oxidised with *m*CPBA to afford the intermediate selenoxide, and subsequently heated under reflux overnight with sodium bicarbonate to afford the silyl enol ether **270**. However, the benzannulation conditions resulted in a complex mixture of products, with no ^{1}H NMR signals resembling alcohol **266**. This result suggested that the free alcohol may be incompatible with the cycloisomerisation conditions and should remain protected until the tetrahydronaphthalene core is established.



*Scheme 4.15: Early-stage deprotection of PMB ether **263a***

4.5.2 Oxidative deprotection of the PMB and oxidation of C19

Considering the poor results obtained through an early deprotection sequence, simultaneous removal of the PMB protecting group and oxidation of the benzylic C19 position was attempted. Treatment of the PMB ether **265** with 2.5 equivalents of DDQ afforded the deprotected aldehyde **268** in 80% yield (Scheme 4.16). Although not ideal to oxidise both positions, C19 of EN4 is in the carboxylic acid oxidation state. This negates the need for selective deprotection and oxidation in two separate steps later on, meaning the overall number of steps should not increase.



265 **268**

*Scheme 4.16: Oxidation of PMB ether **265** with DDQ (2 equivalents)*

The reaction to produce the deprotected aldehyde **268** proceeded remarkably smoothly, with addition of an excess of DDQ in CH_2Cl_2/pH 7 phosphate buffer mixture (10:1) allowed to stir for 16 hours. Following column chromatography (20% EtOAc/X4) the aldehyde was isolated in high purity as a colourless oil.

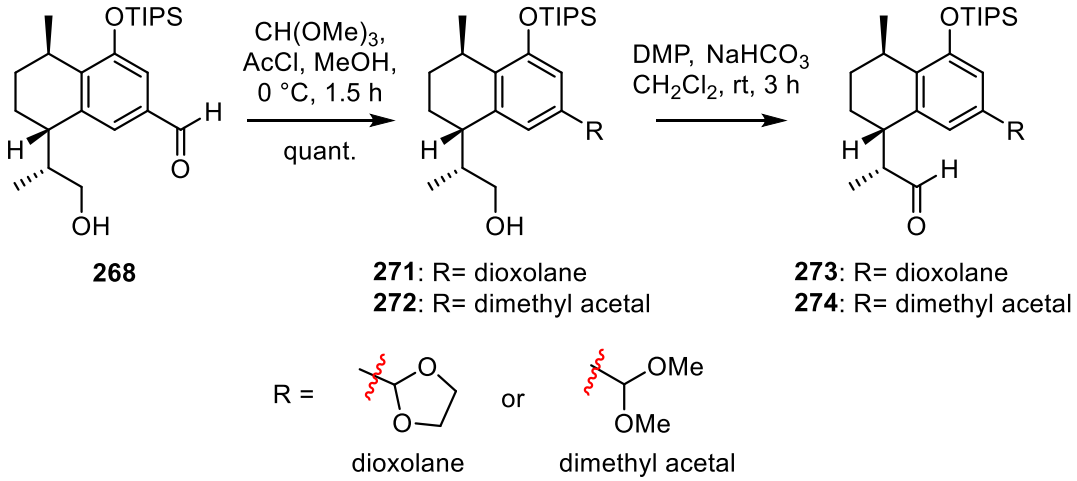
4.6 Attempted Wittig Olefination Conditions

With aldehyde **268** synthesised efficiently, the next steps in the synthetic sequence focused on side chain installation. In order to attach the prerequisite prenyl side chain, the simplest method of attachment could be seen as Wittig olefination. Oxidation of the alcohol at C12 to the corresponding aldehyde was required. However, the benzylic aldehyde would also react under Wittig olefination conditions to give a mixture of side-products.

4.6.1 Protection of the benzylic aldehyde

Protection of the aldehyde was essential to avoid chemoselectivity issues associated with side chain installation. Initial attempts at protecting aldehyde **268** as either the dimethyl acetal **271** or dioxolane **272** were successful, with each synthesised in near

quantitative yield (Scheme 4.17).[143] However, benzylic acetals are susceptible to acidic conditions, and this was highlighted when NMR in deuterated solvents was conducted. Preparation of NMR samples with newly opened $CDCl_3$ resulted in no observable acetal signals. Only when using deuterated chloroform that had been stored over K_2CO_3 were any acetal signals detected. This instability was exemplified during oxidation of the substrates. Even when Dess-Martin Periodinane was used in the presence of sodium bicarbonate, there were multiple aldehyde signals detected in the ^{1}H NMR for aldehydes **273** and **274**. This approach of aldehyde protection as the acetal was therefore abandoned.



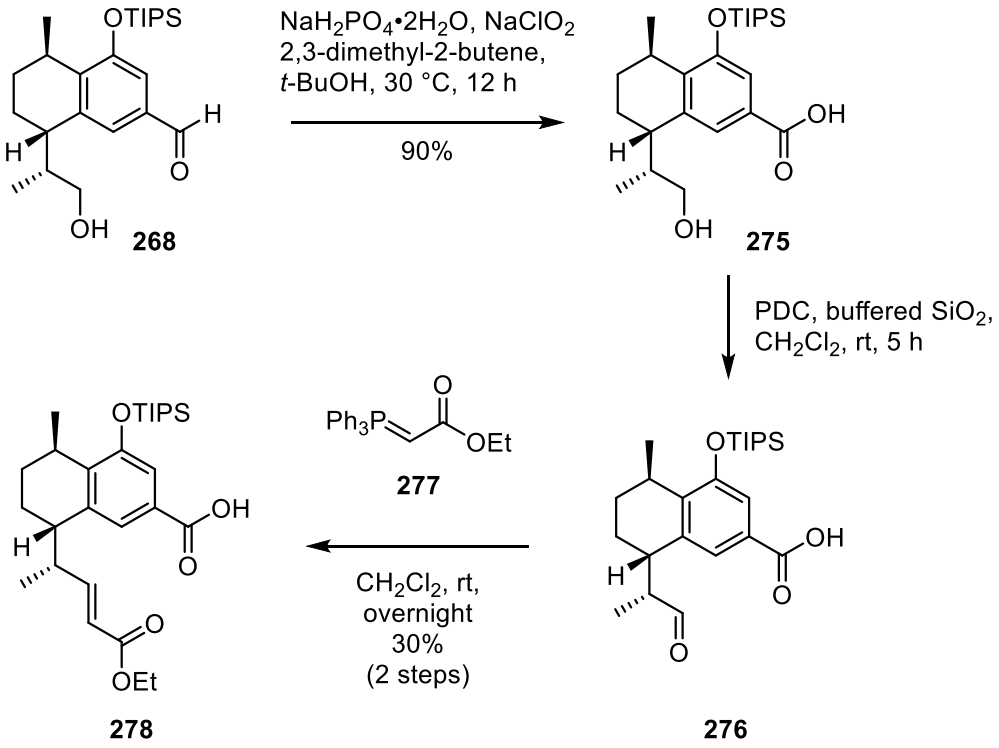
*Scheme 4.17: Acetalisation of aldehyde **268** and attempted oxidation*

4.6.2 Protection as the carboxylic acid

The instability of the benzylic acetals highlighted the need for a more robust protecting group at C13 that would be stable over multiple steps. Instead of protecting C13 in the aldehyde oxidation state, protection in the carboxylic acid oxidation state could be possible. This meant that the C13 aldehyde needed to be oxidised selectively in the presence of the C12 alcohol. Oxidation to the carboxylic acid would be useful as EN4 contains the carboxylic acid functionality at the benzylic position.

The first oxidation attempted was the Pinnick oxidation (Scheme 4.18).[144,145] Treatment of aldehyde **268** with NaH_2PO_4 and $NaClO_2$ afforded the carboxylic acid **275** in 90% yield. The reaction was conducted in the presence of 2, 3-dimethyl-2-butene as a scavenger for electrophilic chlorine that was generated during the reaction. Analysis of the ^{1}H NMR spectrum revealed that the aldehyde signal previously observed at 9.85 ppm had disappeared. The two aromatic protons previously at 7.26 and 7.11 ppm for

aldehyde **268** had shifted downfield to 7.52 and 7.34 ppm due to the increased electron withdrawing effect of the carboxylic acid. The ^{13}C NMR spectrum also revealed that the signal at 192.4 ppm corresponding to the aldehyde had disappeared, whilst a signal at 172.1 ppm indicated the presence of a carboxylic acid. Having introduced the necessary oxidation state for the EN4 natural product, side chain installation could now proceed.



*Scheme 4.18: Oxidation of aldehyde **268** and chain extension*

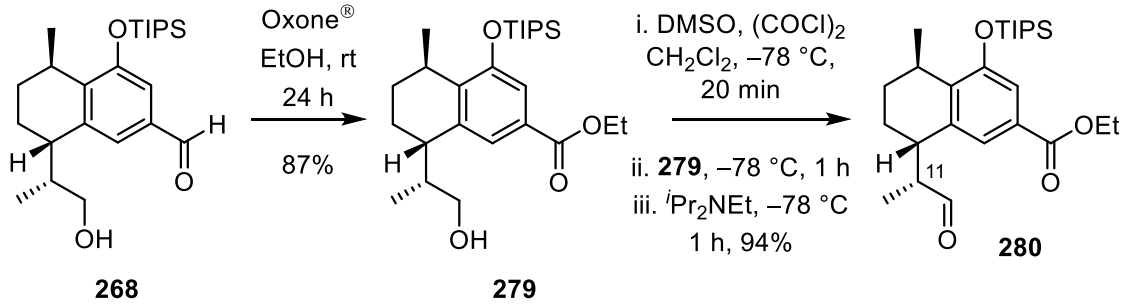
Treatment of carboxylic acid **275** with PDC in CH_2Cl_2 for five hours afforded aldehyde **276**. Addition of stabilised ylide **277**[146] gave α, β-unsaturated ester **278** as a light yellow oil in only 30% yield. Considering the straightforward nature of the chemical transformations, this yield was lower than expected. This was most likely due to issues associated with the polarity or instability of the carboxylic acid.

4.6.3 Protection as the benzylic ester

Another option allowing for the selective oxidation of the benzylic aldehyde was Oxone® esterification.[147] Aldehyde **268** was dissolved in ethanol and Oxone® added at room temperature (Scheme 4.19). After stirring for 16 hours, the reaction mixture was filtered (ethanol) and the organic layer concentrated *in vacuo*. The residue was then taken up in EtOAc and water, and the aqueous layer extracted with EtOAc. Importantly,

EtOAc was not used as solvent until removal of the Oxone® through filtration, due to its ability to promote the transesterification of the alcohol functionality at C12. Following column chromatography, aromatic ester **279** was obtained as a colourless oil in 87% yield.

Disappearance of the aldehyde signal at 9.85 ppm indicated that the starting material had reacted. There was appearance of a multiplet at 4.38–4.27 ppm and triplet at 1.37 ppm corresponding to the oxymethylene and methyl group of the ethyl ester. As with the carboxylic acid, the aromatic protons were shifted downfield to 7.45 ppm and 7.30 ppm whilst the oxymethylene protons of the primary alcohol appeared at a similar chemical shift.



*Scheme 4.19: Oxone® Esterification and Swern oxidation for synthesis of aldehyde **280***

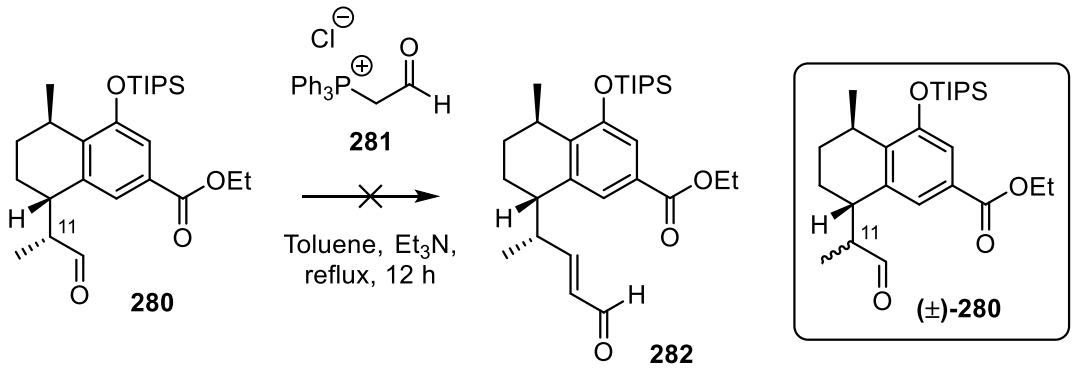
Swern Oxidation[48,148] of aromatic ester **279** was conducted using the sterically hindered diisopropylethyl amine as base to avoid epimerisation. The aldehyde **280** was obtained in 94% yield as a colourless oil. Analysis of the ^{1}H NMR spectrum indicated one aldehyde signal and therefore no epimerisation occurred.

With the benzylic aldehyde protected in the carboxylic acid oxidation state, but as the more stable and lipophilic ester **280**, the side chain could be extended. Considering that the tetrahydronaphthalene **280** had an ester functional group, the chain extension strategy could not employ reduction steps due to the obvious chemoselectivity issues. The ylides therefore had to possess the correct or lower oxidation state for chain extension.

*4.6.4 Attempted Wittig olefination with ylide **281***

Treatment of aldehyde **280** with semi-stabilised ylide **281** in toluene heated at reflux with triethylamine unfortunately produced none of the expected enal **282** (Scheme 4.20). Instead, due to the presence of the α-methly substituent, epimerisation of

aldehyde **280** occurred. Therefore, an alternative olefination reagent or protocol was sought.

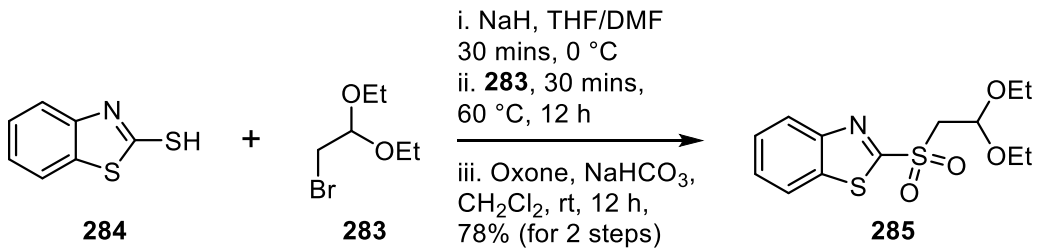


*Scheme 4.20: Attempted Wittig olefination with semi-stabilised ylide **281***

4.7 Investigation of Julia-Kocienski Olefination Conditions

Considering the poor reactivity of aldehyde **280** with semi-stabilised ylides, the reactivity of sulfones in the Julia-Kocienski olefination reaction was investigated. Bromoacetaldehyde diethyl acetal **283** is commercially available but is also easily synthesised in one step from the commercially available ethyl vinyl ether and NBS. Care was taken during the synthesis and handling of this chemical as it is a lachrymator and has been reported to be fatal if inhaled.[149]

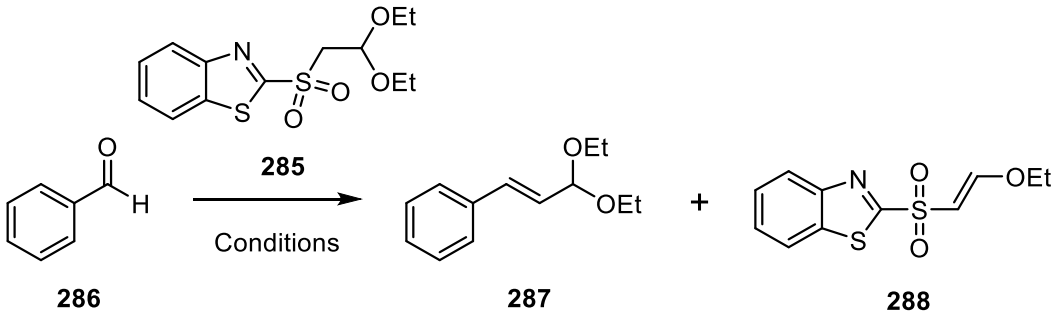
The sodium salt of 2-mercaptobenzothiazole **284** was alkylated through addition of bromoacetaldehyde diethyl acetal **283** (Scheme 4.21). The crude sulfide was then oxidised using Oxone®. Sulfone **285** was obtained as light yellow needles with a melting point of 89–91.5 °C. Analysis of the ^{1}H NMR spectrum identified signals characteristic of the benzothiazole at 8.22, 8.01, 7.63 and 7.58 ppm. The acetal proton was apparent at 5.11 (t, J = 5.4 Hz, 1H), whilst the oxymethylene protons appeared at 3.58 (dq, *J*=9.2, 7.0 Hz, 2H) and 3.49 ppm (dq, *J*=9.2, 7.1 Hz, 2H). Resonances attributed to the methyl groups appeared at 0.98 ppm (t, *J*=7.0 Hz, 6H).



*Scheme 4.21: Synthesis of sulfone diethyl acetal **285***

4.7.1 Julia-Kocienski olefination with model aldehydes

It is well documented that sulfones containing β-hydroxy, β-alkoxy and β-acyloxy functional groups are prone to β-elimination when treated with base.[150] However, the elimination can be mitigated by employing Barbier conditions, whereby the sulfone and aldehyde are pre-mixed followed by slow addition of base. To this end, benzaldehyde was chosen as a model aldehyde to react with sulfone **285** under a variety of conditions (Scheme 4.22). Sulfone **285** was dissolved in tetrahydrofuran and cooled to −78 °C with LiHMDS (1.1 equivalents) added dropwise. The pre-metallation time was varied from 10 seconds to 5 minutes before the addition of benzaldehyde **286**, with the resulting yellow solution allowed to stir at −78 °C for 1 hour. Following isolation, the crude ^{1}H NMR spectra were used to determine the ratio of cinnamaldehyde diethyl acetal **287** to residual benzaldehyde **286**.



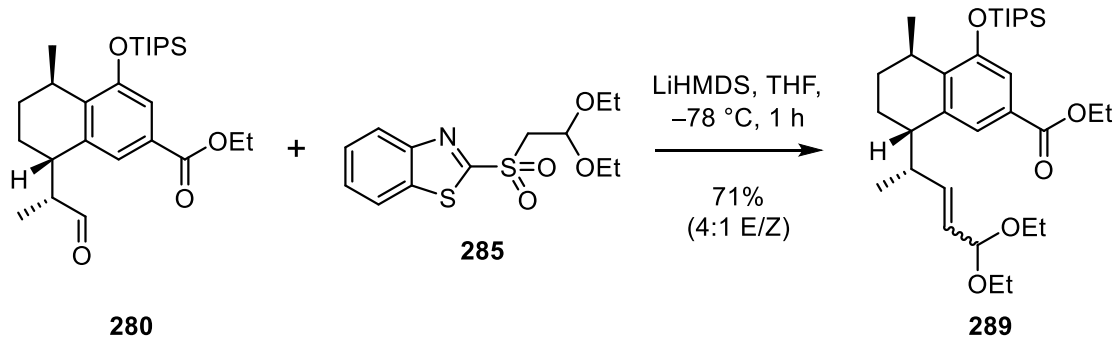
*Scheme 4.22: Model Julia-Kocienski olefination with benzaldehyde **286***

The longer pre-metalation times of 2 and 5 minutes resulted in negligible yields of allylic acetal **287**, instead returning the starting benzaldehyde and eliminated sulfone **288**. Even with a pre-metallation time of 10 seconds only minute quantities of the cinnamaldehyde diethyl acetal **287** was obtained, with almost quantitative β-elimination of the sulfone diethyl acetal **285**. Instead, Barbier conditions were used whereby the sulfone **285** (2 equivalents) and benzaldehyde **286** were pre-mixed. By treating the

mixture at −78 °C to LiHMDS dropwise over 5 minutes, and allowing the solution to stir for 1 hour at −78 °C, the corresponding alkene **287** was obtained in 77% yield with modest selectivity for the (*Z*)-alkene. The β-eliminated sulfone **288** was also obtained, but due to the excess of sulfone used, did not influence the yield of the reaction significantly.

*4.7.2 Attempted side chain installation with sulfone **285***

With the reaction conditions optimised for benzaldehyde, addition of sulfone diethyl acetal **285** to aldehyde **280** was attempted (Scheme 4.23). Aldehyde **280** and sulfone **285** (2 equivalents) were dissolved in THF and the resulting solution cooled to −78 °C. LiHMDS (2 equivalents) was added dropwise over 5 minutes, and the resulting yellow solution stirred for 1 hour then allowed to warm to −10 °C over 3 hours. Column chromatography attained separation of allylic acetal **289** and the unsaturated sulfone **288**.



*Scheme 4.23: Julia-Kocienski olefination with aldehyde **280***

Analysis of the ^{1}H NMR spectrum (Figure 4.5) revealed two distinct sets of signals attributable to the major (*E*)-isomer and minor (*Z*)-isomer. The vinyl protons associated with **(*E*)-289** were apparent at 5.52 and 5.43 ppm, appearing as a triplet and doublet of doublets respectively. The olefinic protons of **(*Z*)-289** appeared at 5.63 ppm and 5.36 ppm as doublets of doublets. The diagnostic acetal protons appeared at 5.05 ppm and 4.76 ppm for the major and minor isomers, respectively. **(*Z*)-289** was not separable from **(*E*)-289**, but considering the double bond geometry would be lost following hydrogenation; both were carried through into the following reactions.

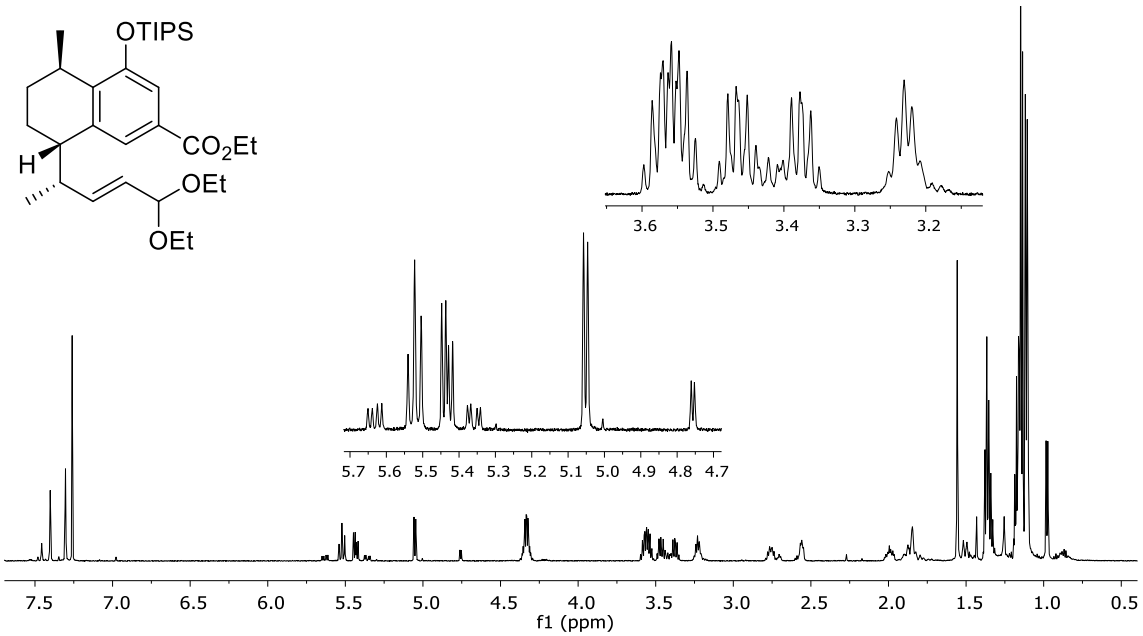
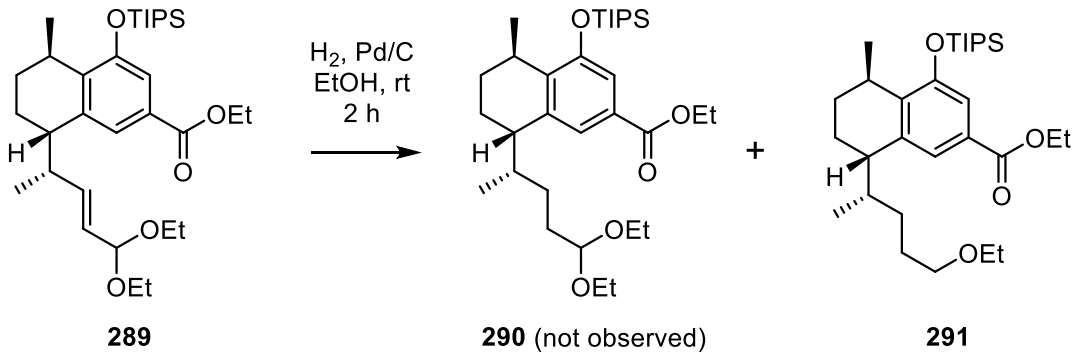


*Figure 4.5: ^{1}H NMR spectrum of allylic acetal **289***

*4.7.3 Hydrogenation of allylic acetal **289***

The allylic acetal **289** was subjected to hydrogenation conditions (Scheme 4.24). The reaction was monitored through TLC, with the reaction stopped following disappearance of the R_f spot corresponding to the starting material. Analysis of the ^{1}H NMR spectrum (Figure 4.6) indicated the presence of only one product.



*Scheme 4.24: Hydrogenation of allylic acetal **289***

The ^{1}H NMR spectrum revealed that there was no longer an alkene in the molecule. Disappearance of the 4:1 mixture of olefinic proton signals corresponding to the *E/Z* isomers between 5.65-5.35 ppm indicated that the double bond had been reduced. Interestingly though, there was no longer a signal corresponding to the acetal, which would be expected at ~5 ppm. There were four signals characteristic of oxymethylene protons. However, the product corresponding to loss of the acetal and an ethoxy group

would also have four signals in this region. Perhaps more characteristic was the integration of the triplet at 1.14 ppm, which integrated for 3H, confirming the loss of an ethoxy group. The characteristic NMR signals indicated that instead of isolating the expected aliphatic acetal **290**, the aliphatic ether **291** was obtained.

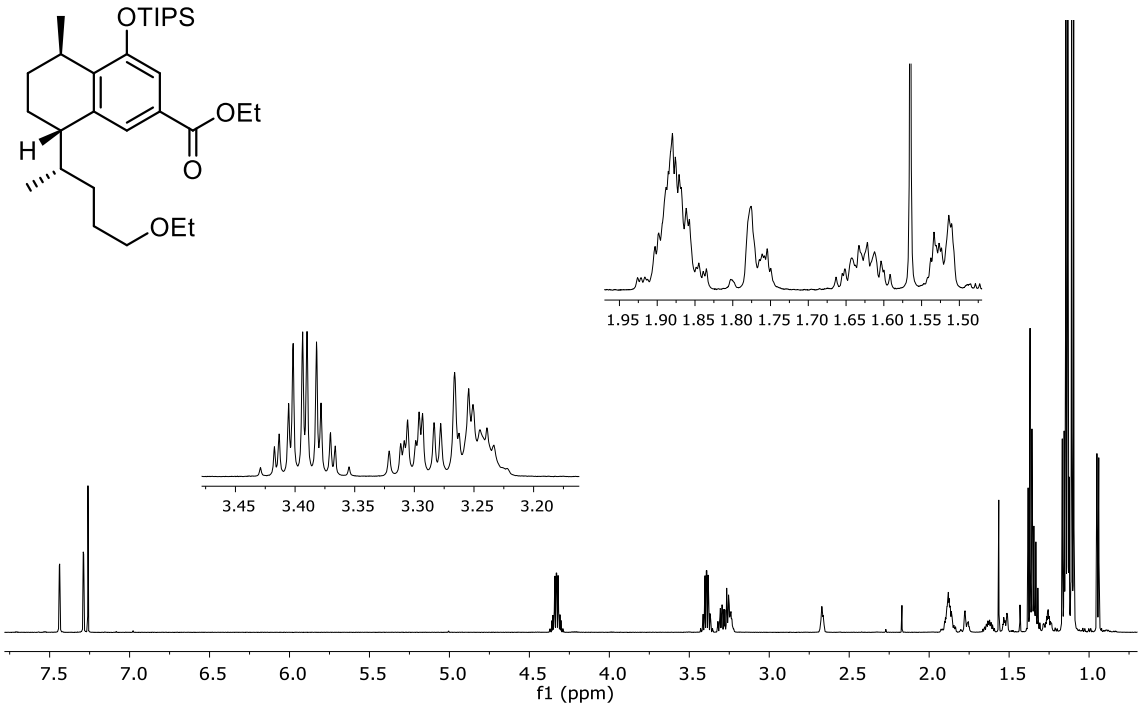
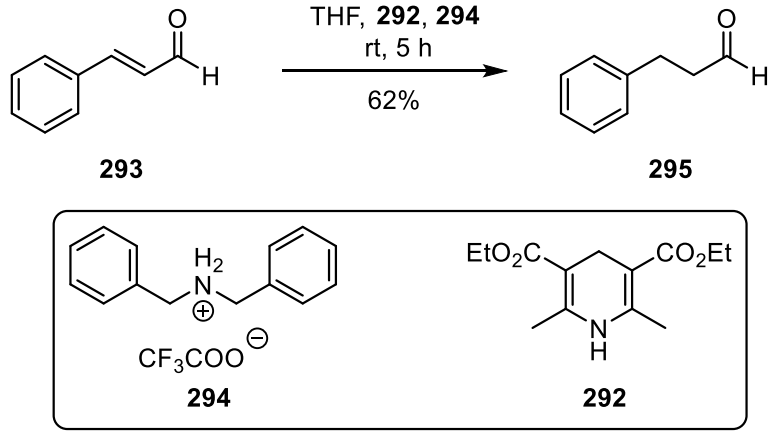


*Figure 4.6: ^{1}H NMR spectrum of ether **291***

4.7.4 Organocatalytic Transfer Hydrogenation

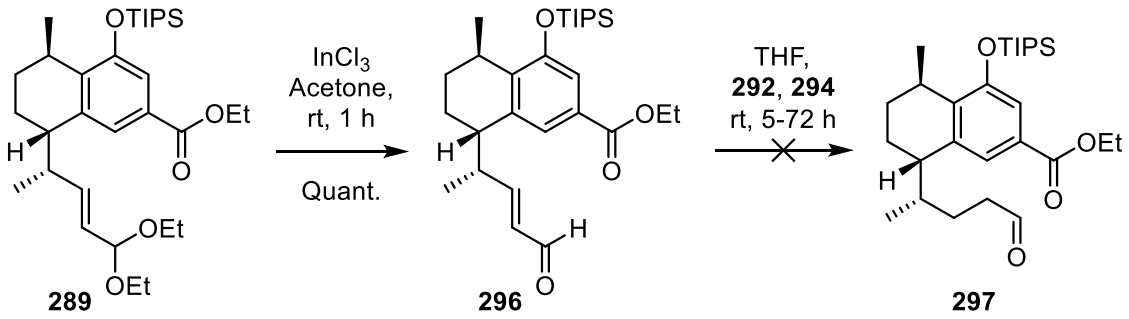
The unfortunate reduction of the acetal meant that an alternative reducing agent was needed. In the literature, Hantzsch ester **292** has been used for the organocatalytic transfer hydrogenation of enals.[151] The Hantzsch ester **292** was synthesised in one step from ethyl acetoacetate, paraformaldehyde and ammonium acetate,[152] whilst the dibenzylammonium trifluoroacetate salt was prepared from dibenzylamine and trifluoroacetic acid. To test the reaction conditions cinnamaldehyde (**293**), Hantzsch ester **292** and dibenzylammonium trifluoroacetate (**294**) were dissolved in THF and the resulting yellow solution stirred for 5 hours at room temperature (Scheme 4.25). Following purification, the aliphatic aldehyde **295** was obtained in 62% yield.



*Scheme 4.25: Organocatalytic Transfer Hydrogenation of cinnamaldehyde **293***

The diethyl acetal **289** was hydrolysed using indium (III) chloride, which afforded enal **296** as a 4:1 mixture of E/Z isomers in quantitative yield (Scheme 4.26).[153] The enal **296** was subjected to the hydrogenation conditions, with the time varied between 5 hours and 72 hours. Unfortunately, even after stirring for 72 hours at room temperature, aliphatic aldehyde **297** was not observed. Isomerisation of the alkene led to a 50/50 mixture of E/Z isomers being observed. This indicated that the iminium ion was forming, but reduction of the iminium ion with the Hantzsch ester **292** did not occur, potentially due to the sterics of the substrate.

The inability to remove the double bond chemoselectively meant an alternative sulfone was required with the oxygen functionality protected in a lower oxidation state.

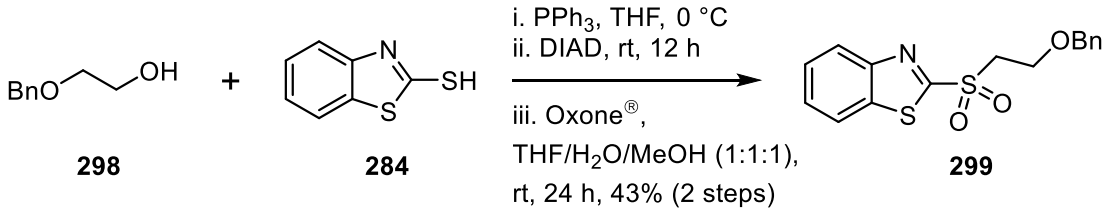


*Scheme 4.26: Attempted Organocatalytic Transfer Hydrogenation of enal **296***

*4.7.5 Julia-Kocienski olefination with benzyl sulfone **299***

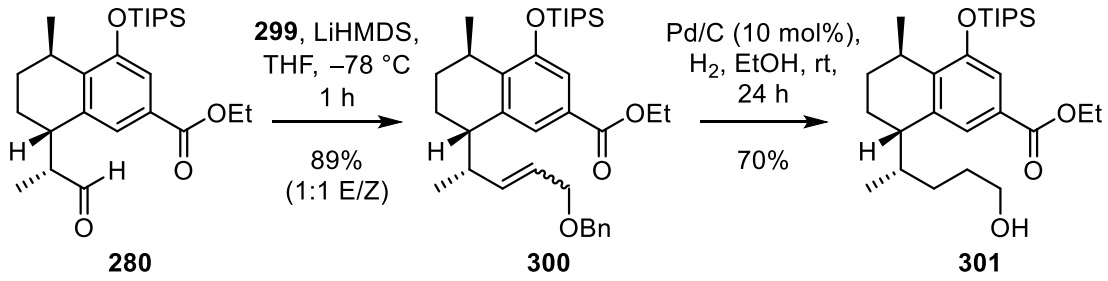
Mitsunobu reaction with 2-mercaptobenzothiazole **284** and benzyl ether **298** afforded the sulfide in modest yield, which was oxidised to sulfone **299** using Oxone® as the oxidant (Scheme 4.27). Purification of the sulfone by column chromatography was not possible as the sulfone co-eluted with an unknown side-product. After trialling a

number of solvents for recrystallisation, dissolving the substrate in diethyl ether, followed by slow evaporation of the solvent, led to off-white needles of the benzyl sulfone.



*Scheme 4.27: Synthesis of the benzyl sulfone **299***

Using the same Julia-Kocienski olefination conditions that were employed in the test reaction, the sulfone **299** and aldehyde **280** were dissolved in THF (Scheme 4.28). Upon slow addition of base, disappearance of the starting materials was observed by TLC. After 1 hour, analysis of the crude ^{1}H NMR spectrum revealed that the reaction was successful. However, where the sulfone diethyl acetal **285** afforded a modest ratio of 4:1 *E*/*Z* isomers, the benzyloxy sulfone **299** afforded roughly a 1:1 mixture of *E*/*Z* isomers. Although the selectivity was poor, the allylic benzyl ether **300** was obtained in 89% yield. Furthermore, the double bond would later be removed, meaning the geometry was inconsequential.



*Scheme 4.28: Synthesis of aliphatic alcohol **301***

Because the molecule now contained a benzylic ether, during the hydrogenolysis it was expected that saturation of the double bond as well as benzyl ether deprotection would be possible. The purity of **300** proved to be vital, as small quantities of sulfur-containing compounds are known to poison palladium catalysts. This meant that even minute quantities of residual sulfone **299** may be capable of rendering all of the catalyst inactive. The double bond was removed easily, with the saturated benzyl ether observed

after 2 hours. The hydrogenolysis was continued for a further 12 hours to remove the benzyl protecting group, affording alcohol **301** in 70% yield.

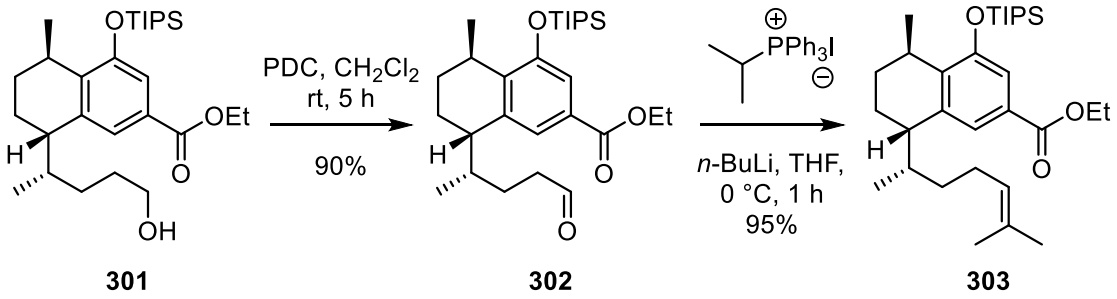
^{1}H NMR analysis revealed that the signals associated with the vinyl protons at 5.57-5.38 ppm and the benzyl ether were absent. The integration of the signal at 4.33 ppm had been reduced to 2H, indicating that the oxymethylene of the benzyl ether was no longer present. The oxymethylene associated with the deprotected primary alcohol appeared at 3.58-3.47 ppm as a multiplet. The ^{13}C NMR spectrum showed only six carbon resonances associated with the tetrahydronaphalene ring, compared to the previously observed 24 carbon resonances associated with the two aromatic rings and alkene isomers. Final structural confirmation was obtained from the HRESIMS, with a molecular ion of 499.3213 m/z observed, corresponding to a molecular formula of $C_{28}H_{48}O_4SiNa^+$.

A minor product was also obtained from this reaction that eluted first during column chromatography, which appeared to have an additional methyl triplet but lacked the oxymethylene functionality of the primary alcohol. Based on the ^{1}H NMR this side-product was proposed to be the saturated alkyl chain, but constituted less than five percent of the overall yield.

4.8 Introduction of the Prenyl Tail

In order to install the prenyl side chain, alcohol **301** was oxidised with PDC to aldehyde **302** in 90% yield (Scheme 4.29). Following column chromatography, the aldehyde was isolated as a colourless oil with an impurity that co-eluted. Reaction success was determined by analysis of the ^{1}H NMR spectrum. The majority of the chemical shifts exhibited little variation from the starting material. The major differences observed were the disappearance of the oxymethylene signals at 3.58-3.47 ppm and the appearance of an aldehyde triplet at 9.65 ppm.

The prenyl tail was introduced through a final Wittig olefination reaction between the ylide of isopropyltriphenylphosphonium iodide and aldehyde **302** (Scheme 4.29). Following column chromatography the prenylated compound **303** was isolated as a colourless oil in 95% yield.



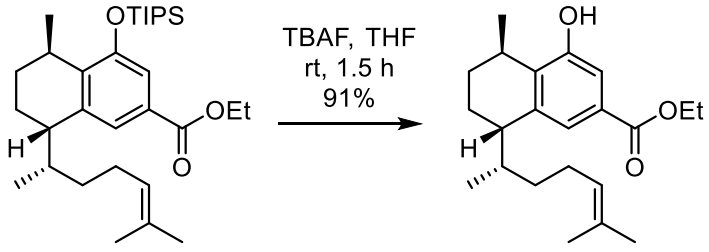
301 **302** **303**

*Scheme 4.29: Synthesis of synthon **303***

Aside from the change in R_f, reaction progress was again determined based on the ^{1}H NMR spectrum. The signal corresponding to the aldehyde was absent, with appearance of an olefinic signal at 4.99–4.91 ppm and an additional two methyl singlets observed at 1.63 and 1.52 ppm corresponding to the prenyl tail. The side chain was now installed successfully, and although **303** varied slightly from the initially proposed bis-silyl synthon **241**, only two steps would be required to synthesise each natural product.

4.9 Total Synthesis of EN3 and EN4

In order to minimise the total number of steps, the silyl protecting group could be removed first. From the free phenol, both natural products could then be accessed through either reduction or hydrolysis of the ester. Silyl ether **303** was treated with TBAF (Scheme 4.30). The solution was stirred for 1.5 hours at room temperature until TLC showed consumption of starting material. Following column chromatography, the phenolic ester **304** was obtained in 91% yield.



303 **304**

*Scheme 4.30: Synthesis of the phenolic ester **304***

The ^{1}H NMR spectrum (Figure 4.7) of phenol **304** reveals that the silyl deprotection was successful, with no signals representative of the triisopropylsilyl group present.

Instead, there was a signal at 5.24 ppm (1H, s) corresponding to the phenol proton. The signal corresponding to the vinyl proton was present at 5-4.92 ppm (1H, m), whilst the benzylic protons were apparent at 3.18 (1 H, pd, *J* 6.9, 2.3) and 2.66 ppm (1 H, td, *J* 5.7, 2.7). The two methyl singlets corresponding to the prenyl side chain were apparent at 1.63 (3 H, s) and 1.54 ppm (3 H, s).

The ^{13}C NMR spectrum (Figure 4.8) contained 22 carbon signals matching the chemical formula of $C_{22}H_{32}O_3$. The signal at 167.1 ppm was attributable to the ester carbonyl, whilst the signals at 131.4 and 124.9 ppm were attributable to the prenyl side chain. The remaining 6 signals ranging from 153.4-113 ppm were attributable to the aromatic ring. The signal at 61 ppm was assigned to the oxymethylene of the ester, whilst the two signals at 42.6 and 38.3 ppm were attributable to the benzylic methines.

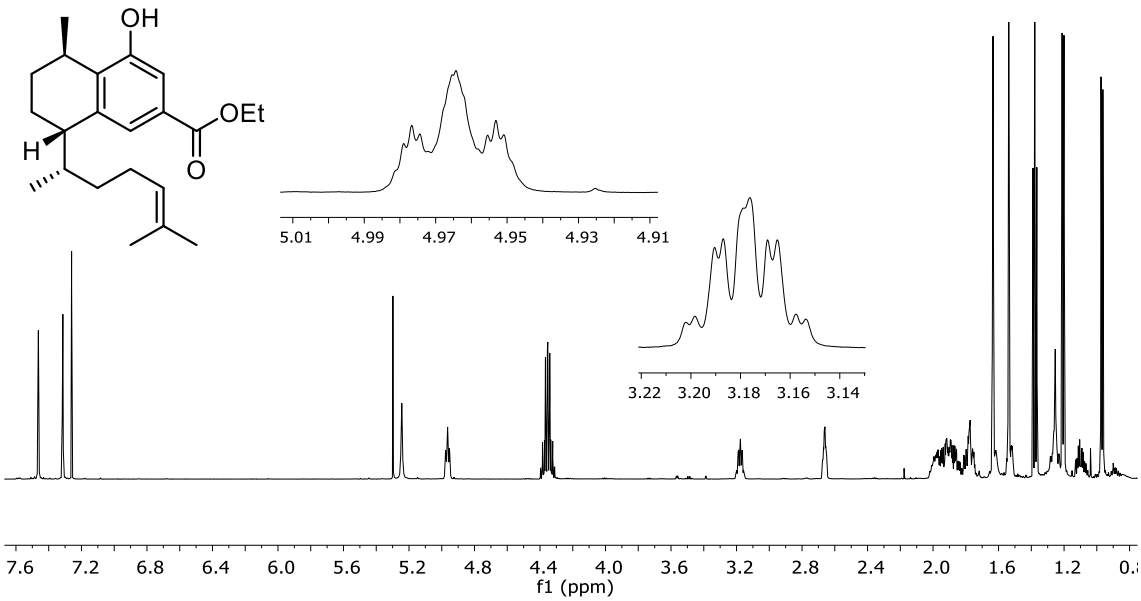


*Figure 4.7: ^1H NMR spectrum of phenolic ester **304***

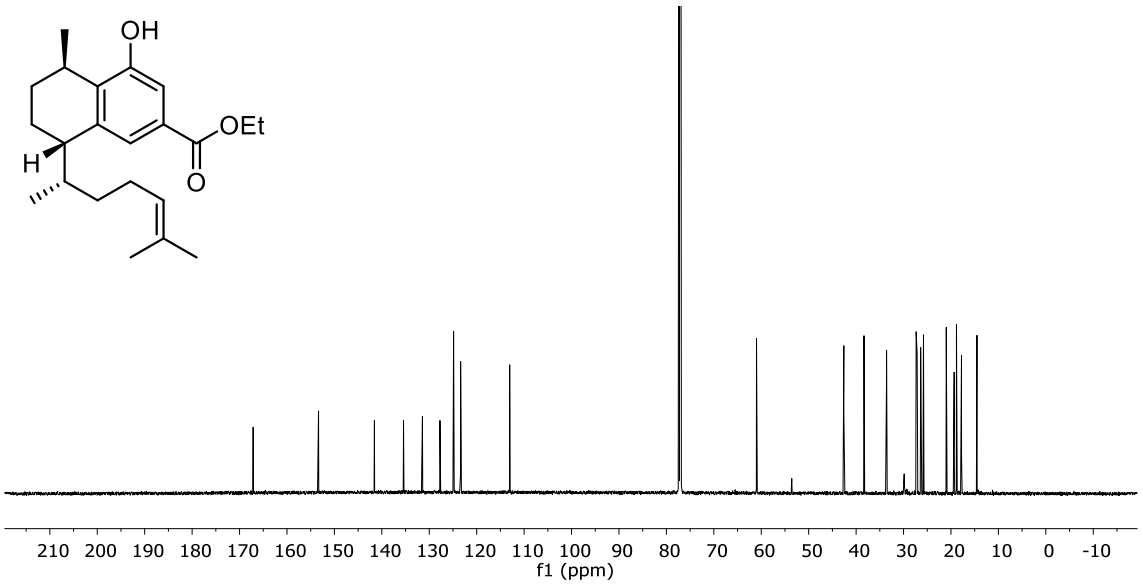
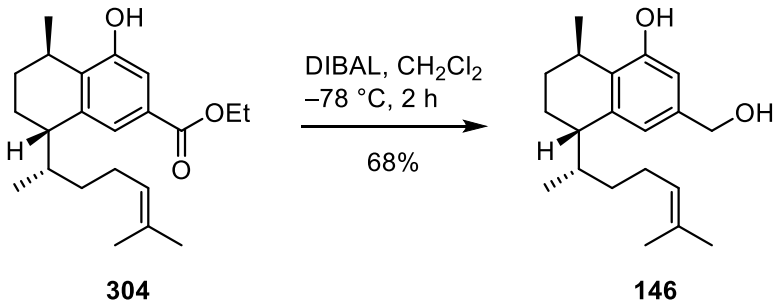


*Figure 4.8: ^{13}C NMR spectrum of phenolic ester **304***

*4.9.1 Synthesis of diol **146***

With the structure of the free phenol **304** confirmed, the final step in the synthesis for diol **146** was reduction of the ester. DIBAL was added slowly to a solution of phenol **304**, with the reaction progress monitored *via* TLC (Scheme 4.31). Following purification, diol **146** was obtained as a colourless oil in 68% yield.



*Scheme 4.31: Synthesis of diol **146***

Analysis of the ^{1}H NMR spectrum (Figure 4.9) revealed that the ester reduction was successful, with disappearance of the ester oxymethylene signal previously at 4.41-4.29 ppm. The signal at 4.59 ppm was assigned to the benzylic oxymethylene. The chemical environment for the aromatic protons had also changed, as they were more shielded appearing at 6.74 and 6.63 ppm. Analysis of the ^{13}C NMR spectrum (Figure 4.10) revealed that the ester carbonyl signal previously at 167.1 ppm in the starting material was absent, whilst there was a signal at 65.5 ppm corresponding to the benzylic alcohol. Whilst confident that diol **146** had been synthesised, in order to confirm the

structure of natural EN3, spectroscopic data for diol **146** was compared to literature data. Table 4.1 shows the ^{1}H NMR data for isolated EN3[94] as well as semi-synthetic EN3; prepared by Lu[96] through reduction of EN4 during SAR studies for leubethanol (**156**).

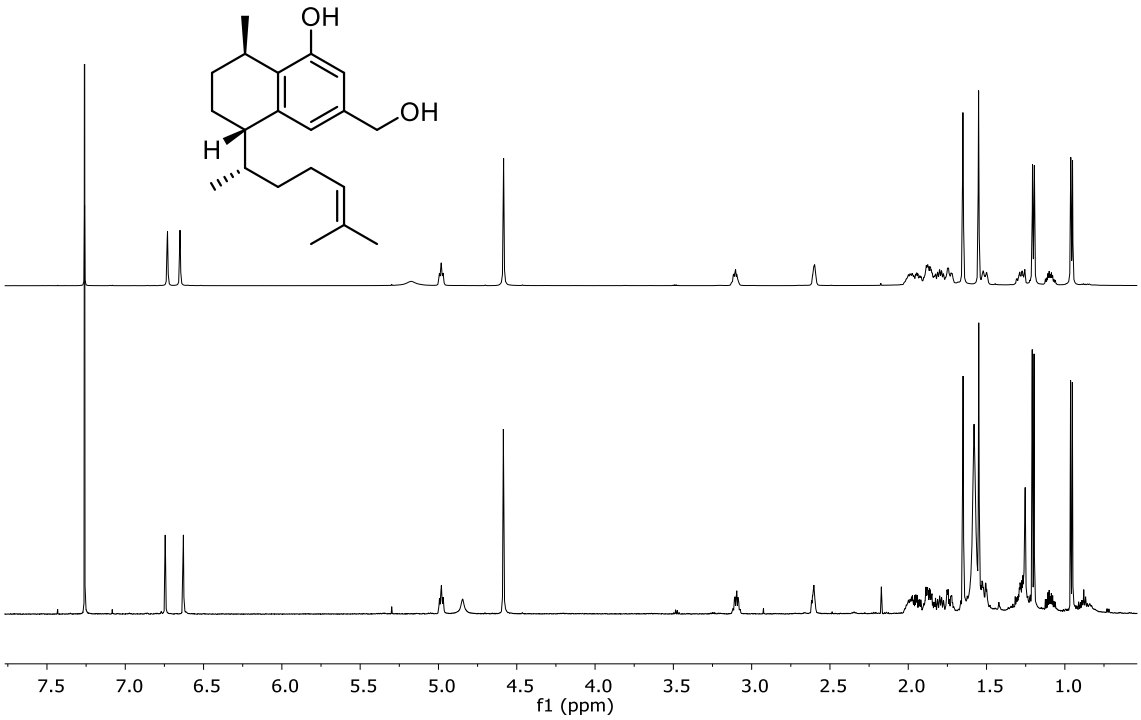


*Figure 4.9: ^{1}H NMR comparison of diol **146** (bottom) and semi-synthetic EN3 (top)*

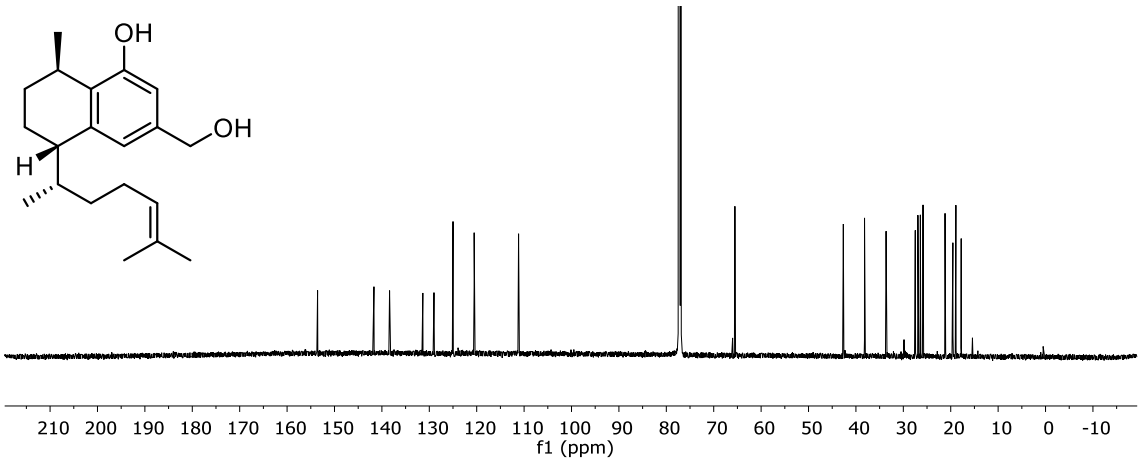


*Figure 4.10: ^{13}C NMR spectrum of diol **146***

Comparison of the spectral data for the three samples revealed that the regions associated with the cyclohexyl and prenyl chain were remarkably similar. Visual inspection of the overlayed ^{1}H NMR spectra (Figure 4.9) revealed a discrepancy between the aromatic hydrogen signals for semi-synthetic EN3 and diol **146**. Whilst the diol **146** had signals at 6.74 ppm and 6.63 ppm, semi-synthetic EN3 had signals at 6.70 ppm and 6.66 ppm. This resulted in the aromatic hydrogen signals appearing to be split for diol **146** when compared to semi-synthetic EN3. However, the difference in chemical shift between the two aromatic hydrogens for natural EN3 was 6.7−6.64 ppm (Δ 0.06 ppm). Compared to semi-synthetic EN3; 6.7−6.66 (Δ 0.04 ppm) and diol **146**; 6.74−6.63 (Δ 0.11 ppm), the splitting would not be as pronounced if overlayed with diol **146**.

The ^{13}C NMR spectrum was also compared to the literature (Figure 4.11), and the differences in chemical shifts for each carbon position calculated. Most chemical shifts were off by +0.2 ppm, indicating a discrepancy associated with referencing. Considering diol **146** was referenced to chloroform at 77.16 ppm, this was rectified by referencing to chloroform at 77 ppm. Comparison to natural EN3 revealed remarkably similar chemical shifts following re-calibration of the reference signal. Seventeen out of the twenty carbon signals exhibited a difference of ±0.1 ppm or less, indicating an excellent agreement with the literature. The remaining three carbon signals attributed to C6 (+0.3 ppm), C8 (−0.2 ppm) and C9 (−0.3 ppm) were all within acceptable limits.

The ^{13}C NMR chemical shift differences were also calculated for natural EN3 and semi-synthetic EN3. Figure 4.11 indicated that diol **146** matched the literature more closely than semi-synthetic EN3. Whilst the chemical shift differences were less for C6 and C9, C19 exhibited greater variation (Δ 0.6 ppm) between semi-synthetic EN3 and natural EN3. Considering these carbon positions were associated with the phenolic, oxymethylene or neighbouring carbons, the differences observed may have been due to sample concentration or acidity.

Importantly, all carbon signals associated with stereogenic centers were in good agreement with the literature. This indicated that diol **146** had the same (1*R*, 4*S*, 11*S*) stereochemistry or was the enantiomer (1*S*, 4*R*, 11*R*) of EN3. It was rationalised though, that because EN3 was isolated from an *Eremophila* species, and similar compounds possessing the serrulatane skeleton have been isolated with the stereochemistry elucidated as (1*R*, 4*S*, 11*S*), that EN3 possessed the (1*R*, 4*S*, 11*S*) stereochemistry.

For confirmation of the stereochemical assignment, the optical rotation was recorded using methanol as the solvent. The specific rotation was recorded as $[\alpha]^{20}_{D}$ −46.5 (*c* 0.19 in MeOH) and compared to the literature value of $[\alpha]^{25}_{D}$ = −64.8 (*c* 0.216 in MeOH). Diol **146** was the same sign and similar magnitude as EN3. This in combination with the matching NMR data indicated that EN3 had the (1*R*, 4*S*, 11*S*) stereochemistry reported by Ndi *et al*.[94]

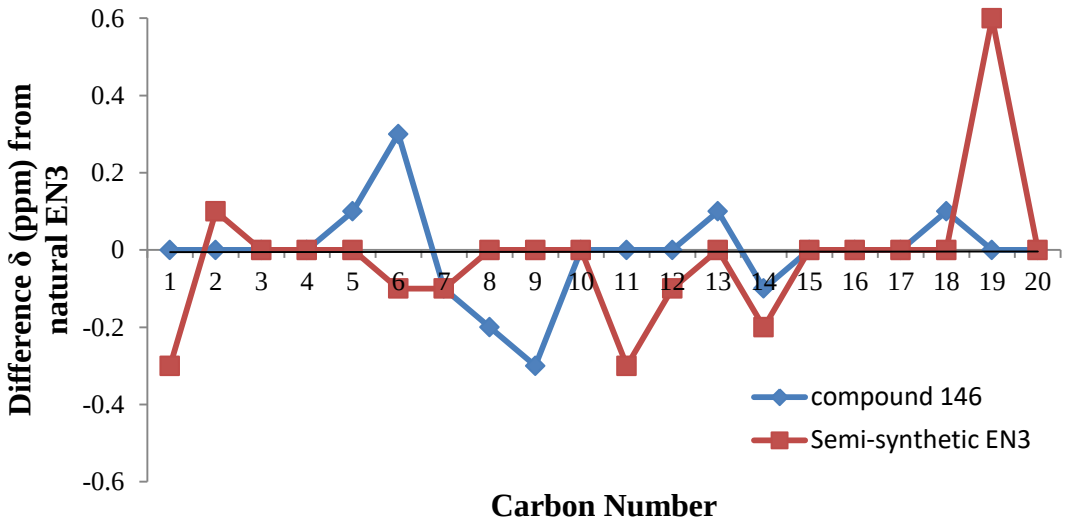
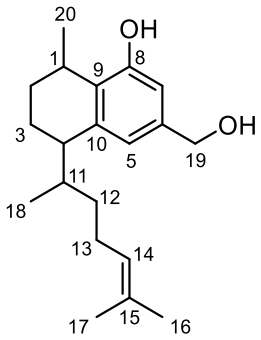


*Figure 4.11: ^{13}C NMR chemical shift differences between natural EN3, compound **146** and semi-synthetic EN3 (Referenced to $CDCl_3$ at 77 ppm).*

*Table 4.1: ^{1}H NMR comparison of Diol **146**, Semi-synthetic EN3 and natural EN3 (Referenced to chloroform at 7.26 ppm)*

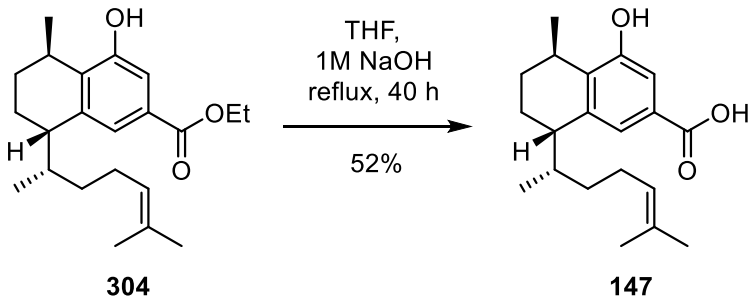


Carbon Number	EN3 δ ppm (J in Hz)	Semi-synthetic EN3 δ ppm (J in Hz)	Diol 146 δ ppm (J in Hz)
1	3.09 (d. quin., 6.6, 3)	3.10 (m)	3.10 pd (6.8, 2.4)
2	a) 1.88 (m); b) 1.48 (ddt, 13, 5, 3)	a) 1.97-1.88 (m) b) 1.48 (m)	a) 1.94 (ddd, 13.1, 6.0, 3.2); b) 1.51 (m)
3	a) 1.86 (m); b) 1.69 (ddt, 13.5, 5, 3)	a) 1.86 (m) b) 1.68 (m)	a) 1.86 (m); b) 1.74 (ddt, 13.7, 5.9, 3.1)
4	2.58 (dt, 5.6, 3)	2.58 (m)	2.61 (td, 5.6, 2.8)
5	6.70 (br. d, 1.4)	6.70 (s)	6.74 (s)
7	6.64 (br. d, 1.4)	6.66 (s)	6.63 (d, 1.6)
11	1.86 (m)	1.86 (m)	1.86 (m)
12	a) 1.27 (dddd, 13, 10, 7, 3); b) 1.09 (dddd, 13, 10, 9.4, 5)	a) 1.27 (m) b) 1.09 (m)	a) 1.33–1.23 (m); b) 1.09 (dtd, 13.3, 9.7, 5.1)
13	a 1.97 (m); b 1.79 (m)	a) 1.97-1.88 (m) b) 1.79 (m)	a) 2.03–1.96 (m); b) 1.79 (dd, 15.0, 7.7)
14	4.96 (t, 7)	4.99 (t, 6.8)	4.98 (t, 7.1)
16	1.63 (br. s)	1.64 (s)	1.65 (s)
17	1.53 (br. s)	1.54 (d, 1.3)	1.55 (s)
18	0.94 (d, 6.6)	0.91 (d, 6.8)	0.96 (d, 6.8)
19	4.56 (br. s)	4.57 (s)	4.59 (s)
20	1.18 (d, 6.6)	1.19 (d, 6.8)	1.20 (d, 7.0)

4.9.2 Synthesis of acid **147**

Having completed the total synthesis of EN3, the last remaining natural product to synthesise was EN4, with carboxylic acid functionality at C19. It was thought that a simple hydrolysis of the ester functional group with a hydroxide base would afford the corresponding carboxylic acid. The phenolic ester **304** was dissolved in a biphasic mixture of THF and 1M solution of NaOH (Scheme 4.32). The biphasic mixture was heated overnight at reflux but returned only partial hydrolysis of the ester. Instead, the reaction time was extended to 40 hours at vigorous reflux, and following isolation afforded the natural product EN4 (**147**) in 52% yield.

The ^{1}H NMR spectrum (Figure 4.12) revealed the presence of two aromatic protons at 7.53 and 7.27 ppm, whilst the olefinic proton appeared as a triplet at 4.97 ppm. The benzylic methines were apparent at 3.18 ppm and 2.67 ppm and the two methyl singlets corresponding to the prenyl tail appeared at 1.64 and 1.54 ppm. Comparison to the literature revealed that the ^{1}H NMR spectrum was in agreement, although the synthetic EN4 possessed an impurity that co-eluted during purification.



304 **147**

*Scheme 4.32: Synthesis of compound **147***

The differences in the ^{13}C NMR spectra of the synthesised EN4 and isolated material were calculated for each carbon position (Figure 4.14). The chloroform signal was referenced to 77 ppm, resulting in 16 of the carbon signals exhibiting a difference of 0.05 ppm or less. The biggest chemical shift differences occurred for C4 (−0.07 ppm), C6 (−0.09 ppm), C9 (−0.21 ppm) and C19 (−1.21 ppm). The chemical shift differences for C4 and C6 are less than 0.1 ppm and were therefore not considered significant. The discrepancy observed for C9 of −0.21 ppm was also relatively small, whilst the difference observed for C19 of −1.21 ppm was significant. Considering C19 corresponds to the carboxylic acid, it may be expected that similar to EN3, the

substrates chemical shifts at C6, C9 and C19 may be influenced by the acidity or concentration of the NMR sample.

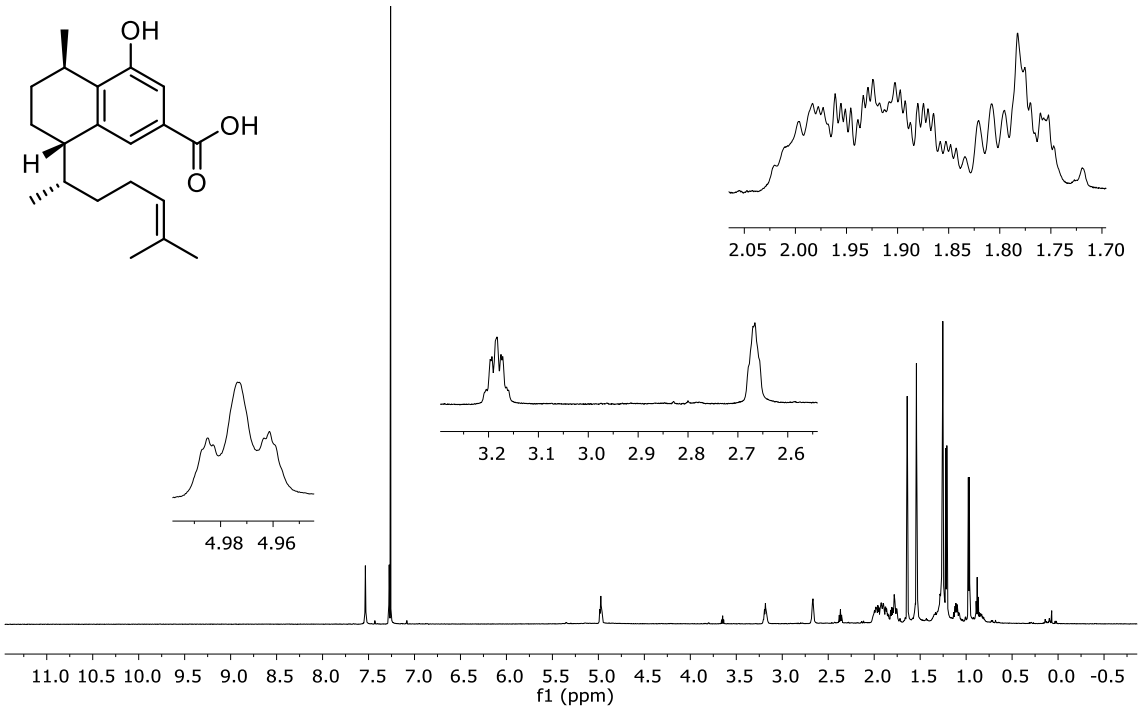


*Figure 4.12: ^{1}H NMR spectrum of acid **147***

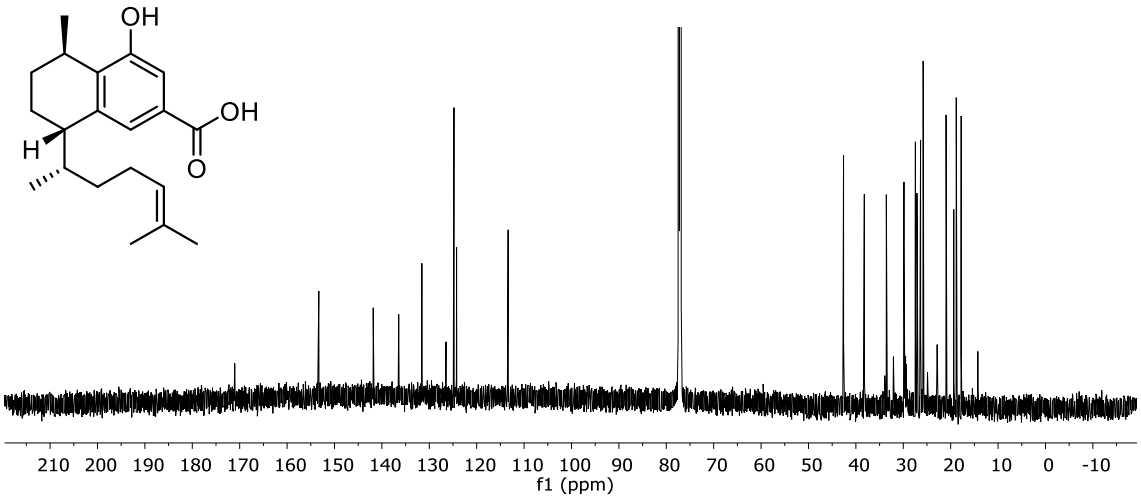


*Figure 4.13: ^{13}C NMR of acid **147***

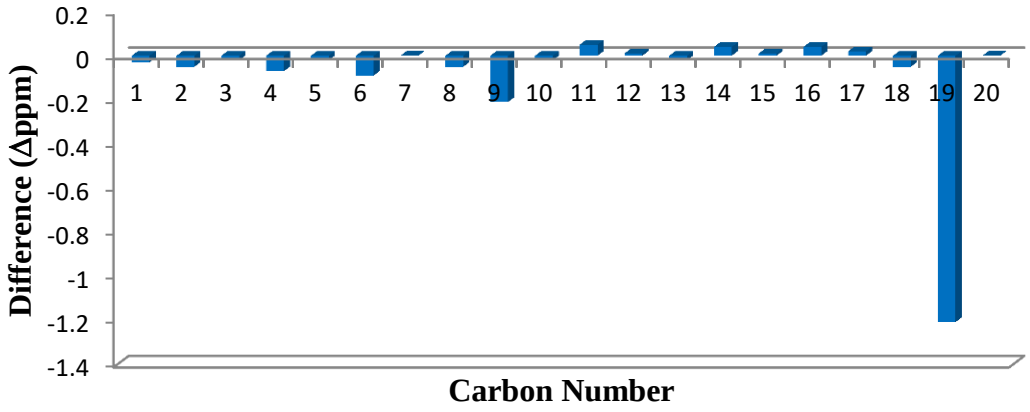


*Figure 4.14: ^{13}C NMR chemical shift difference of acid **147** and natural EN4*

4.10 Conclusions

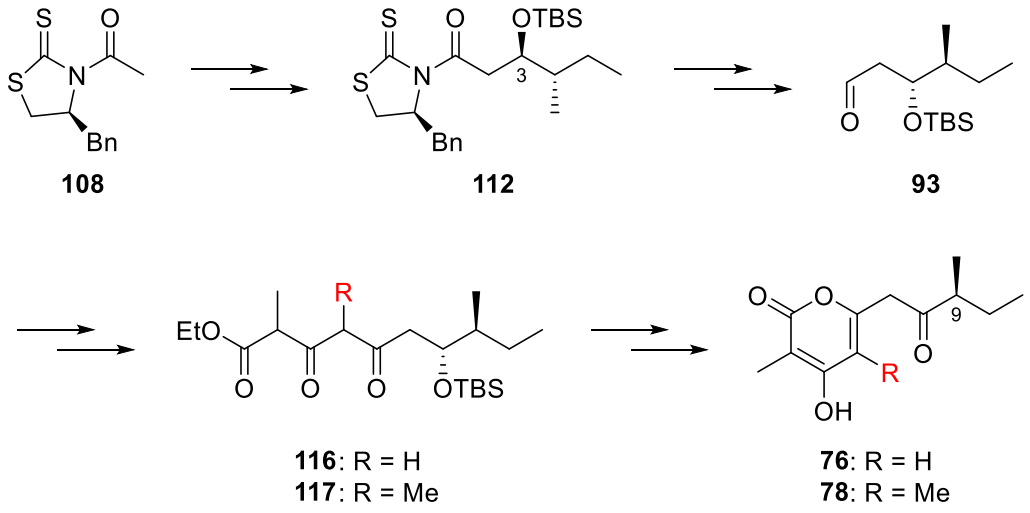
This chapter detailed the total synthesis of the two serrulatane natural products, EN3 and EN4. EN3 was synthesised in 17 steps and 5% overall yield, whilst EN4 was synthesised in 17 steps and 3.8% overall yield from the commercially available (−)-isopulegol. The stereochemistry of EN3 and EN4 was confirmed as the 1*R*, 4*S*, 11*S* stereochemistry from comparison of the ^{1}H and ^{13}C NMR spectra, as well as comparison of the reported specific rotation to that of the measured rotation for EN3.

Chapter 5
Conclusions and Future Directions

5.1 Phomapyrone B and Paecilopyrone A

Chapter 2 described efforts to determine the stereochemistry of phomapyrone B and paecilopyrone A at C9 through total synthesis. By using (*S*)-2-methylbutyraldehyde **68** as a starting material, the stereochemistry at C9 was fixed as the (*S*)-stereochemistry. Following the synthesis of each natural product, comparison of the specific rotations allowed for elucidation of stereochemistry at C9.

During the synthetic studies, attempts were made to improve the yield of pyrone ring formation with dioxinones, as well as minimise the number of linear steps through nucleophilic displacement of amides. Ultimately, the most successful strategy involved dianion addition to the common aldehyde fragment **93** and cyclisation of diketo esters to produce the pyrone rings.[53]



Scheme 5.1: Summary of the total synthesis of phomapyrone B and paecilopyrone A

The synthetic strategy used an asymmetric acetate aldol reaction with *N*-acetyl thiazolidinethione **108** to install the oxygen functionality at C3, which was subsequently masked as the silyl ether **112**. Conversion to the common aldehyde fragment **93** was achieved through a sequence of reductive cleavage and oxidation. Coupling of aldehyde **93** with β-keto esters and subsequent oxidation yielded complex diastereomeric mixtures of diketo esters **116-117**. The linear diketo esters were cyclised to the corresponding α-pyrone moieties, with conversion to the natural products achieved through silyl deprotection and oxidation.

Ent-Phomapyrone B (**76**) was synthesised in 9 steps and 11% overall yield from (*S*)-2-methylbutyraldehyde **68**, whilst paecilopyrone A (**78**) was obtained in 22% yield over 9 steps. The improvement in yield associated with the paecilopyrone A (**78**) synthesis was

attributed to the marked effects of the C4 substituent of the pyrone ring. Spectroscopic data for the synthesised natural products was compared to the respective literature sources, with the stereochemistries of the natural products determined as (9*S*)-paecilopyrone A and (9*R*)-phomapyrone B.

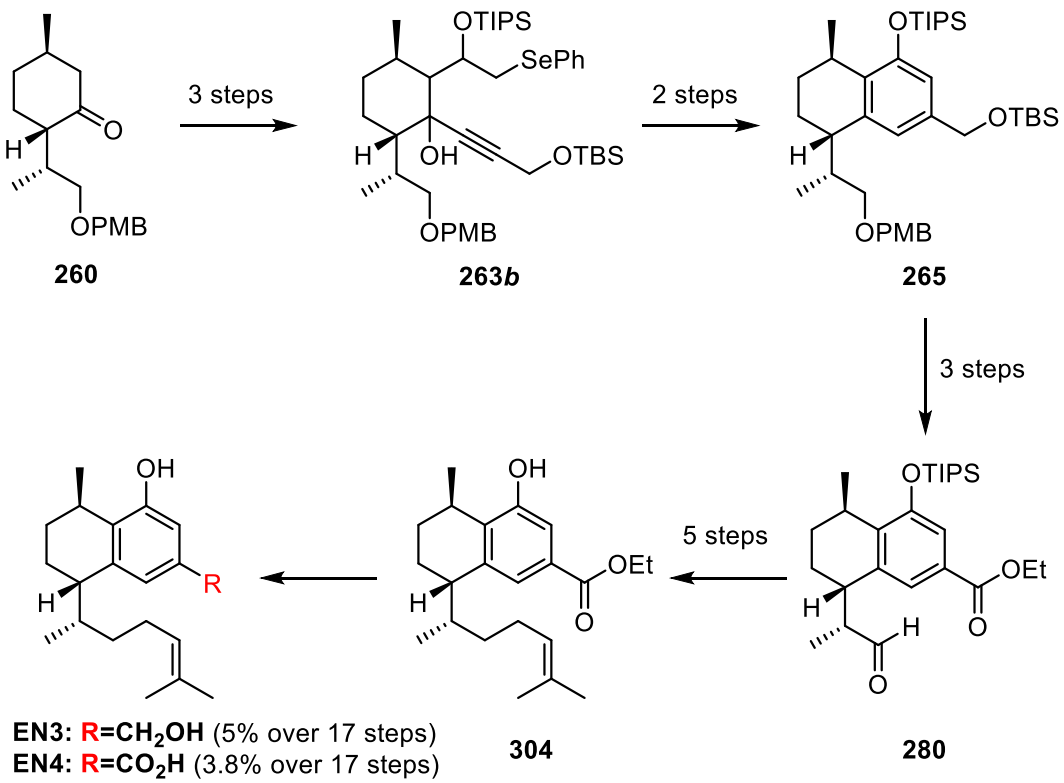
5.2 EN3 and EN4 Serrulatanes

Chapter 3 introduced the terpene natural products and their respective total syntheses. In particular, previous synthetic efforts by Lu[105] and March[138] culminated in a synthetic strategy that could be applied to C19 functionalised serrulatanes. Chapter 4 described the extension of this methodology to serrulatanes isolated from *Eremophila neglecta*.[94] The total synthesis of EN3 and EN4 was achieved in 17 steps with incorporation of C19 functionality.

The synthesis used (−)-isopulegol as a cheap, commercially available starting material containing two of the prerequisite stereocenters. In just three steps, (−)-isopulegol was converted to the protected ketone **260**, with the third stereocenter in place. Through a LiHMDS aldol with phenylselenoacetaldehyde (**223**), followed by protection and lithium acetylide addition, the alkyne **263*b*** was synthesised efficiently in three steps.

The 3-hydroxy alkyne **263*b*** was oxidised to the selenoxide, which underwent elimination to form the silyl enol ether. Silver catalysed ene-yne cycloisomerisation of the 3-hydroxy-1, 5-enyne afforded the tetrahydronaphthalene **265** in 23% yield over 8 steps.[138]

With the aromatic ring installed, deprotection of the 4-methoxybenzyl protecting group was investigated. Ultimately, the most successful strategy was the PMB deprotection/C19 oxidation with DDQ. The reactive benzylic aldehyde was converted to the more stable ester derivative **279** through an Oxone® esterification. Efforts to couple aldehyde **280** with semi-stabilised and stabilised ylides were unsuccessful. Instead, the more reactive sulfone analogues were used. After initially trialling an allylic acetal, attachment of the prenyl side chain was realised using the benzyloxy sulfone **299** under Barbier conditions. The silyl protecting group was easily removed affording the phenolic ester **304**, which was converted into both natural products.

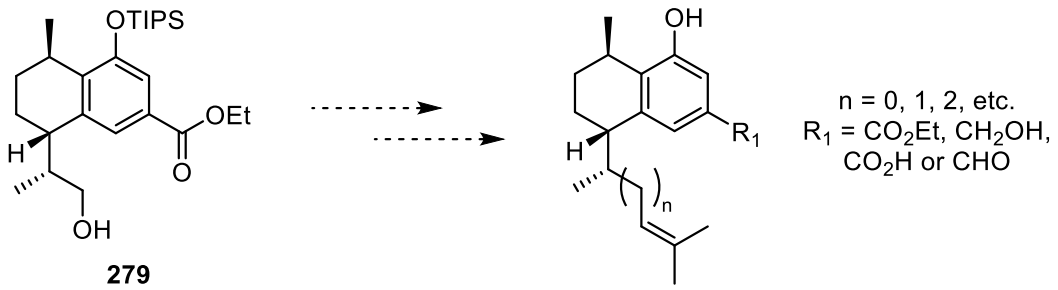


Scheme 5.2: Overview of the total synthesis of EN3 and EN4

The total synthesis of EN3 was realised following reduction of ester **304**, affording EN3 in 17 steps and 5% overall yield. EN4 was synthesised following hydrolysis in 17 steps and 3.8% overall yield. Through comparison of NMR data and specific rotations, the stereochemistry of EN3 at the C1, C4 and C11 stereocenters was determined as 1*R*, 4*S*, 11*S*.

5.3 Future Directions

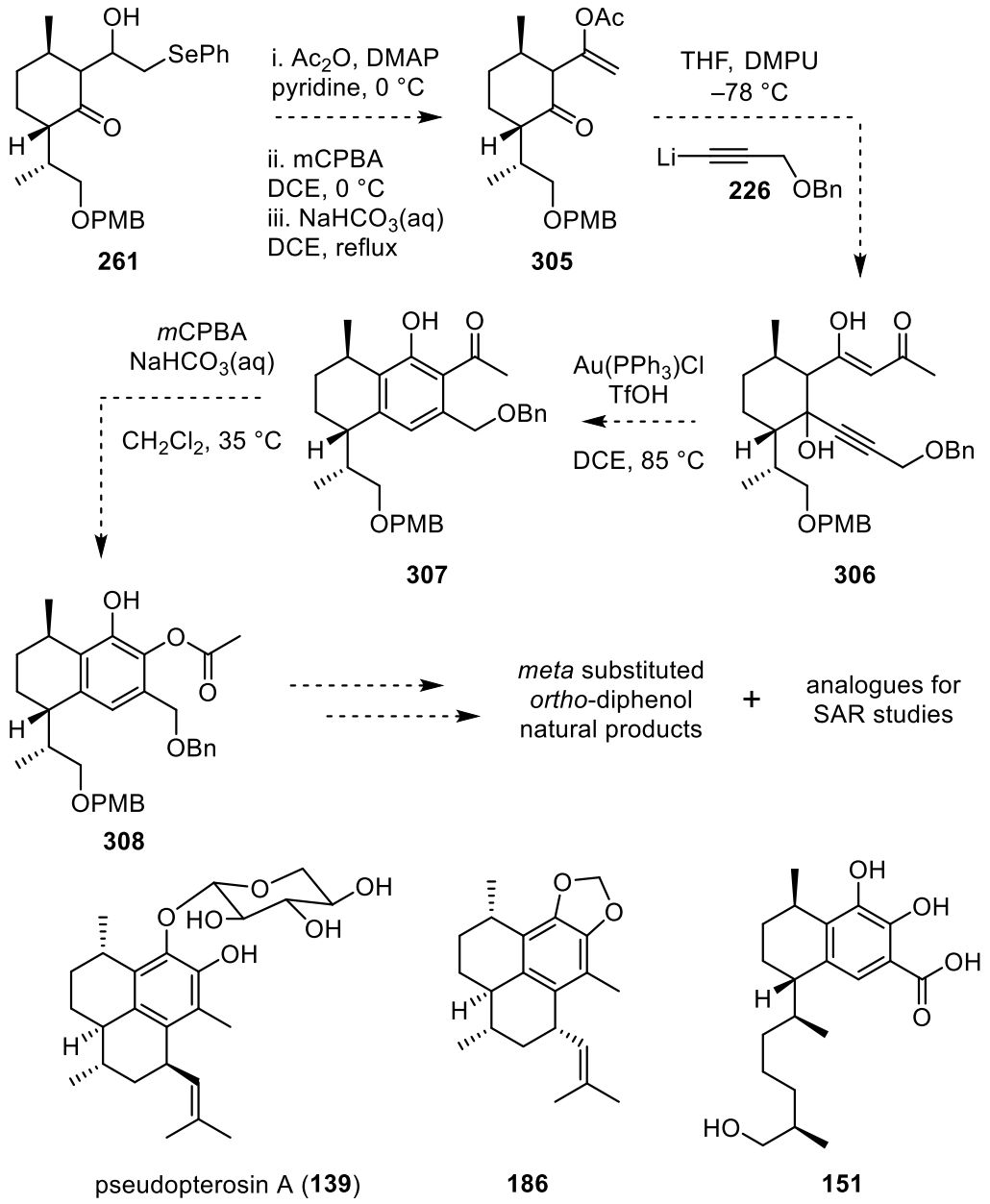
In this thesis the total synthesis of paecilopyrone A and *ent*-phomapyrone B was accomplished. The approach is applicable to a broad range of natural products, with ongoing work in the Perkins research group focusing on the synthesis of both *alpha* and *gamma* pyrones. Similarly, the approach used for EN3 and EN4 could be applied to other serrulatane natural products. Using the tetrahydronaphthalene ester **279** as a precursor (Scheme 5.3), synthesis of the short chain analogues (n = 0) of EN3 and EN4 could be investigated. Considering the increased activity observed by Lu for the short chain analogue of leubethanol (**156**), analogues of EN4 could be useful antimicrobial compounds.[96]



Scheme 5.3: Proposed synthesis of EN3 and EN4 analogues for SAR studies

Future investigations may also include the application of the enol-acetate rearrangement observed by March[138] to *ortho*-diphenol natural products. Previous approaches targeting *ortho*-diphenols have used a starting material containing the *ortho*-diphenol functionality pre-installed. The drawback here is that expensive chiral catalysts were then required to install stereocenters. The enol-acetate rearrangement could prove useful in this situation. A chiral starting material could be used, with the *ortho*-diphenol functionality installed at a later stage in the synthesis.

Starting from the hydroxyselenide **261**, protection as the acetate followed by selenoxide elimination could afford the enol acetate **305** (Scheme 5.4). Lithium acetylide addition with alkyne **226** could afford the rearranged enol acetone **306**, which following treatment with $Au(PPh_3)Cl$, could afford the corresponding aromatic ketone **307**. Bayer-Villager oxidation could afford the aromatic ester **308**, which can be seen as a precursor to a number of natural product carbon skeletons. The synthesis of the serrulatane **151**, the pseudopterosin skeleton or the amphilectane skeleton such as helioporin E (**186**) may be possible, providing a starting material with the correct stereochemistry could be sourced.



*Scheme 5.4: Proposed synthesis of ortho-diphenol precursor **308***

Chapter 6 :
Experimental Procedures for Chapters 2 and 4

6.1 General Experimental Procedures

All reactions were carried out under an inert atmosphere of nitrogen unless otherwise specified. All glassware was either oven or flame-dried prior to use. Benzene, dichloromethane and triethylamine were distilled over CaH_2. DMPU was distilled under reduced pressure from CaH_2. Tetrahydrofuran and diethyl ether were distilled over sodium and benzophenone. All other reagents were used as they were received.

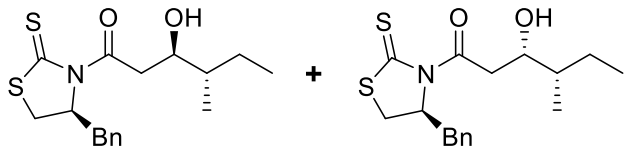
Thin layer chromatography was performed with Merck Silicagel 60 F254 aluminium backed sheets and developed with $KMnO_4$, anisaldehyde or monitored by ultraviolet lamp. Column chromatography was conducted with Merck Silicagel (particle size: 0.04-0.063 mm) 230-400 mesh silica. Buffered silica was prepared by mixing 250 g of Merck Silicagel (particle size: 0.04-0.063 mm) with 25 mL of pH 7 phosphate buffer overnight at atmospheric pressure by spinning slowly on a rotary evaporator.

^{1}H NMR spectra were recorded using either a Bruker 400 MHz or Bruker 600 MHz Spectrometer. Where $CDCl_3$ was used as the solvent and internal lock, it was referenced to $CHCl_3$ (δ 7.26 ppm) for ^{1}H NMR and $CDCl_3$ (δ 77.16 ppm) for ^{13}C NMR. Chemical shift values are reported in parts per million (ppm) and coupling constants are reported in Hertz (Hz). Abbreviations used for assigning ^{1}H NMR spectra: Ar = aromatic, s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet, br = broad, app. = apparent.

Optical rotations were recorded on a PolA AR21 polarimeter referenced to the sodium D line (589 nm) at 20°C. Concentrations are reported in g/100 mL using analytical grade solvents.

X-Ray Crystallography was performed by Dylan Innes at the University of Adelaide. Single crystals suitable for X-ray diffraction experiments were covered in Paratone-N oil and mounted on a glass fibre. Data ($2\theta_{max}$ 55°) were collected at 123 K using a Mo target Oxford Diffraction X-Calibur X-ray diffractometer and $Mo_{K\alpha}$ (λ 0.71073Å) radiation. After integration and scaling, the datasets were merged into N unique reflections (R_{int}). The structures were solved using conventional methods and refined by using full-matrix least-squares using the SHELX-14 software in conjunction with the X-Seed interface. Non-hydrogen atoms were refined with anisotropic thermal parameters and hydrogen atoms were placed in calculated positions.

6.2 Experimental Procedures for Chapter 2



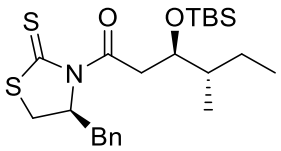
(3R, 4S)-1-((S)-4-benzyl-2-thioxothiazolidin-3-yl)-3-hydroxy-4-methylhexan-1-one

111a. The aldol reaction was carried out according to a modified procedure by Crimmins *et al.*[73] To a stirred solution of thiazolidinethione **108** (5.99 g, 23.8 mmol) in CH_2Cl_2 (180 mL) at −40 °C was added 1M $TiCl_4$ in CH_2Cl_2 (27.4 mL, 27.4 mmol) dropwise and the resulting solution stirred for 20 minutes. iPr_2NEt (5.0 mL, 28.7 mmol) was added and the solution stirred for 1 hour at −40 °C. The reaction mixture was cooled to −78 °C and (*S*)-2-methylbutyraldehyde (3.42 g, 39.7 mmol) added *via* cannulation (CH_2Cl_2). The reaction mixture was stirred for 1 hour at −78 °C, then quenched with NH_4Cl (100 mL, half sat. aq.) and warmed to room temperature. The mixture was diluted with CH_2Cl_2 (50 mL) and washed with NH_4Cl (100 mL, half sat. aq.). The aqueous layer was extracted with CH_2Cl_2 (3×50 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (40% Et_2O/X4) attained separation of the major diastereomer **111*a*** (6.13 g, 76%) as a yellow gum and minor diastereomer **111*b*** (1.44 g, 18%) as yellow needles.

The stereochemistry for the two diastereomers was determined through analysis of the coupling constants and chemical shifts in the ^{1}H NMR, and comparison to the trends observed by Olivo *et al.* for acetate aldol diastereomers.[68]

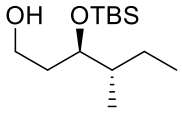
Major Diastereomer **111*a***: $[\alpha]^{20}_D$ +114 (*c* 0.76 in $CHCl_3$); IR ($CHCl_3$, cm^{-1}) 3027, 2957, 2927, 2857, 1700, 1605, 1495, 1455, 1341, 1254, 1163, 1083, 1049, 1827, 701; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37–7.32 (2H, m, Ar-*H*), 7.31–7.27 (3H, m, Ar-*H*), 5.40 (1H, ddd, *J*=10.8, 7.1, 4.0 Hz, C*H*N), 4.06–4.00 (1H, m, C*H*OH), 3.61 (1H, dd, *J*=17.8, 2.0 Hz, C(=O)CH_AH$_B$), 3.41 (1H, dd, *J*=11.5, 7.2 Hz, SCH_AH$_B$), 3.23 (1H, dd, *J*=13.2, 4.0 Hz, CH_AH$_B$Ph), 3.16 (1H, dd, *J*=17.8, 10.1 Hz, C(=O)CH$_A$$H_B$), 3.06 (1H, dd, *J*=13.2, 10.5 Hz, CH$_A$$H_B$Ph), 2.90 (1H, d, *J*=11.5 Hz, SCH$_A$$H_B$), 2.66 (1H, br. s, O*H*), 1.62–1.51 (2H, m, C*H*CH$_3$ and CH_AH$_B$CH$_3$), 1.24–1.16 (1H, m, CH$_A$$H_BCH_3$), 0.94 (3H, t, *J*=7.3 Hz, CH$_2$CH_3), 0.92 (3H, d, *J*=6.7 Hz, CHCH_3). ^{13}C NMR (150 MHz, $CDCl_3$) δ 201.6, 174.0, 136.5, 129.6, 129.1, 127.4, 71.3, 68.5, 42.8, 39.9, 36.9, 32.2, 25.2, 14.7, 11.7 ppm; HRESIMS calcd. for $C_{17}H_{23}NO_2S_2Na^+$, $[M+Na]^+$ 360.1068 found 360.1068

Minor Diastereomer **111*b***: Mp. 57.4–59.2 °C (from CH_2Cl_2); $[\alpha]^{20}_D$ +138 (*c* 0.57 in $CHCl_3$); IR (ATR, cm^{-1}) 3388, 3028, 2965, 2923, 2875, 1712, 1453, 1354, 1341, 1256, 1150, 1129, 1028, 745, 701; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38–7.32 (2H, m, Ar-*H*), 7.31–7.27 (3H, m, Ar-*H*), 5.44–5.38 (1H, m, C*H*N), 4.02 (1H, ddd, *J*=10.2, 4.2, 2.1 Hz, C*H*OH), 3.54 (1H, dd, *J*=17.3, 10.2 Hz, C(=O)CH_AH$_B$), 3.40 (1H, ddd, *J*=11.5, 7.2, 1.1 Hz, SCH_AH$_B$), 3.27 (1H, dd, *J*=17.3, 2.1 Hz, C(=O)CH$_A$$H_B$), 3.23 (1H, dd, *J*=13.3, 4.0 Hz, CH_AH$_B$Ph), 3.05 (1H, dd, *J*=13.3, 10.5 Hz, CH$_A$$H_B$Ph), 2.91 (1H, dd, *J*=11.5, 0.7 Hz, SCH$_A$$H_B$), 1.61–1.53 (1H, m, C*H*CH$_3$), 1.52–1.45 (1H, m, CH_AH$_B$CH$_3$), 1.24–1.15 (1H, m, CH$_A$$H_BCH_3$), 0.94 (3H, d, *J*=6.8 Hz, CHCH_3), 0.93 (3H, t, *J*=7.4 Hz, CH$_2$CH_3), OH absent; ^{13}C NMR (150 MHz, $CDCl_3$) δ 201.70, 174.46, 136.50, 129.56, 129.07, 127.40, 71.53, 68.47, 43.12, 40.09, 36.86, 32.10, 25.6, 14.2, 11.98; HRESIMS calcd. for $C_{17}H_{23}NO_2S_2Na^+$, $[M+Na]^+$ 360.1068 found 360.1066

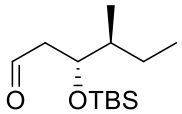


(3R,4S)-1-((S)-4-benzyl-2-thioxothiazolidin-3-yl)-3-((tert-butyldimethylsilyl)oxy)-4-methylhexan-1-one ***112.*** To a stirred solution of alcohol **111*a*** (1.23 g, 3.6 mmol) in CH_2Cl_2 (60 mL) at −78 °C was added 2, 6–Lutidine (0.85 mL, 7.3 mmol) and TBSOTf (1.3 mL, 5.7 mmol). The resulting solution was stirred for 1.5 hours at −78 °C then warmed to 0 °C for 10 minutes. The reaction mixture was quenched with $NaHCO_3$ (30 mL, 5% aq.) and extracted with CH_2Cl_2 (3×20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (CH_2Cl_2) afforded the *title compound* **112** (1.64 g, quant.) as a yellow waxy solid. $[\alpha]^{20}_D$ +189 (*c* 0.72 in $CHCl_3$); IR ($CHCl_3$, cm^{-1}) 3027, 2957, 2927, 2857, 1700, 1605, 1495, 1455, 1341, 1254, 1191, 1163, 1083, 1049, 827 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40–7.33 (2H, m, Ar-*H*), 7.32–7.27 (3H, m, Ar-*H*), 5.25 (1H, ddd, *J*=10.7, 7.0, 3.7 Hz, C*H*N), 4.42–4.30 (1H, m, C*H*OTBS), 3.57 (1H, dd, *J*=16.9, 9.3 Hz, C(=O)CH_AH$_B$), 3.34 (1H, ddd, *J*=11.5, 7.0, 1.1 Hz, SCH_AH$_B$), 3.27 (1H, dd, *J*=13.2, 3.6 Hz, CH_AH$_B$Ph), 3.05 (1H, dd, *J*=13.2, 10.8 Hz, CH$_A$$H_B$Ph), 2.92 (1H, dd, *J*=16.9, 2.3 Hz, C(=O)CH$_A$$H_B$), 2.89 (1H, d, *J*=11.5 Hz, SCH$_A$$H_B$), 1.62–1.52 (1H, m, C*H*CH$_3$), 1.40–1.30 (1H, m, CH_AH$_B$CH$_3$), 1.20–1.10 (1H, m, CH$_A$$H_BCH_3$), 0.94 (3H, t, *J*=7.4 Hz, CH$_2$CH_3), 0.90 (3H, d, *J*=6.8 Hz, CHCH_3), 0.85 (9H, s, SiC(CH_3)$_3$), 0.10 (3H, s, Si(CH_3)$_A$(CH$_3$)$_B$), 0.04 (3H, s,

$Si(CH_3)_A(CH_3)_B$); ^{13}C NMR (150MHz, $CDCl_3$) δ 201.20, 173.17, 136.64, 129.44, 128.91, 127.17, 72.28, 68.80, 41.31, 41.25, 36.38, 32.19, 25.87, 25.81, 18.05, 13.69, 12.23, −4.62, −4.71; HRESIMS calcd. for $C_{23}H_{37}NO_2S_2SiNa^+$, $[M+Na]^+$ 474.1933 found 474.1927

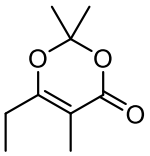


(3R, 4S)-3-tert-butyldimethylsilyloxy-4-methyl-hexan-1-ol ***95.*** To a stirred solution of TBS ether **112** (1.64 g, 3.6 mmol) in dry Et_2O (45 mL) at −10 °C was added anhydrous EtOH (0.92 mL, 15.8 mmol) and $LiBH_4$ (2M in THF, 4.4 mL, 8.8 mmol). The reaction mixture was stirred for 1 hour at −10 °C and quenched through addition of NaOH (1M, 40 mL). The cloudy solution was stirred for 15 minutes at −10 °C and poured into brine (40 mL). The layers were separated and the aqueous layer extracted with Et_2O (3×15 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (20% Et_2O/X4) afforded the *title compound* ***95*** (0.77 g, 86%) as a colourless liquid. $[\alpha]^{20}_D$ +29.3 (*c* 0.85 in $CHCl_3$); IR (ATR, cm^{-1}) 3336, 2958, 2930, 2880, 2858, 1463, 1379, 1253, 1060, 834, 773, 735, 664; ^1H NMR (600 MHz, $CDCl_3$) δ 3.80 (1H, ddd, *J*=8.4, 4.8, 3.4 Hz, C*H*OTBS), 3.74 (2H, td, *J*=5.8, 1.6 Hz, CH_2OH), 2.18 (1H, br. s, CH_2OH), 1.71–1.51 (3H, m, CH_2OHCH_2 and $CHCH_3$), 1.39–1.31 (1H, m, $CHCH_3CH_AH_B$), 1.12–1.04 (1H, m, $CHCH_3CH_AH_B$), 0.91–0.89 (12H, m, $SiC(CH_3)_3$ and CH_2CH_3), 0.86 (3H, d, *J*=6.8 Hz, $CHCH_3$), 0.09 (3H, s, $Si(CH_3)_A(CH_3)_B$), 0.07 (3H, s, $Si(CH_3)_A(CH_3)_B$); ^{13}C NMR (150MHz, $CDCl_3$) δ 74.78, 60.93, 40.48, 33.08, 25.95, 25.83, 18.00, 13.31, 12.14, −4.38, −4.68; HRESIMS calcd. for $C_{13}H_{30}O_2SiNa^+$, $[M+Na]^+$ 269.1913 found 269.1912



(3R, 4S)-3-tert-butyldimethylsilyloxy-4-methyl-hexanal ***93.*** The oxidation was conducted according to a procedure by Mancuso and Swern.[48] To a stirred solution of DMSO (210 μL, 2.96 mmol) in CH_2Cl_2 (7 mL) at −78 °C was added oxalyl chloride (2M, 740 μL, 1.48 mmol) dropwise and the solution stirred for 20 minutes. Alcohol **95** (262 mg, 1.06 mmol) in CH_2Cl_2 was added *via* cannula and the resulting solution stirred

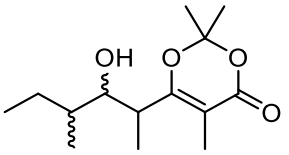
for a further hour at −78 °C. Et_3N (750 μL; 5.4 mmol) was added and the solution stirred for 1 hour at −78 °C before addition of NH_4Cl (10 mL, sat. aq.) and warming to room temperature. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with aqueous $NaHCO_3$ (10 mL, sat. aq.) and brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification through a plug of silica (10% EtOAc/X4) afforded the *title compound* **93** (244 mg, 94%) as a colourless oil. IR (ATR, cm^{-1}) 2959, 2930, 2882, 2858, 2716, 1728, 1464, 1382, 1253, 1090, 1042, 834, 774; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.81 (1H, dd, *J*=3.2, 1.9 Hz, C*H*O), 4.15 (1H, ddd, *J*=8.2, 4.5, 3.7 Hz, C*H*OTBS), 2.51 (1H, ddd, *J*=15.6, 8.2, 3.2 Hz, CHOCH_AH_B), 2.35 (1H, ddd, *J*=15.6, 3.7, 1.9 Hz, CHOCH_AH_B), 1.60–1.53 (1H, m, C*H*CH_3), 1.39–1.30 (1H, m, $CHCH_3CH_AH_B$), 1.12–1.04 (1H, m, $CHCH_3CH_AH_B$), 0.91 (3H, t, *J*=7.4 Hz, CH_2CH_3), 0.87 (3H, d, *J*=6.8 Hz, $CHCH_3$), 0.86 (9H, s, $SiC(CH_3)_3$), 0.06 (3H, s, $Si(CH_3)_A(CH_3)_B$), 0.04 (3H, s, $Si(CH_3)_A(CH_3)_B$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 203.1, 71.4, 46.5, 41.2, 25.9, 25.8, 18.1, 13.6, 12.1, −4.3, −4.6 ppm.



*6-Ethyl-2,2,5-trimethyl-1,3-dioxin-4-one **55***. Synthesis of dioxinone **55** was conducted according to a procedure from Omura *et al.*[7] To a stirred solution of β-keto ester **71** (2.88 g, 18.2 mmol) in THF (15 mL) and water (100 mL) at room temperature was added NaOH (0.5M, 62 mL) and the solution stirred for 3.5 hours. The reaction mixture was washed with EtOAc (2×50 mL), quenched *via* acidification to pH~2 with 1M HCl and saturated with NaCl. The aqueous layer was extracted with EtOAc (3×50 mL) and the combined organic extracts dried (Na_2SO_4) and concentrated *in vacuo* to give the β-keto acid **99** (2.26 g, 96%) as a colourless oil. The β-keto acid **99** was used without purification.

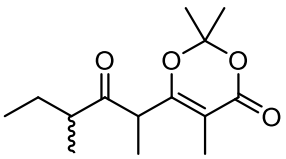
To a stirred solution of β-keto acid **99** (1.1 g, 11 mmol) in acetone (3.5 mL) at 0 °C was added Ac_2O (2.1 mL, 23 mmol) and H_2SO_4 (150 μL, 2.8 mmol), with the resulting solution warmed to room temperature and stirred for 12 hours. The reaction mixture was quenched by slow addition of $NaHCO_3$ (15 mL, sat. aq.) and the aqueous layer extracted using EtOAc (3×15 mL). The combined organic layers were washed with

brine (15 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (20% EtOAc/Hexanes) afforded the *title compound* **55** (1.1 g, 76%) as a colourless liquid. ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.28 (2H, q, *J*=7.6 Hz), 1.80 (3H, s), 1.63 (6H, s), 1.09 (3H, t, *J*=7.6 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ 166.9, 163.1, 104.7, 99.6, 25.1, 24.4, 10.4, 10.0 ppm.

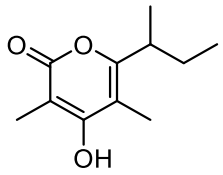


6-(2-Hydroxy-1,3-dimethyl-pentyl)-2,2,5-trimethyl-1,3-dioxin-4-one. The alkylation was conducted according to a procedure from Omura *et al.*[7] To a stirred solution of diisopropylamine (0.34 mL, 2.4 mmol) in THF (10 mL) at −78 °C was added ^{n}BuLi (1.54 mL, 2.4 mmol) and the resulting solution warmed to 0 °C for 30 minutes. The solution was re-cooled to −78 °C and dioxinone **55** (251 mg, 1.47 mmol) added *via* cannula (THF). The resulting solution was stirred at −78 °C for 1 hour then 2-methylbutyraldehyde (**68**) (0.47 mL, 4.4 mmol) was added dropwise. The solution was allowed to stir for 2.5 hours at −78 °C before warming to room temperature and quenching through addition of NH_4Cl (10 mL, sat. aq.). Layers were separated and the aqueous layer extracted with Et_2O (3×10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (30% EtOAc/X4) afforded the *title compound* (214 mg, 56%) as a light yellow oil and mixture of isomers.

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.72–3.59 (1H, m), 3.57–3.41 (1H, m), 2.98–2.80 (1H, m), 1.87–1.84 (3H, m), 1.70–1.62 (6H, m), 1.54–1.27 (2H, m), 1.22–1.09 (2H, m), 1.04 (1H, d, *J*=7.0 Hz), 0.99–0.76 (9H, m). ^{13}C NMR (150 MHz, $CDCl_3$): δ 167.47, 167.46, 163, 162.8, 104.9, 104.8, 104.8, 101.4, 100, 77.6, 74.9, 38.41, 38.41, 37.7, 37.2, 36.3, 27, 25.4, 25.1, 25, 24.8, 22.3, 16.34, 16.34, 14.3, 13.8, 12.01, 12.00, 11.7, 11.6, 10.1, 10 ppm.

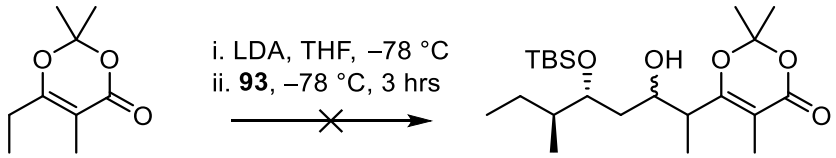


2,2,5-trimethyl-6-(4-methyl-3-oxohexan-2-yl)-4H-1,3-dioxin-4-one ***100***. The oxidation was conducted according to a procedure from Omura *et al.*[7] To a stirred solution of DMSO (140 μL, 2 mmol) in CH_2Cl_2 (6 mL) at −78 °C was added oxalyl chloride (2M in CH_2Cl_2, 0.5 mL, 1 mmol) dropwise and the solution stirred for 30 minutes. β-hydroxy dioxinone (183 mg, 0.71 mmol) was added *via* cannula (CH_2Cl_2) and the solution stirred for 1.5 hours. Et_3N (0.5 mL, 3.6 mmol) was added dropwise and the solution maintained at −78 °C for a further hour. The reaction mixture was quenched through addition of NH_4Cl (5 mL, sat. aq.) and allowed to warm to room temperature. Layers were separated and the aqueous layer extracted with CH_2Cl_2 (3×10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification through a plug of buffered silica (CH_2Cl_2) afforded the *title compound* **100** (124 mg, 68%) as a colourless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.78 (0.5H, q, *J*=6.9 Hz), 3.71 (0.5H, q, *J*=6.9 Hz), 2.59 (1H, dh, *J*=27.6, 6.9 Hz), 1.92 (1.5H, s), 1.91 (1.5H, s), 1.74–1.66 (0.5H, m), 1.63 (3H, d, *J*=2.2 Hz), 1.63 (3H, s), 1.59 (2H, s), 1.45–1.30 (1H, m), 1.28 (1.5H, d, *J*=5.0 Hz), 1.26 (1.5H, d, *J*=4.9 Hz), 1.08 (1.5H, d, *J*=7.0 Hz), 1.05 (1.5H, d, *J* = 6.7 Hz), 0.88 (1.5H, t, *J*=7.5 Hz), 0.84 (1.5H, t, *J*=7.4 Hz).

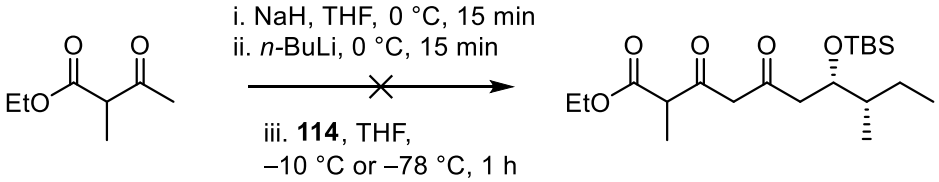


6-(sec-butyl)-4-hydroxy-3,5-dimethyl-2H-pyran-2-one ***101***. The cyclisation was conducted according to a procedure from Omura *et al.*[7] A sodium methoxide solution was prepared by addition of MeOH (3 mL) to Na (0.24 g, 10.4 mmol) at 0 °C followed by stirring at room temperature until all sodium dissolved. The solution was re-cooled to 0 °C and dioxinone **100** (130 mg, 0.51 mmol) added *via* cannula (MeOH). The resulting solution was stirred for 1 hour at 0 °C then quenched through addition of NH_4Cl (3 mL, sat. aq.). The aqueous layer was acidified to pH 1 and extracted with EtOAc (3×5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (10% MeOH/CH_2Cl_2) afforded the *title compound* **101** (99 mg, 95%) as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.80

(1H, dp, *J*=8.8, 6.8 Hz, C*H*CH$_3$), 1.99 (3H, s, =CC*H$_3$*), 1.98 (3H, s, =CC*H$_3$*), 1.77–1.66 (1H, m, C*H$_A$*H$_B$CH$_3$), 1.60–1.49 (1H, m, CH$_A$*H$_B$*CH$_3$), 1.19 (3H, d, *J*=6.9 Hz, CHC*H$_3$*), 0.83 (3H, t, *J*=7.4 Hz, CH$_2$C*H$_3$*), O*H* absent. ^{13}C NMR (150 MHz, $CDCl_3$): δ 166.6, 165.3, 162.1, 106.8, 98.2, 36.4, 27.7, 18.2, 12.2, 9.8, 8.7 ppm

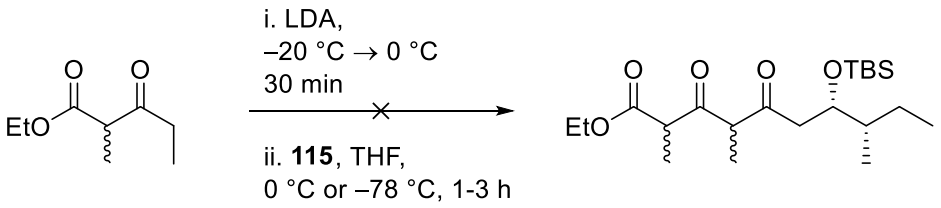


6-((5R,6S)-5-((tert-butyldimethylsilyl)oxy)-3-hydroxy-6-methyloctan-2-yl)-2,2,5-trimethyl-4H-1,3-dioxin-4-one ***113***. The alkylation was conducted according to a procedure from Omura *et al.*[7] To a stirred solution of diisopropylamine (50 μL, 0.36 mmol) in THF (2 mL) at −78 °C was added *n*-BuLi (200 μL, 0.33 mmol) and the resulting solution warmed to 0 °C for 30 minutes. The solution was re-cooled to −78 °C and dioxinone **55** (61 mg, 0.36 mmol) added *via* cannula (THF). The resulting solution was stirred at −78 °C for 1 hour then aldehyde **93** (40 mg, 0.16 mmol) added dropwise. The solution was allowed to stir for 3 hours at −78 °C before warming to room temperature and quenching through addition of NH_4Cl (5 mL, sat. aq.). Layers were separated and the aqueous layer extracted with Et_2O (3×5 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Crude ^{1}H NMR revealed no signals indicative of product, with only starting dioxinone **55** recoverable by column chromatography.

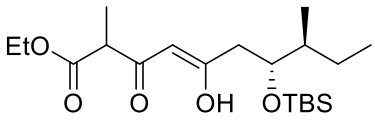


(7S,8S)-7-(tert-Butyl-dimethyl-silanyloxy)-2,8-dimethyl-3,5-dioxo-decanoic acid ethyl ester ***(7S,8S)-116***. Attempted coupling of β-keto ester **51** with auxiliary **114** was conducted according to a procedure by Yadav *et al.*[45] To a stirred solution of NaH (1.2 equivalents) in THF at 0 °C was added ethyl-2-methyl acetoacetate **51** (1.2 equivalents) and the resulting solution stirred for 15 minutes. *n*-BuLi (1.2 equivalents) was added dropwise, with stirring continued at 0 °C for a further 15 minutes. The reaction mixture was cooled to −10 °C or −78 °C and thiazolidine **114**

(1 equivalent) or Weinreb amide **115** (1 equivalent) added *via* cannulation (THF). After 1 hour at −10 °C or −78 °C the reaction was quenched by addition of NH_4Cl. The layers were separated and the aqueous layer extracted with Et_2O. The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification of the crude mixture by column chromatography (buffered SiO_2, EtOAc/X4) returned the starting β-keto ester, starting amide or hydrolysis products.



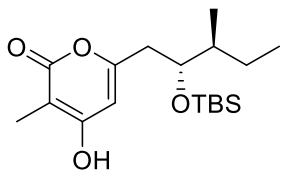
Ethyl (7S,8S)-7-((tert-butyldimethylsilyl)oxy)-2,4,8-trimethyl-3,5-dioxodecanoate ***(7S,8S)-117***. Attempted coupling of β-keto ester **71** with Weinreb amide **115** was conducted according to a procedure by Meshram *et al.*[44] To a stirred solution of LDA (2 equivalents) in THF at −20 °C was added β-keto ester **71** (1 equivalent) and the solution stirred for 30 minutes at 0 °C. Weinreb amide **115** (1 equivalent) was added *via* cannulation (THF) and the resulting solution stirred for 1-3 hours at 0 °C or −78 °C. The reaction mixture was quenched with NH_4Cl and the layers separated. The aqueous layer was extracted using Et_2O, with the combined organic layers dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (buffered SiO_2, EtOAc/X4) returned only starting β-keto ester **71** and Weinreb amide **115**.



(7R,8S)-7-(tert-Butyl-dimethyl-silanyloxy)-2,8-dimethyl-3,5-dioxo-decanoic acid ethyl ester ***116***. The dianion addition was conducted according to a procedure by Gregg and Perkins.[53] To a stirred solution of NaH (336 mg, 14 mmol) in THF (20 mL) at 0 °C was added ethyl-2-methyl acetoacetate **51** (700 μL, 4.95 mmol) and the resulting solution stirred for 30 minutes. *n*-BuLi (2.07M, 2.25 mL, 4.66 mmol) was added dropwise, with stirring continued at 0 °C for a further 30 minutes. The reaction mixture was cooled to –78 °C and aldehyde **93** (0.57 g, 2.33 mmol) added *via* cannulation (THF). After 1 hour at −78 °C the reaction was quenched by addition of NH_4Cl (mL, sat. aq.). The layers were separated and the aqueous layer extracted with Et_2O (3×20 mL). The combined organic

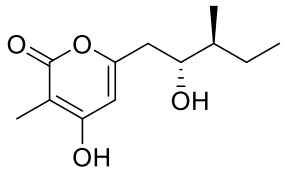
layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification through a plug of buffered silica (10% EtOAc/X4) afforded alcohol **118** (703 mg, 79%) as a colourless oil and inseparable mixture of isomers.

The oxidation was conducted according to a procedure by Dess and Martin.[154] To a stirred solution of crude **118** (256 mg, 0.66 mmol) in CH_2Cl_2 (8 mL) was added DMP (612 mg, 1.44 mmol) at room temperature followed by a saturated H_2O/CH_2Cl_2 mixture every 5 minutes for 1 hour (0.5 mL aliquots) and the resulting suspension stirred in darkness for 16 hours. The reaction mixture was diluted with Et_2O (20 mL), quenched with $Na_2S_2O_3$ (9 g) in $NaHCO_3$ (20 mL, sat. aq.) and the biphasic mixture stirred for 1 hour. The layers were separated and the organic layer washed with $NaHCO_3$ (10 mL, sat. aq.), brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo.* Purification by column chromatography (buffered SiO_2, 50% X4/CH_2Cl_2) afforded the *title compound* **117** (240 mg, 94%) as a light yellow oil. IR (ATR, cm^{-1}) 2961, 2933, 2881, 2858, 1739, 1607, 1463, 1377, 1251, 1186, 1075, 1035, 939, 834, 775; ^{1}H NMR (600MHz, $CDCl_3$) δ 15.21 (1H, d, *J*=12.5 Hz, O*H*) *5*.60 (1H, s, C*H*=COH), 4.20–4.15 (2H, app q, *J*=7.1 Hz, $CH_3CH_2OC(=O)$), 4.09–4.06 (1H, m, C*H*OTBS), 3.38–3.34 (1H, m, EtOC(=O)C*H*CH_3), 2.31–2.23 (2H, m, COHCH_2CHOTBS), 1.47–1.45 (1H, m, CHOTBSC*H*CH_3), 1.38 (3H, dd, *J*=7.2 and 2.7 Hz, EtOC(=O)CHCH_3), 1.36–1.32 (1H, m), 1.25 (3H, td, *J*=7.2 and 2 Hz, $CH_3CH_2OC(=O)$), 1.14–1.07 (1H, hept., *J*=7.5 Hz), 0.92 (3H, t, *J*=7.4 Hz, $CHCH_3CH_2CH_3$), 0.87 (3H, d, *J*=6.8 Hz, CHOTBSCHCH_3), 0.84 (9H, s, $Si(CH_3)_3$), 0.01 (3H, s, $Si(CH_3)_A(CH_3)_B$), −0.06 (3H, s, $Si(CH_3)_A(CH_3)_B$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 193.01, 190.65, 100.37, 100.11, 72.90, 61.28, 49.52, 41.14, 40.56, 41.14, 40.50, 25.76, 17.97, 14.20, 13.82, 12.12, −4.74, −5.10; HRESIMS calcd. for $C_{20}H_{38}O_5SiNa^+$, $[M+Na]^+$ 409.2386 found 409.2394



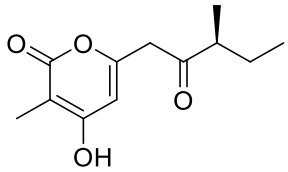
6-((2R,3S)-2-((tert-butyldimethylsilyl)oxy)-3-methylpentyl)-4-hydroxy-3-methyl-2H-pyran-2-one ***119***. To a stirred solution of enol tautomer **116*a*** (312 mg, 0.81 mmol) in benzene (25 mL) was added DBU (60 μL, 0.4 mmol) and the resulting solution heated at reflux for 3 hours then allowed to cool to room temperature. The reaction mixture was quenched through addition of NH_4Cl (10 mL, sat. aq.), extracted with EtOAc

(3×10 mL), dried (Na_2SO_4) and concentrated *in vacuo.* Purification by column chromatography (10% Et_2O/CH_2Cl_2) afforded the *title compound* **119** (110 mg, 40%, 2 cycles) as white needles. Mp 137-140 °C; $[\alpha]^{20}_D$ +121.5 (*c* 0.91 in $CHCl_3$); IR (thin film, cm^{-1}) 3018, 2959, 2929, 2859, 2705, 1666, 1636, 1583, 1494, 1429, 1407, 1253, 1126, 1082, 827 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.68 (1H, s, O*H*), 6.01 (1H, s, =C*H*), 4.02 (1H, dt, *J*=9.5, 3.5 Hz, C*H*OTBS), 2.50 (1H, dd, *J*=14.0, 3.3 Hz, $CH_AH_BCHOTBS$), 2.38 (1H, dd, *J*=14.1, 9.3 Hz, $CH_AH_BCHOTBS$), 1.96 (3H, s=CCH_3), 1.58–1.52 (1H, m, C*H*CH_3), 1.44–1.34 (1H, m, $CHCH_3CH_AH_B$), 1.16–1.06 (1H, m, $CHCH_3CH_AH_B$), 0.93 (3H, t, *J*=7.4 Hz, CH_2CH_3), 0.89 (3H, d, *J*=6.8 Hz, $CHCH_3$), 0.82 (9H, s, $SiC(CH_3)_3$), −0.01 (3H, s, $Si(CH_3)_A(CH_3)_B$), −0.18 (3H, s, $Si(CH_3)_A(CH_3)_B$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 168.7, 167.1, 161.6, 103.3, 98.8, 73.0, 41.1, 36.9, 25.9, 25.9, 18.1, 13.6, 12.3, 8.2, −4.6, −5.0 ppm; HRESIMS calcd. for $C_{18}H_{32}O_4SiNa^+$, $[M+Na]^+$ 363.1968 found 363.1965

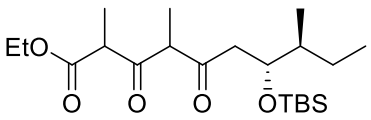


4-hydroxy-6-((2R,3S)-2-hydroxy-3-methylpentyl)-3-methyl-2H-pyran-2-one ***121***. To a stirred solution of TBS pyrone **119** (81 mg, 0.24 mmol) in 1:1 CH_2Cl_2/CH_3CN (10 mL) was added HF (0.9 mL, 30% aq.) and the mixture stirred at room temperature for 3 hours. The reaction mixture was diluted with H_2O (5 mL) and the layers separated. The aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (2×10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification through a plug of buffered silica (10% $MeOH/CH_2Cl_2$) afforded the *title compound* **121** (50 mg, 93%) as white needles. Mp. 208–209 °C (dec.); $[\alpha]^{20}_D$ +125 (*c* 0.48 in MeOH); IR (ATR, cm^{-1}) 3430, 2963, 2933, 2877, 2658, 1661, 1620, 1555, 1404, 1258, 1137, 1070, 1006, 752; ^1H NMR (600 MHz, $(CD_3)_2CO$) δ 9.70 (1H, s, =CO*H*), 6.07 (1H, s, =C*H*), 3.80 (1H, ddd, *J*=9.3, 5.5, 3.1 Hz, CH_2CHOH), 2.60 (1H, dd, *J*=14.4, 3.0 Hz, CH_AH_BCHOH), 2.40 (1H, dd, *J*=14.4, 9.7 Hz, CH_AH_BCHOH), 1.83 (3H, s, =CCH_3), 1.63–1.55 (1H, m, C*H*CH_3), 1.54–1.46 (1H, m, $CHCH_3CH_AH_B$), 1.25–1.14 (1H, m, $CHCH_3CH_AH_B$), 0.93 (3H, d, *J*=7.1 Hz, $CHCH_3$), 0.90 (3H, t, *J*=7.6 Hz, CH_2CH_3), O*H* absent; ^{13}C NMR (151 MHz, $(CD_3)_2CO$) δ 166.1, 165.2, 162.3, 101.8, 98.4, 72.9, 41.5,

39.0, 25.3, 15.1, 11.9, 8.5; HRESIMS calcd. for $C_{12}H_{18}O_4Na^+$, $[M+Na]^+$ 249.1103 found 249.1113



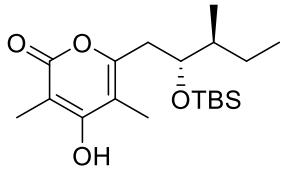
(S)-4-hydroxy-3-methyl-6-(3-methyl-2-oxopentyl)-2H-pyran-2-one ***76***. The oxidation was conducted according to a procedure from Shone *et al.*[155] To a stirred solution of pyrone **121** (29 mg, 0.13 mmol) in acetone (5 mL) at 0 °C was added Jones reagent dropwise until the orange colour was sustained. The reaction mixture was stirred for a further 20 minutes and then quenched through addition of isopropanol (2 mL). The reaction mixture was filtered (EtOAc) and the layers separated. The aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (EtOAc) afforded the *title compound* **76** (19 mg, 66%) as white needles. Mp 118–121 °C; $[\alpha]^{20}_D$ +18 (*c* 0.95 in $CHCl_3$); IR (ATR, cm^{-1}) 2965, 2924, 2878, 2661, 1712, 1673, 1635, 1555, 1403, 1258, 1134, 1054, 872, 751; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.71 (1H, br. s, =CO*H*), 6.20 (1H, s, =C*H*), 3.70–3.54 (2H, m, CH_2C=O), 2.57 (1H, h, *J*=6.8 Hz, C*H*CH_3), 1.93 (3H, s, =CCH_3), 1.70 (1H, dp, *J*=14.1, 7.3 Hz, $CHCH_3CH_AH_B$), 1.42 (1H, dp, *J*=14.4, 7.3 Hz, $CHCH_3CH_AH_B$), 1.10 (3H, d, *J*=6.9 Hz, CHCH_3), 0.88 (3H, t, *J*=7.4 Hz, CH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.5, 168.2, 166.6, 155.8, 104.2, 99.8, 48.2, 45.3, 25.8, 15.6, 11.6, 8.3; HRESIMS calcd. for $C_{12}H_{16}O_4Na^+$, $[M+Na]^+$ 247.0946 found 247.0944.



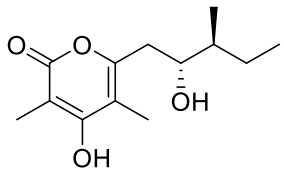
Ethyl (7R,8S)-7-((tert-butyldimethylsilyl)oxy)-2,4,8-trimethyl-3,5-dioxodecanoate ***117.*** The dianion addition was conducted according to a procedure by Gregg and Perkins.[53] To a stirred solution of NaH (72 mg, 3 mmol) in THF (5 mL) at 0 °C was added β-keto ester **71** (251 mg, 1.59 mmol) in THF (3 mL) and the resulting solution stirred for 15 minutes. The solution was cooled to −10 °C and *n*-BuLi (1.35 M, 1.2 mL, 2.78 mmol) added dropwise, with stirring continued at −10 °C for a further 15 minutes. The reaction

mixture was cooled to –78 °C and aldehyde **93** (181 mg, 0.74 mmol) added *via* cannula (THF). After 1 hour at −78 °C the reaction was quenched by addition of NH_4Cl (10 mL, sat. aq.). The layers were separated and the aqueous layer extracted with Et_2O (3×10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification through a plug of buffered silica (10% EtOAc/X4) afforded alcohol **122** (241 mg, 81%) as a colourless oil and inseparable mixture of isomers.

The oxidation was conducted according to the modified procedure by Meyer *et al.*[156] To a stirred solution of crude **122** (216 mg, 0.54 mmol) in CH_2Cl_2 (6 mL) was added DMP (450 mg, 1.06 mmol) at room temperature followed by a saturated H_2O/CH_2Cl_2 mixture every 5 minutes for 1 hour (0.3 mL aliquots) and the resulting suspension stirred in darkness for 72 hours. The reaction mixture was diluted with Et_2O (15 mL), quenched with $Na_2S_2O_3$ (5 g) in $NaHCO_3$ (12.5 mL, sat. aq.) and the biphasic mixture stirred for 1 hour. The layers were separated and the organic layer washed with $NaHCO_3$ (10 mL, sat. aq.), brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo.* Purification by column chromatography (buffered SiO_2, 10% EtOAc/X4) afforded the *title compound* **117** (198 mg, 92%) as a colourless oil. IR ($CHCl_3$, cm^{-1}) 2960, 2934, 2880, 2858, 1730, 1611, 1463, 1378, 1253, 1073, 836, 776 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 4.24–4.12 (2.4H, m), 3.98–3.88 (0.5H, m), 3.83 (0.1H, q, *J*=7.1 Hz), 3.77–3.70 (0.5H, m), 3.70–3.64 (0.4H, m), 2.74–2.52 (0.8H, m), 2.39–2.31 (0.6H, m), 2.20 (0.3H, dt, *J*=13.8, 2.9 Hz), 1.91 (0.5H, s), 1.91 (0.7H, s), 1.58–1.46 (1H, m), 1.39–1.21 (9H, m), 1.16–0.99 (1H, m), 0.95–0.88 (5H, m), 0.87–0.82 (10H, m), 0.11-0.14 (6H, m); ^{13}C NMR (151 MHz, $CDCl_3$) δ 206.4, 206.2, 205.7, 205.1, 203.9, 203.3, 202.7, 202.4, 191.93, 191.90, 191.2, 191.1, 171.7, 171.13, 171.06, 170.3, 170.23, 170.15, 170.10, 105.9, 105.7, 73.6, 73.5, 72.2, 71.5, 71.2, 71, 61.8, 61.69, 61.67, 61.4, 61.3, 60.9, 60.8, 60.6, 60.5, 52.5, 52.2, 51.8, 51.7, 46.1, 46, 44.2, 44, 43.6, 43.5, 41.7, 41.2, 41.1, 41.04, 41.01, 37.5, 37.4, 26.01, 26.00, 25.98, 25.98, 25.96, 25.95, 25.92, 25.92, 25.79, 25.77, 25.6, 18.2, 18.13, 18.11, 18.1, 14.26, 14.25, 14.2, 13.9, 13.8, 13.79, 13.7, 13.6, 13.53, 13.52, 13.5, 13.3, 13.2, 13, 12.96, 12.92, 12.73, 12.67, 12.63, 12.60, 12.5, 12.4, 12.31, 12.28, −3.4, −4.47, −4.50, −4.55, −4.56, −4.59, −4.60, −4.62, −4.62, −4.64, −4.8, −4.91, −4.94 ppm; HRESIMS calcd. for $C_{21}H_{40}O_5SiNa^+$, $[M+Na]^+$ 423.2543 found 423.2540

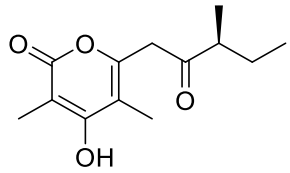


6-((2R,3S)-2-((tert-butyldimethylsilyl)oxy)-3-methylpentyl)-4-hydroxy-3,5-dimethyl-2H-pyran-2-one ***123.*** To a stirred solution of di-ketoester **117** (113 mg, 280 μmol) in benzene (10 mL) was added DBU (80 μL, 0.53 mmol) and the resulting solution heated at reflux for 12 hours. The reaction mixture was cooled to room temperature and quenched through addition of NH_4Cl (10 mL, sat. aq.). The layers were separated and the aqueous layer extracted with EtOAc (3×10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (buffered silica, 20% Et_2O/CH_2Cl_2) afforded the *title compound* **123** (99 mg, 99%) as white needles. Mp. 108–111 °C; $[\alpha]^{20}_D$ +163.6 (*c* 0.94 in $CHCl_3$); IR ($CHCl_3$, cm^{-1}) 3175, 2959, 2931, 2881, 2859, 1796, 1668, 1566, 1463, 1385, 1252, 1225, 1074; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.82 (1H, s, O*H*), 4.07 (1H, dt, *J*=9.9, 3.4 Hz, C*H*OTBS), 2.68 (1H, dd, *J*=13.9, 9.9 Hz, CH_AH$_B$CHOTBS), 2.36 (1H, dd, *J*=13.9, 3.1 Hz, CH$_A$$H_B$CHOTBS), 1.99 (3H, s, =CCH_3), 1.98 (3H, s, =CCH_3), 1.59–1.50 (1H, m, C*H*CH$_3$), 1.46–1.36 (1H, m, CHCH$_3$CH_AH$_B$), 1.17–1.07 (1H, m, CHCH$_3$CH$_A$$H_B$), 0.94 (3H, t, *J*=7.4 Hz, CH$_2$CH_3), 0.93 (3H, d, *J*=6.9 Hz, CHCH_3), 0.81 (9H, s, SiC(CH$_3$)$_3$), −0.03 (3H, s, Si(CH_3)$_A$(CH$_3$)$_B$), −0.24 (3H, s, Si(CH$_3$)$_A$(CH_3)$_B$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.5, 163.9, 157.8, 107.9, 98.2, 73.7, 41.5, 33.3, 25.9, 24.4, 18.0, 13.3, 12.5, 10.2, 8.4, −4.7, −4.9 ppm; HRESIMS calcd. for $C_{19}H_{34}O_4SiNa^+$, $[M+Na]^+$ 377.2124 found 377.2130.



4-hydroxy-6-((3S)-2-hydroxy-3-methylpentyl)-3,5-dimethyl-2H-pyran-2-one ***124***. To a stirred solution of TBS pyrone **123** (49.6 mg, 140 μmol) in 1:1 CH_2Cl_2/CH_3CN (8 mL) was added HF (0.55 mL, 30% aq.) and the mixture stirred at room temperature for 3 hours. The reaction mixture was diluted with H_2O (10 mL) and $NaHCO_3$ (10 mL, sat. aq.), washed with EtOAc (10 mL) and the aqueous layer acidified with HCl. The aqueous layer was extracted with EtOAc (3×10 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give the *title compound* **124** (33 mg, 98%) as an amorphous white solid.

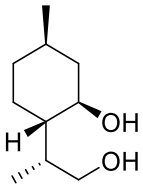
$[\alpha]^{20}_{D}$ +75.1 (*c* 0.96 in MeOH); IR (MeOH, cm^{-1}) 3400, 2964, 2927, 2877, 1670, 1567, 1494, 1452, 1404, 1380, 1238, 1211 cm^{-1}; ^{1}H NMR (600 MHz, DMSO) δ 5.67 (2H, br. s, =CO*H* and CHO*H*), 3.60 (1H, dt, *J*=9.0, 4.4 Hz, C*H*OH), 2.53–2.42 (2H, m, CH_2CHOH), 1.87 (3H, s, =CCH_3), 1.82 (3H, s, =CCH_3), 1.53–1.45 (1H, m, C*H*CH_3), 1.42–1.34 (1H, m, $CHCH_3CH_AH_B$), 1.15–1.06 (1H, m, $CHCH_3CH_AH_B$), 0.86 (3H, d, *J*=6.4 Hz, CHCH_3), 0.84 (3H, t, *J*=7.1, 6.6 Hz, CH_2CH_3); ^{13}C NMR (151 MHz, MeOD) δ 168.6, 167.9, 158.4, 110.8, 98.9, 74.4, 42.1, 36.2, 25.8, 15.2, 11.9, 10.4, 8.9; HRESIMS calcd. for $C_{13}H_{20}O_4Na^+$, $[M+Na]^+$ 263.1259 found 263.1267



(S)-4-hydroxy-3,5-dimethyl-6-(3-methyl-2-oxopentyl)-2H-pyran-2-one ***78****.*

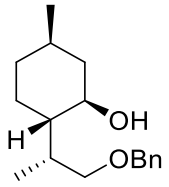
The oxidation was conducted according to a procedure from Shone *et al.*[155] To a stirred solution of pyrone **124** (15 mg, 62 μmol) in acetone (2 mL) at 0 °C was added Jones reagent dropwise until the orange colour was sustained. The reaction mixture was stirred for a further 10 minutes and then quenched through addition of isopropanol (1 mL). The reaction mixture was filtered (EtOAc), layers separated and the aqueous layer extracted with EtOAc (3×10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (buffered silica, 100% EtOAc) afforded the *title compound* **78** (7 mg, 47%) as white needles. $[\alpha]^{20}_{D}$ +16 (*c* 0.25 in MeOH); IR ($CHCl_3$, cm^{-1}) 3244, 2966, 2928, 2861, 1714, 1674, 1568, 1494, 1454, 1382, 1236, 1109 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.67 (2H, s, CH_2C=O), 2.58 (1H, h, *J*=6.8 Hz, C=OC*H*CH_3), 1.96 (3H, s, =CCH_3), 1.89 (3H, s, =CCH_3), 1.73 (1H, dp, *J*=14.2, 7.3 Hz, $CHCH_3CH_AH_B$), 1.44 (1H, dp, *J*=14.3, 7.3 Hz, $CHCH_3CH_AH_B$), 1.12 (3H, d, *J*=7.0 Hz, CHCH_3), 0.89 (3H, t, *J*=7.4 Hz, CH_2CH_3), O*H* absent; ^{13}C NMR (151 MHz, $CDCl_3$) δ 208.1, 165.4, 164.1, 151.8, 109.7, 99.4, 48.0, 43.9, 25.9, 15.9, 11.7, 10.2, 8.6; HRESIMS calcd. for $C_{13}H_{18}O_4Na^+$, $[M+Na]^+$ 261.1103 found 261.1108

6.3 Experimental Procedures for Chapter 4



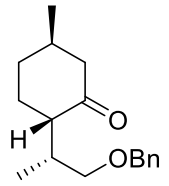
(1R,2S,5R)-2-((R)-1-hydroxypropan-2-yl)-5-methylcyclohexan-1-ol **203*a***. The hydroboration was conducted according to a procedure by Correa and Moreira.[127] To a stirred solution of (−)-isopulegol (**202**) (15.98 g, 104 mmol) in THF (150 mL) at 0 °C was added BH_3 (1M in THF, 130 mL, 130 mmol) dropwise and the resulting solution stirred for 3 hours at 0 °C. The reaction was quenched by addition of H_2O (60 mL), H_2O_2 (30%, 95 mL) and NaOH (30% w/v, 60 mL). The mixture was diluted with H_2O (100 mL) until the solution was clear. The layers were separated and the aqueous layer extracted with Et_2O (2×100 mL), with the combined organic extracts washed with brine (2×100 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. Recrystallisation from cyclohexane gave an inseparable mixture of the *title compound* **203*a*** and minor diastereomer **203*b*** (17.4 g, 98%) as colourless needles. The ratio of **203*a***:**203*b*** was determined by integration of ^{1}H NMR signals as 11.5:1.

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.66 (1H, dd, *J*=10.7, 5.6 Hz, CH_AH$_B$OH), 3.60 (1H, dd, *J*=10.6, 3.4 Hz, CH$_A$$H_B$OH), 3.47 (1H, td, *J*=10.5, 4.3 Hz, C*H*OH), 3.10 (2H, s, O*H*), 1.95 (1H, dtd, *J*=12.2, 3.8, 2.0 Hz), 1.89–1.82 (1H, m), 1.66–1.61 (1H, m), 1.56 (1H, dq, *J*=13.4, 3.5 Hz), 1.47–1.39 (1H, m), 1.40–1.32 (1H, m), 1.23 (1H, qd, *J*=13.0, 3.6 Hz), 1.00–0.94 (1H, m), 0.96 (3H, d, *J*=7.3 Hz, C5CH_3), 0.92 (3H, d, *J*=6.6 Hz, C2'CH_3), 0.90–0.84 (1H, m). ^{13}C NMR (150 MHz, $CDCl_3$): δ 71.8 (minor isomer), 70.2, 67.2, 66.4 (minor isomer), 48.9 (minor isomer), 48.7, 44.7, 38.8, 34.7, 31.6, 29.7, 22.2, 12.0 ppm.



(1R,2S,5R)-2-((R)-1-(benzyloxy)propan-2-yl)-5-methylcyclohexan-1-ol ***247***. To a stirred solution of NaH (156 mg, 6.5 mmol) in THF (15 mL) at 0 °C was added diol **203*a*** (446 mg, 2.6 mmol) portionwise. The resulting mixture was allowed to stir at 0 °C for 1 hour then BnBr (0.32 mL, 2.7 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature overnight. The reaction was quenched through slow addition of NH_4Cl (15 mL, sat. aq.). Layers were separated and the aqueous layer extracted with Et_2O (3×15 mL) and the combined organic extracts washed with brine (20 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (30% EtOAc/X4) afforded the *title compound* **247** (479 mg, 71%) as a colourless oil.

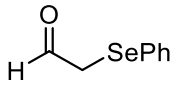
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.38–7.25 (5H, m, Ar-*H*), 4.54 (1H, d, *J*=11.9 Hz, OCH_AH$_B$Ph), 4.49 (1H, d, *J*=11.9 Hz, OCH$_A$$H_B$Ph), 3.68 (1H, d, *J*=2.9 Hz, CHO*H*), 3.51 (1H, dd, *J*=9.1, 6.2 Hz, CH_AH$_B$OBn), 3.48–3.40 (1H, m, C*H*OH), 3.39 (1H, dd, *J*=9.1, 3.6 Hz, CH$_A$$H_B$OBn), 2.10–2.01 (1H, m), 1.96 (1H, dtd, *J*=12.3, 3.8, 2.0 Hz), 1.63 (1H, dtd, *J*=12.7, 3.5, 2.3 Hz), 1.56 (1H, dq, *J*=13.2, 3.4 Hz), 1.47–1.35 (1H, m), 1.35–1.27 (1H, m), 1.14 (1H, qd, *J*=12.9, 3.6 Hz), 0.96 (3H, d, *J*=7.3 Hz, C5CH_3), 0.95–0.91 (1H, m), 0.91 (3H, d, *J*=6.6 Hz, C2'CH_3), 0.86 (1H, qd, *J*=13.0, 3.7 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 137.9, 128.6, 127.9, 127.8, 74.5, 73.5, 70.6, 49.1, 44.1, 35.7, 34.9, 31.6, 28.1, 22.3, 13.7 ppm.



(2S,5R)-2-((R)-1-(benzyloxy)propan-2-yl)-5-methylcyclohexan-1-one ***248***. The oxidation was conducted according to a procedure by Mancuso and Swern.[48] To a stirred solution of DMSO (250 μL, 3.5 mmol) in CH_2Cl_2 (12 mL) at −78 °C was added oxalyl chloride (2M in CH_2Cl_2, 0.9 mL, 1.8 mmol) dropwise and the solution stirred for 30 minutes. Alcohol **247** (0.32 g, 1.2 mmol) was added *via* cannula (CH_2Cl_2) and the solution stirred for 1.5 hours. Et_3N (0.9 mL, 6.5 mmol) was added dropwise and the

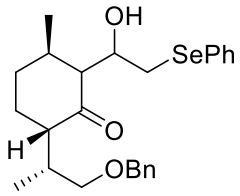
solution maintained at −78 °C for a further hour. The reaction mixture was quenched through addition of NH_4Cl (15 mL, sat. aq.) and allowed to warm to room temperature. Layers were separated and the aqueous layer extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were washed with brine (15 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (CH_2Cl_2) afforded the *title compound* **248** (0.25 g, 78%) as a colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.36–7.26 (5H, m, Ar-*H*), 4.49 (1H, d, *J*=12.1 Hz, OC*H*$_A$H$_B$Ph), 4.46 (1H, d, *J*=12.1 Hz, OCH$_A$*H*$_B$Ph), 3.47 (1H, dd, *J*=9.1, 5.3 Hz, C*H*$_A$H$_B$OBn), 3.38 (1H, dd, *J*=9.1, 6.1 Hz, CH$_A$*H*$_B$OBn), 2.37–2.31 (2H, m, C*H*$_2$C=O), 2.16 (1H, hept, *J*=6.7 Hz), 2.04 (1H, ddt, *J*=12.3, 5.0, 3.0 Hz), 1.99 (1H, td, *J*=12.8, 1.3 Hz), 1.89–1.79 (2H, m), 1.42 (1H, qd, *J*=12.5, 2.8 Hz), 1.35 (1H, tdd, *J*=12.7, 10.8, 3.0 Hz), 1.02 (3H, d, *J*=6.8 Hz, C5C*H*$_3$), 1.00 (3H, d, *J*=5.8 Hz, C2'C*H*$_3$); ^{13}C NMR (150 MHz, $CDCl_3$): δ 212.2, 138.9, 128.4, 127.7, 127.6, 73.2, 73.1, 52.4, 51.2, 35.7, 34.3, 32.8, 29.6, 22.5, 15.7 ppm.



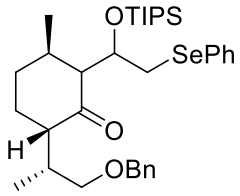
*2-(phenylselanyl)acetaldehyde **223***. The reaction was conducted according to a procedure by Petrzilka and Baudat.[157] To a stirred solution of phenylselenenyl chloride (1.1 g; 5.7 mmol) in THF (50 mL) at 0 °C was added ethyl vinyl ether (2 equiv, 1.2 mL; 12.5 mmol) and the resulting solution stirred for 10 minutes at 0 °C. The reaction mixture was poured into HCl (1M, 130 mL) and the resulting biphasic mixture stirred for 1 hour at room temperature. The layers were separated and the aqueous extracted with Et_2O (3×40 mL), and the combined organic extracts washed with $NaHCO_3$ (2×50 mL) and brine (2×50 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo* to give the crude *title compound* **223** (1.13 g, 99%) as a yellow/orange liquid.

^{1}H NMR ($CDCl_3$, 600 MHz) δ 9.46 (1H, t, *J*=4.0 Hz, C*H*O), 7.50−7.45 (2H, m, Ar-*H*), 7.30−7.20 (3H, m, Ar-*H*), 3.49 (2H, d, *J*=4.0 Hz, C*H*$_2$CHO); ^{13}C NMR (150 MHz, $CDCl_3$) δ 192.9, 133.8, 129.5, 128.4, 127.5, 36.9 ppm.



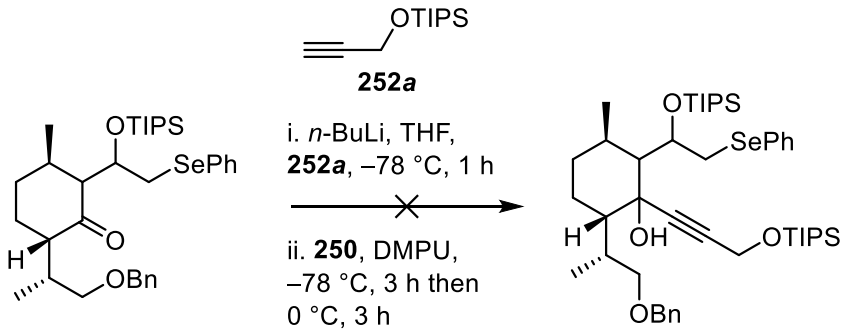
(3R,6S)-6-((R)-1-(benzyloxy)propan-2-yl)-2-(1-hydroxy-2-(phenylselanyl)ethyl)-3-methylcyclohexan-1-one ***249***. The aldol reaction was conducted according to a procedure by March and Perkins.[138] To a stirred solution of diisopropylamine (175 μL, 1.25 mmol) in THF (6 mL) at −78 °C was added *n*-BuLi (1.6M, 0.75 mL, 1.2 mmol) and the resulting solution stirred at −78 °C for 1 hour. Ketone **248** (297 mg, 1.14 mmol) was added *via* cannulation (THF) and the resulting solution stirred at −78 °C for 1.5 hours. DMPU (270 μL, 2.2 mmol) was added followed by phenylselenoacetaldehyde **223** (278 mg, 1.4 mmol) *via* cannulation and the yellow solution stirred for 3 hours at −78 °C. The reaction mixture was warmed to room temperature and quenched through addition of NH_4Cl (10 mL, sat. aq.). Layers were separated and the aqueous layer extracted with Et_2O (3×20 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (20% EtOAc/X4, buffered SiO_2) afforded the *title compound* **249** (342 mg, 65%) as a light yellow oil. NMR spectroscopy indicated the presence of a single diastereomer but the configuration was not assigned.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55–7.45 (2H, m, Ar-*H*), 7.40–7.17 (8H, m, Ar-*H*), 4.49 (1H, d, *J*=12.1 Hz, OCH_AH$_B$Ph), 4.45 (1H, d, *J*=12.1 Hz, OCH$_A$$H_B$Ph), 3.80 (1H, q, *J*=8.7 Hz, C*H*OH), 3.63–3.50 (1H, m, O*H*), 3.41 (1H, dd, *J*=9.1, 4.5 Hz, CH_AH$_B$OBn), 3.36–3.29 (2H, m, CH$_A$$H_B$OBn and C$H_AH_B$SePh), 3.09 (1H, dd, *J*=12.5, 9.0 Hz, CH$_A$$H_B$SePh), 2.46 (1H, dt, *J*=11.5, 1.4 Hz, C*H*CHOH), 2.32–2.21 (1H, m), 2.11–1.99 (3H, m), 1.91–1.81 (1H, m), 1.51–1.29 (2H, m), 1.00 (3H, d, *J*=6.4 Hz, C3CH_3), 0.95 (3H, d, *J*=6.8 Hz, C6'CH_3).

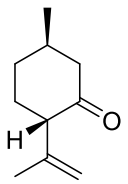


(3R,6S)-6-((R)-1-(benzyloxy)propan-2-yl)-3-methyl-2-(2-(phenylselanyl)-1-((triisopropylsilyl)oxy)ethyl)cyclohexan-1-one ***250***. To a stirred solution of hydroxyselenide **249** (207 mg, 0.45 mmol) in CH_2Cl_2 (5 mL) at −78 °C was added 2, 6-lutidine (100 μL, 0.86 mmol) and TIPSOTf (170 μL, 0.63 mmol) sequentially. The resulting solution was stirred at −78 °C for 4 hours then quenched through addition of $NaHCO_3$ (5 mL, sat. aq.) and warmed to room temperature. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (5% EtOAc/X4, buffered SiO_2) afforded the *title compound* **250** (241 mg, 86%) as a light yellow oil.

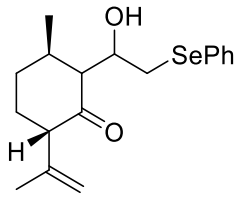
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51–7.43 (2H, m, Ar-*H*), 7.29–7.11 (8H, m, Ar-*H*), 4.53 (1H, s, C*H*OH), 4.44 (1H, d, *J*=12.1 Hz, OCH_AH$_B$Ph), 4.38 (1H, d, *J*=12.1 Hz, OCH$_A$$H_B$Ph), 3.41 (1H, dd, *J*=9.1, 4.7 Hz, CH_AH$_B$OBn), 3.34–3.30 (1H, m, CH_AH$_B$SePh), 3.29 (1H, dd, *J*=9.1, 6.2 Hz, CH$_A$$H_B$OBn), 3.11 (1H, dd, *J*=11.7, 6.6 Hz, CH$_A$$H_B$SePh), 3.07 (0.13H, dd, *J*=11.8, 7.4 Hz, minor isomer), 2.37 (1H, dt, *J*=11.7, 1.4 Hz, C*H*CHOH), 2.23–2.09 (2H, m), 1.98–1.89 (2H, m), 1.82 (1H, dq, *J*=12.8, 3.1 Hz), 1.46–1.29 (2H, m), 1.09 (3H, d, *J*=6.4 Hz, C3CH_3), 1.05–0.94 (12H, m, O*TIPS*), 0.96 (9H, d, *J*=5.6 Hz, O*TIPS*), 0.93 (3H, d, *J*=6.8 Hz, C6'CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 210.9, 138.9, 132.6, 131.6, 129.3, 129.1, 128.4, 127.9, 127.7, 127.5, 126.8, 73.2, 73.1, 70.7, 53.6, 36.3, 35.2, 32.6, 32.2, 28.9, 18.4, 15.9, 13 ppm.



(3R,6S)-6-((R)-1-((benzyl)oxy)propan-2-yl)-3-methyl-2-(2-(phenylselanyl)-1-((triisopropylsilyl)oxy)ethyl)-1-(3-((triisopropylsilyl)oxy)prop-1-yn-1-yl)cyclohexan-1-ol **254**. The acetylide addition was conducted according to a procedure by March and Perkins.[138] To a stirred solution of OTIPS alkyne **252*a*** (127 mg, 0.6 mmol) in THF (4 mL) at −78 °C was added *n*-BuLi (1.6 M in hexane, 0.35 mL, 0.55 mmol) dropwise and the resulting solution stirred for 1 hour at −78 °C. DMPU (1 mL) was added followed by addition of ketone **250** (78 mg, 0.13 mmol) *via* cannulation (THF). The resulting solution was stirred for 3 hours at −78 °C, then warmed to 0 °C and stirred for a further 3 hours. The reaction was quenched with NH_4Cl (5 mL, sat. aq.). The biphasic mixture was diluted with H_2O and Et_2O, layers separated and the aqueous layer extracted with Et_2O (3×20 mL). The combined organic layers were washed with H_2O (10 mL), $NaHCO_3$ (10 mL, sat. aq.) and brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Analysis of the crude ^1H NMR spectrum indicated the presence of only starting materials with the benzyl ketone **250** and alkyne **252*a*** recoverable by column chromatography.

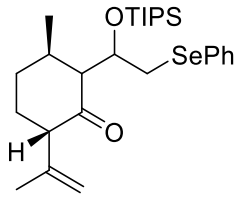


(2S,5R)-5-methyl-2-(prop-1-en-2-yl)cyclohexan-1-one ***255***. The oxidation was conducted according to a procedure by Mancuso and Swern.[48] To a stirred solution of DMSO (3.7 mL, 52 mmol) in CH_2Cl_2 (100 mL) at −78 °C was added oxalyl chloride (2M in CH_2Cl_2, 13.4 mL, 26.8 mmol) dropwise and the solution stirred for 30 minutes. (−)-isopulegol **202** (2.77 g, 18 mmol) was added *via* cannula (CH_2Cl_2) and the solution stirred for 1.5 hours. Et_3N (14 mL, 100 mmol) was added dropwise and the solution maintained at −78 °C for a further hour. The reaction mixture was quenched through addition of NH_4Cl (50 mL, sat. aq.) and allowed to warm to room temperature. Layers were separated and the aqueous layer extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (10% EtOAc/X4) afforded the *title compound* **255** (2.54 g, 93%) as a colourless oil. NMR data matched the reported literature data. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.93 (1H, p, *J*=1.5 Hz, =CH_AH$_B$), 4.71 (1H, dt, *J*=1.7, 0.8 Hz, =CH$_A$$H_B$), 2.95 (1H, ddt, *J*=13.0, 5.4, 1.0 Hz, C*H*C=O), 2.40 (1H, ddd, *J*=13.3, 4.0, 2.2 Hz), 2.07–2.01 (2H, m), 1.95–1.88 (2H, m), 1.79 (1H, qd, *J*=13.0, 3.4 Hz), 1.75–1.73 (3H, m, C(CH_3)=CH$_2$), 1.42 (1H, tdd, *J*=12.9, 11.4, 3.5 Hz), 1.03 (3H, d, *J*=6.5 Hz, C5CH_3)



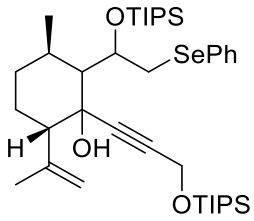
(3R,6S)-2-(1-hydroxy-2-(phenylselanyl)ethyl)-3-methyl-6-(prop-1-en-2-yl)cyclohexan-1-one ***256***. The aldol reaction was conducted according to a procedure by March and Perkins.[138] To a stirred solution of diisopropylamine (1 mL, 7.13 mmol) in THF (20 mL) at −78 °C was added *n*-BuLi (4.29 mL, 6.87 mmol) and the resulting solution warmed to 0 °C for 30 minutes. The solution was re-cooled to −78 °C and ketone **255** (0.996 g, 6.54 mmol) added *via* cannulation. The resulting solution was stirred for 1 hour at −78 °C before subsequent addition of DMPU (1.6 mL, 13.2 mmol) and phenylselenoacetaldehyde **223** (1.01 g, 5.07 mmol). The solution was stirred for 1.5

hours at −78 °C before warming to room temperature. The reaction was quenched through addition of NH_4Cl (20 mL, sat. aq.), layers separated and the aqueous layer extracted with Et_2O (3×20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (20% EtOAc/X4) afforded the *title compound* **256** (1.27 g, 71%) as a colourless oil. NMR spectroscopy indicated the presence of a single diastereomer but the configuration was not assigned. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53–7.48 (2H, m, Ar-*H*), 7.28–7.22 (3H, m, Ar-*H*), 4.93 (1H, t, *J*=1.5 Hz, =CH_AH$_B$), 4.67–4.65 (1H, m, =CH$_A$$H_B$), 3.83 (1H, dddd, *J*=11.1, 9.2, 5.7, 1.6 Hz, C*H*OH), 3.40 (1H, d, *J*=11.4 Hz, O*H*), 3.33 (1H, dd, *J*=12.6, 5.8 Hz, CH_AH$_B$SePh), 3.15 (1H, dd, *J*=12.6, 9.2 Hz, CH$_A$$H_B$SePh), 2.84 (1H, dd, *J*=13.2, 5.3 Hz, C6*H*), 2.52 (1H, dt, *J*=11.6, 1.4 Hz, C*H*CHOH), 2.10 (1H, tqd, *J*=12.5, 6.4, 3.8 Hz), 2.05–2.00 (1H, m), 1.93 (1H, dq, *J*=13.5, 3.6 Hz), 1.78 (1H, qd, *J*=13.2, 3.6 Hz), 1.69 (3H, s, C(CH_3)=CH$_2$), 1.57–1.46 (1H, m), 1.04 (3H, d, *J*=6.4 Hz, C3CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 214.9, 142.8, 133.1, 129.7, 129.4, 127.3, 113.2, 70.3, 59.1, 58.9, 38.2, 34.5, 32.9, 32.2, 21.8, 20.4 ppm.



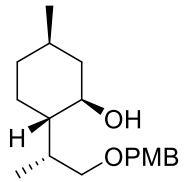
*(3R,6S)-3-methyl-2-(2-(phenylselanyl)-1-((triisopropylsilyl)oxy)ethyl)-6-(prop-1-en-2-yl)cyclohexan-1-one **257***. To a stirred solution of alcohol **256** (0.495 g, 1.41 mmol) in CH_2Cl_2 (20 mL) at −78 °C was added 2, 6-lutidine (0.35 mL, 3 mmol) and TIPSOTf (0.6 mL, 2.2 mmol) sequentially. The solution was stirred at −78 °C for 2 hours then allowed to warm to 0 °C. The reaction was quenched through addition of $NaHCO_3$ (15 mL, sat. aq.), layers separated and the aqueous layer extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (10% EtOAc/X4, buffered SiO_2) afforded the *title compound* **257** (0.71 g, 99%) as a light yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.55–7.50 (2H, m, Ar-*H*), 7.26–7.19 (3H, m, Ar-*H*), 4.92 (1H, p, *J*=1.5 Hz, =CH_AH$_B$), 4.69 (1H, dt, *J*=1.8, 0.9 Hz, =CH$_A$$H_B$), 4.58 (1H, s, C*H*OTIPS), 3.45 (1H, t, *J*=10.4 Hz, CH_AH$_B$SePh), 3.16 (1H, dd, *J*=11.9, 5.9 Hz, CH$_A$$H_B$SePh), 2.84 (1H, dd, *J*=13.4, 5.1 Hz, C6*H*), 2.46 (1H, d, *J*=11.6 Hz, C*H*CHOTIPS), 2.11–2.01 (1H, m), 1.98–1.90 (2H, m), 1.82 (1H, qd, *J*=13.9, 13.3, 3.5 Hz), 1.71 (3H, s, C(CH_3)=CH$_2$),

1.57–1.47 (1H, m), 1.15 (3H, d, *J*=6.4 Hz, C3C*H*$_3$), 1.06–1.03 (12H, m, O*TIPS*), 1.03–0.99 (9H, m, O*TIPS*); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.7, 143.9, 132.9, 129.2, 127, 113.3, 70.8, 59.2, 35.7, 34.8, 32.3, 30.5, 21, 18.4, 13 ppm.



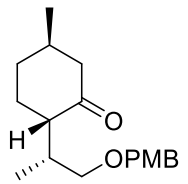
(3R,6S)-3-methyl-2-(2-(phenylselanyl)-1-((triisopropylsilyl)oxy)ethyl)-6-(prop-1-en-2-yl)-1-(3-((triisopropylsilyl)oxy)prop-1-yn-1-yl)cyclohexan-1-ol ***258***. The acetylide addition was conducted according to a procedure by March and Perkins.[138] To a stirred solution of OTIPS alkyne **252*a*** (439 mg, 2.07 mmol) in THF (13 mL) at −78 °C was added *n*-BuLi (1.6 M in hexane, 1.25 mL, 2.0 mmol) dropwise and the resulting solution stirred for 1 hour at −78 °C. DMPU (0.25 mL, 2.07 mmol) was added and the solution stirred for 10 minutes at −78 °C before addition of Ketone **257** (256 mg, 0.5 mmol) *via* cannulation (THF). The resulting solution was stirred for 4 hours at −78 °C, then warmed to room temperature and quenched with NH_4Cl (20 mL, sat. aq.). The biphasic mixture was diluted with H_2O and Et_2O, layers separated and the aqueous layer extracted with Et_2O (3×20 mL). The combined organic layers were washed with H_2O (10 mL), $NaHCO_3$ (10 mL, sat. aq.) and brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (20% CH_2Cl_2/X4, buffered SiO_2) afforded the *title compound* **258** (0.263 g, 72%) as a colourless oil. NMR spectroscopy indicated the presence of two diastereomers (3:2 as determined by ^{1}H NMR integration).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.61–7.49 (2H, m), 7.29–7.10 (3H, m), 5.03–4.94 (1H, m), 4.91 (0.5H, s), 4.83 (1.5H, m,), 4.55–4.44 (1H, m), 4.42 (1H, s), 4.27 (1H, q, *J*=15.5 Hz), 3.77 (0.4H, d, *J*=12.5 Hz), 3.16 (0.4H, t, *J*=11.2 Hz), 3.07 (0.6H, dd, *J*=11.8, 3.4 Hz), 2.28 (0.4H, s), 2.18 (0.6H, d, *J*=14.9 Hz), 2.09–1.94 (3H, m), 1.90–1.81 (3H, m), 1.73 (2H, m), 1.47–1.35 (1H, m), 1.17–1.05 (33H, m), 1.02 (9H, d, *J*=10.7 Hz), 0.94 (3H, d, *J*=6.5 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ 148.7, 147.1, 134.5, 132.4, 131.5, 123, 129.1, 128.9, 127.6, 125.8, 113.4, 112.4, 89.6, 88.1, 84.5, 84.1, 75.5, 75.3, 71.3, 70.1, 58.7, 56.6, 54.6, 52.4, 52, 51.2, 36.3, 36, 35.2, 33.4, 29.9, 29.2, 27.9, 27.1, 27, 26.4, 23.3, 21.9, 21, 18.6, 18.23, 18.22, 18.17, 18.08, 13, 12.1 ppm.



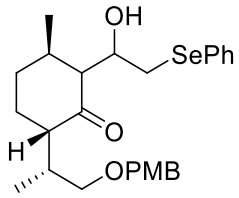
(1R, 2S, 5R)-2-((R)-1-((4-methoxybenzyl)oxy)propan-2-yl)-5-methylcyclohexan-1-ol ***259***. To a stirred suspension of NaH (0.82 g, 34.2 mmol) in DMF (90 mL) at 0 °C was added diol **203*a*** (2.9 g, 16.8 mmol) portionwise and the resulting suspension stirred for 1 hour. The reaction mixture was cooled to −50 °C and PMBCl (2.28 mL, 16.8 mmol) added slowly over 10 minutes. The reaction mixture was stirred for 1.5 hours at −50 °C then allowed to warm to room temperature overnight. The reaction was quenched by addition of NH_4Cl (90 mL, sat. aq.) and layers separated. The aqueous layer was extracted with EtOAc (3×100 mL) and the combined organic layers washed with LiCl (5% aq., 3×100 mL), brine (2×100 mL), dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography (20% EtOAc/X4) afforded the *title compound* **259** (3.54 g, 72%) as a colourless oil.

$[\alpha]^{20}_D$ −10.4 (*c* 0.96 in $CHCl_3$); IR ($CHCl_3$, cm^{-1}) 3420, 2998, 2949, 2920, 2866, 1613, 1586, 1514, 1455, 1364, 1302, 1248, 1174, 1041 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.27–7.21 (2H, m, Ar-*H*), 6.90–6.84 (2H, m, Ar-*H*), 4.47 (1H, d, *J*=11.5 Hz, OC$H_A$$H_B$PMP), 4.42 (1H, d, *J*=11.5 Hz, OC$H_A$$H_B$PMP), 3.80 (3H, s, OC$H_3$), 3.69 (1H, s, CHO*H*), 3.47 (1H, dd, *J*=9.1, 6.3 Hz, C$H_A$$H_B$OPMB), 3.42 (1H, td, *J*=10.5, 4.2 Hz, C*H*OH), 3.36 (1H, dd, *J*=9.1, 3.4 Hz, C$H_A$$H_B$OPMB), 2.03 (1H, dtd, *J*=14.1, 6.9, 3.5 Hz), 1.96 (1H, dtd, *J*=12.4, 3.8, 2.1 Hz), 1.63 (1H, dp, *J*=12.6, 3.4 Hz), 1.55 (1H, dq, *J*=13.2, 3.4 Hz), 1.40 (1H, tdp, *J*=13.0, 6.5, 3.0 Hz), 1.30 (1H, ddt, *J*=12.6, 10.0, 3.1 Hz), 1.13 (1H, qd, *J*=13.0, 3.7 Hz), 0.96–0.92 (1H, m), 0.94 (3H, d, *J*=7.3 Hz, C5CH_3), 0.91 (3H, d, *J*=6.6 Hz, C2'CH_3), 0.86 (1H, qd, *J*=12.9, 3.6 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.4, 130.0, 129.5, 114.0, 74.2, 73.1, 70.5, 55.4, 49.2, 44.1, 35.7, 34.9, 31.6, 28.2, 22.3, 13.6 ppm; HRESIMS calcd. for $C_{18}H_{28}O_3Na^+$, $[M+Na]^+$ 315.1936 found 315.1942

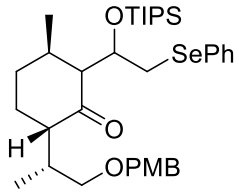


(2S, 5R)-2-((R)-1-((4-methoxybenzyl)oxy)propan-2-yl)-5-methylcyclohexan-1-one ***260***. The oxidation was conducted according to a procedure by Mancuso and Swern.[48] To a stirred solution of DMSO (3 mL, 42.2 mmol) in CH_2Cl_2 (70 mL) at −78 °C was added oxalyl chloride (2M in CH_2Cl_2, 9.4 mL, 18.8 mmol) dropwise and the solution stirred for 30 minutes. Alcohol **259** (3.54 g, 12.1 mmol) was added *via* cannula (CH_2Cl_2) and the solution stirred for 1.5 hours. Et_3N (10 mL, 71.7 mmol) was added dropwise and the solution maintained at −78 °C for a further hour. The reaction mixture was quenched through addition of NH_4Cl (40 mL, sat. aq.) and allowed to warm to room temperature. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3×30 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (10% EtOAc/X4) afforded the *title compound* **260** (3.25 g, 92%) as a colourless oil.

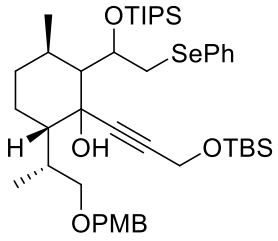
$[\alpha]^{20}_D$ −10.9 (*c* 0.92 in $CHCl_3$); IR ($CHCl_3$, cm^{-1}) 2954, 2926, 2865, 1709, 1586, 1514, 1455, 1375, 1302, 1247, 1172, 1089, 823 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.26–7.21 (2H, m, Ar-*H*), 6.90–6.84 (2H, m, Ar-*H*), 4.40 (2H, AB quartet, 12.0 Hz, C*H*$_2$PMP), 3.80 (3H, s, OC*H*$_3$), 3.44 (1H, dd, *J*=9.1, 5.4 Hz, C*H*$_A$H$_B$OPMB), 3.35 (1H, dd, *J*=9.1, 6.0 Hz, CH$_A$*H*$_B$OPMB), 2.36–2.29 (2H, m, C*H*$_2$C=O), 2.14 (1H, hept, *J*=6.6 Hz), 2.02 (1H, ddt, *J*=12.0, 5.5, 3.1 Hz), 1.97 (1H, t, *J*=13.0 Hz), 1.89–1.79 (2H, m), 1.41 (1H, qd, *J*=12.5, 2.8 Hz), 1.34 (1H, qd, *J*=12.5, 3.0 Hz), 1.00 (3H, d, *J*=6.4 Hz), 0.99 (3H, d, *J*=6.9 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 212.0, 159.1, 130.9, 129.2, 113.7, 72.8, 72.7, 55.3, 52.3, 51.1, 35.6, 34.2, 32.8, 29.6, 22.4, 15.6 ppm; HRESIMS calcd. for $C_{18}H_{26}O_3Na^+$, $[M+Na]^+$ 313.1780 found 313.1779.



(3R, 6S)-2-(1-hydroxy-2-(phenylselanyl)ethyl)-6-((R)-1-((4-methoxybenzyl)oxy)propan-2-yl)-3-methylcyclohexan-1-one ***261***. To a stirred solution of ketone **260** (2.02 g, 6.96 mmol) in THF (10 mL) at −78 °C was added LiHMDS (1M in THF, 9 mL, 9 mmol) dropwise and the resulting solution stirred for 1 hour. Aldehyde **223** (1.99 g, 9.99 mmol) was added dropwise over 10 minutes and the resulting solution stirred at −78 °C for 3 hours. The reaction mixture was diluted with Et_2O (20 mL), quenched through addition of NH_4Cl (10 mL) and extracted with Et_2O (3×20 mL). The combined organic extracts were washed with $NaHCO_3$ (10 mL), H_2O (10 mL) and brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (10% EtOAc/X4) to afford the *title compound* **261** (2.84 g, 83%) as a light yellow oil. NMR spectroscopy indicated the presence of a single diastereomer but the configuration was not assigned. $[\alpha]^{20}_{D}$ negligible rotation; IR ($CHCl_3$, cm^{-1}) 3517, 3056, 2927, 2854, 1692, 1612, 1579, 1513, 1302, 1248, 1173, 1086, 1035, 820, 738, 692 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.52–7.47 (2H, m, Ar-*H*), 7.28–7.20 (5H, m, Ar-*H*), 6.90–6.86 (2H, m, Ar-*H*), 4.42 (1H, d, *J*=11.7 Hz, C$H_A$$H_B$PMP), 4.37 (1H, d, *J*=11.7 Hz, C$H_A$$H_B$PMP), 3.81 (4H, m, OC$H_3$ and C*H*OH), 3.56 (1H, s, O*H*), 3.37 (1H, dd, *J*=9.1, 4.5 Hz, C$H_A$$H_B$OPMB), 3.32 (1H, dd, *J*=12.5, 5.9 Hz, C$H_A$$H_B$SePh), 3.29 (1H, dd, *J*=9.2, 5.7 Hz, C$H_A$$H_B$OPMB), 3.09 (1H, dd, *J*=12.5, 8.9 Hz, C$H_A$$H_B$SePh), 2.46 (1H, dt, *J*=11.6, 1.4 Hz, C*H*CHOH), 2.29–2.22 (1H, m), 2.08–1.98 (3H, m), 1.85 (1H, dq, *J*=13.2, 3.4 Hz), 1.43 (1H, qd, *J*=13.2, 3.6 Hz), 1.34 (1H, qd, *J*=12.9, 3.4 Hz), 1.00 (3H, d, *J*=6.4 Hz, C3CH_3), 0.93 (3H, d, *J*=6.9 Hz, C6'CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 217.3, 159.2, 133.0, 130.9, 129.7, 129.3, 129.3, 127.3, 113.9, 72.9, 72.4, 70.2, 59.2, 55.4, 54.6, 38.7, 34.7, 32.9, 32.3, 31.1, 20.3, 16.3 ppm; HRESIMS calcd. for $C_{26}H_{34}O_4{}^{80}SeNa^+$, $[M+Na]^+$ 513.1520 found 513.1500

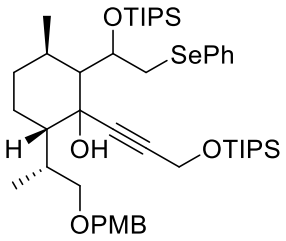


(3R, 6S)-6-((R)-1-((4-methoxybenzyl)oxy)propan-2-yl)-3-methyl-2-(2-(phenylselanyl)-1-((triisopropylsilyl)oxy)ethyl)cyclohexan-1-one ***262***. To a stirred solution of alcohol **261** (1.15 g, 2.35 mmol) in CH_2Cl_2 (30 mL) at −78 °C was added 2, 6-lutidine (0.52 mL, 4.5 mmol) and TIPSOTf (0.89 mL, 3.3 mmol) sequentially. The resulting solution was stirred for 3 hours at −78 °C then warmed to room temperature. The reaction was quenched by addition of $NaHCO_3$ (30 mL, sat. aq.), layers separated and the aqueous layer extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (5% EtOAc/X4) gave the *title compound* **262** (1.49 g, 98%) as a light yellow oil. $[\alpha]^{20}_D$ −13.4 (*c* 0.97 in $CHCl_3$); IR ($CHCl_3$, cm^{-1}) 3050, 2926, 2865, 1705, 1613, 1580, 1513, 1463, 1364, 1301, 1248, 1172, 1109, 1040, 883, 821, 736, 681 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.55–7.50 (2H, m, Ar-*H*), 7.27–7.19 (5H, m, Ar-*H*), 6.89–6.84 (2H, m, Ar-*H*), 4.61 (1H, br. s, C*H*OTIPS), 4.40 (2H, AB quartet, 11.4 Hz, CH_AH_BPMP), 3.79 (3H, s, OCH_3), 3.44 (1H, dd, *J*=9.1, 4.8 Hz, CH_AH$_B$OPMB), 3.41–3.35 (1H, m, CH_AH$_B$SePh), 3.32 (1H, dd, *J*=9.1, 6.2 Hz, CH$_A$$H_B$OPMB), 3.17 (1H, dd, *J*=11.7, 6.5 Hz, CH$_A$$H_B$SePh), 2.43 (1H, d, *J*=11.6 Hz, C*H*CHOH), 2.24 (1H, dt, *J*=13.3, 5.4 Hz), 2.17 (1H, hept, *J*=6.7 Hz), 2.04–1.94 (2H, m), 1.92–1.85 (1H, m), 1.49–1.34 (2H, m), 1.15 (3H, d, *J*=6.4 Hz, C3CH_3), 1.08–1.01 (21H, m, O*TIPS*), 0.98 (3H, d, *J*=6.9 Hz, C6'CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 210.8, 159.2, 132.6, 131.6, 131.0, 129.3, 129.1, 126.8, 113.8, 72.9, 72.8, 70.8, 55.4, 53.6, 36.2, 35.3, 32.6, 32.2, 28.9, 21.7, 18.4, 17.8, 15.9, 13.0 ppm; HRESIMS calcd. for $C_{35}H_{54}O_4{}^{80}SeSiNa^+$, $[M+Na]^+$ 669.2854 found 669.2825

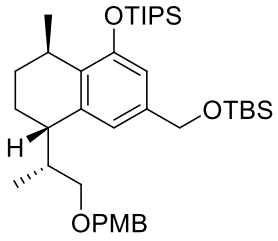


(1R, 3R, 6S)-1-(3-((tert-butyldimethylsilyl)oxy)prop-1-yn-1-yl)-6-((R)-1-((4-methoxybenzyl)oxy)propan-2-yl)-3-methyl-2-(2-(phenylselanyl)-1-((triisopropylsilyl)oxy)ethyl)cyclohexan-1-ol ***263b***. The acetylide addition was conducted according to a procedure by March and Perkins.[138] To a stirred solution of OTBS alkyne **252*b*** (1.28 g, 7.51 mmol) in THF (40 mL) at −78 °C was added *n*-BuLi (1.6M in hexane, 4.5 mL, 7.2 mmol) dropwise and the resulting solution stirred for 1 hour. Ketone **262** (1.18 g, 1.83 mmol) in THF (10 mL) was added *via* cannula and the reaction mixture stirred for 2 hours at −78 °C. The reaction was quenched through addition of NH_4Cl (30 mL, sat. aq.), layers separated and the aqueous layer extracted with Et_2O (3×30 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (5% EtOAc/X4) afforded the *title compound* **263*b*** (1.28 g, 86%) as a colourless oil. NMR spectroscopy indicated the presence of a single diastereomer but the configuration was not assigned. $[\alpha]^{20}_D$ +35.7 (*c* 0.95 in $CHCl_3$); IR ($CHCl_3$, cm^{-1}) 3335, 3057, 2928, 2863, 1613, 1581, 1515, 1463, 1362, 1303, 1251, 1160, 1083, 836 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.52–7.49 (2H, m, Ar-*H*), 7.28 –7.24 (2H, m, Ar-*H*), 7.09–7.04 (3H, m, Ar-*H*), 6.86–6.82 (2H, m, Ar-*H*), 5.40 (1H, s, O*H*), 4.94 (1H, d, *J*=10.3 Hz, C*H*OTIPS), 4.52 (1H, d, *J*=11.6 Hz, CH_AH$_B$PMP), 4.46 (1H, d, *J*=11.5 Hz, CH$_A$$H_B$PMP), 4.22 (1H, d, *J*=15.9 Hz, CH_AH$_B$OTBS), 4.14 (1H, d, *J*=15.9 Hz, CH$_A$$H_B$OTBS), 3.94–3.88 (1H, m, CH_AH$_B$SePh), 3.75 (3H, s, OCH_3), 3.29 (1H, t, *J*=10.4 Hz, CH_AH$_B$OPMB), 3.21 (1H, dd, *J*=9.9, 3.2 Hz, CH$_A$$H_B$OPMB), 3.09 (1H, dd, *J*=12.7, 10.3 Hz, CH$_A$$H_B$SePh), 2.90 (1H, t, *J*=7.6 Hz, C6'*H*), 2.01–1.90 (1H, m), 1.77 (1H, dd, *J*=12.9, 3.5 Hz), 1.59 (1H, d, *J*=11.4 Hz, C*H*CHOTIPS), 1.48–1.41 (2H, m), 1.40–1.34 (2H, m), 1.19 (3H, h, *J*=6.8 Hz, O*TIPS*), 1.13 (3H, d, J=6.1 Hz, C3CH_3), 1.06 (9H, d, 10.9 Hz, O*TIPS*), 1.05 (9H, d, 10.9 Hz, O*TIPS*), 0.89 (12H, m, SiC(CH_3)$_3$ and C6'CH_3), 0.08 (6H, s, Si(CH_3)$_2$). ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.5, 132.7, 130.7, 129.7, 129.2, 128.7, 125.2, 114, 89.1, 84.4, 75.8, 73, 72.4, 71.6, 59.4, 55.3, 54, 51.9, 36.7, 33.4, 32.8, 29.9, 28.2, 25.9,

22, 19.6, 18.7, 18.6, 18.5, 18.3, 13, 1.2, −5.06, −5.08 ppm; HRESIMS calcd. for $C_{44}H_{72}O_5Si_2(80)SeNa^+$, $[M+Na]^+$ 839.3987 found 839.3977



(3R,6S)-6-((R)-1-((4-methoxybenzyl)oxy)propan-2-yl)-3-methyl-2-(2-(phenylselanyl)-1-((triisopropylsilyl)oxy)ethyl)-1-(3-((triisopropylsilyl)oxy)prop-1-yn-1-yl)cyclohexan-1-ol **263*a***. The procedure previously used for the preparation of **263*b*** was used with TIPS alkyne **252*a*** (1.20 g, 5.65 mmol) and ketone **262** (870 mg, 1.35 mmol). Purification by column chromatography (5% EtOAc/X4) afforded the *title compound* **263*a*** (0.96 g, 83%) as a colourless oil. NMR spectroscopy indicated the presence of a single diastereomer but the configuration was not assigned. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56–7.44 (2H, m, Ar-*H*), 7.31–7.21 (2H, m, Ar-*H*), 7.14–6.99 (3H, m, Ar-*H*), 6.92–6.75 (2H, m, Ar-*H*), 5.40 (1H, s, O*H*), 4.94 (1H, d, *J*=10.3 Hz, C*H*OTIPS), 4.54 (1H, d, *J*=11.6 Hz, CH_AH$_B$PMP), 4.45 (1H, d, *J*=11.5 Hz, CH$_A$$H_B$PMP), 4.30 (1H, d, *J*=15.6 Hz, CH_AH$_B$OTIPS), 4.21 (1H, d, *J*=15.7 Hz, CH$_A$$H_B$OTIPS), 3.91 (1H, d, *J*=12.6 Hz, CH_AH$_B$SePh), 3.75 (3H, s, OCH_3), 3.29 (1H, t, *J*=10.5 Hz, CH_AH$_B$OPMB), 3.20 (1H, dd, *J*=9.9, 3.2 Hz, CH$_A$$H_B$OPMB), 3.09 (1H, dd, *J*=12.7, 10.3 Hz, CH$_A$$H_B$SePh), 2.96–2.91 (1H, m, C6'*H*), 1.95 (1H, ddq, *J*=14.2, 6.8, 4.0, 2.8 Hz), 1.77 (1H, dd, *J*=13.0, 3.6 Hz), 1.59 (2H, d, *J*=11.5 Hz, C*H*CHOTIPS), 1.48–1.39 (2H, m), 1.39–1.34 (1H, m), 1.27–1.15 (4H, m), 1.13 (3H, d, *J*=6.5 Hz, C3CH_3), 1.10–1.02 (39H, m, O*TIPS*), 0.86 (3H, d, *J*=7.2 Hz, C6'CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.50, 132.74, 130.71, 129.61, 129.24, 128.74, 125.16, 114.01, 88.97, 84.41, 77.37, 77.16, 76.95, 75.86, 72.93, 72.41, 71.60, 59.44, 55.38, 54.05, 52.25, 36.69, 33.39, 32.87, 28.20, 21.96, 19.63, 18.65, 18.63, 18.44, 18.08, 18.07, 13.22, 13.02, 12.14, 11.94 ppm.

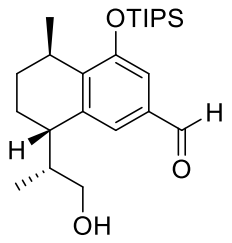


Tert-butyl(((5R, 8S)-8-((R)-1-((4-methoxybenzyl)oxy)propan-2-yl)-5-methyl-4-((triisopropylsilyl)oxy)-5,6,7,8-tetrahydronaphthalen-2-yl)methoxy)dimethylsilane ***265***. The selenoxide elimination was conducted according to a procedure by Engman.[139] To a stirred solution of phenylselenide **263*b*** (1.08 g, 1.32 mmol) in benzene (20 mL) at 10 °C was added *m*CPBA (290 mg, 1.68 mmol) in portions and the resulting solution stirred for 20 minutes. Benzene (40 mL) and $NaHCO_3$ (60 mL, sat. aq.) were added and the biphasic mixture heated at 90 °C for 12 hours. The reaction mixture was allowed to cool to room temperature and the layers separated. The organic layer was washed with $NaHCO_3$ (30 mL) and brine (30 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude yellow enyne **264** was used without further purification.

The cycloisomerisation was conducted according to a procedure by March and Perkins.[138] To a stirred solution of crude enyne **264** (233 mg, 0.35 mmol) in 1, 2-dichloroethane (10 mL) at reflux was added $AgNO_3$ (10 mg; 59 μmol) and the resulting yellow solution heated at reflux overnight in darkness. The reaction mixture was allowed to cool to room temperature then diluted with CH_2Cl_2 (10 mL) and quenched by addition of $NaHCO_3$ (10 mL). The organic layer was separated and washed with brine (15 mL), dried (Na_2SO_4) and concentrated *in vacuo.* Purification by column chromatography (5% EtOAc/X4) afforded the *title compound* **265** (142 mg, 51%) as a colourless oil.

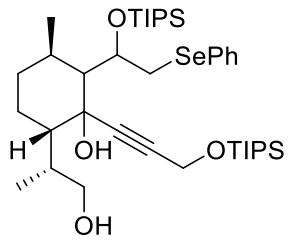
$[\alpha]^{20}_{D}$ −21.3 (C 0.75 in $CHCl_3$); IR ($CHCl_3$, cm^{-1}) 2926, 2864, 1717, 1611, 1576, 1514, 1494, 1463, 1368, 1249, 1092, 777 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.22 (2H, d, *J*=8.3 Hz, PMP-*H*), 6.87–6.83 (2H, m, PMP-*H*), 6.68 (1H, s, Ar-*H*), 6.60 (1H, s, Ar-*H*), 4.61 (2H, s, C*H*$_2$OTBS), 4.38 (1H, d, *J*=11.6 Hz, C*H*$_A$H$_B$PMP), 4.33 (1H, d, *J*=11.6 Hz, CH$_A$*H*$_B$PMP), 3.80 (3H, s, OC*H*$_3$), 3.31 (1H, dd, *J*=9.0, 4.3 Hz, C*H*$_A$H$_B$OPMB), 3.24 (1H, t, *J*=8.6 Hz, CH$_A$*H*$_B$OPMB), 3.20–3.14 (1H, m, C1*H*), 2.71 (1H, t, *J*=5.5 Hz, C4*H*), 2.15–2.06 (1H, m), 1.90 (1H, tdd, *J*=13.7, 6.1, 3.2 Hz), 1.82–1.75 (1H, m), 1.73–1.66 (1H, m), 1.49 (1H, d, *J*=12.9 Hz), 1.31 (3H, dq, *J*=13.7, 6.9, 6.3 Hz, O*TIPS*), 1.15 (3H, d, *J*=6.8 Hz,

C1C*H*$_3$), 1.13 (9H, d, *J*=7.5 Hz, O*TIPS*), 1.09 (9H, d, *J*=7.5 Hz, O*TIPS*), 0.94 (3H, d, *J*=6.9 Hz, C11C*H*$_3$), 0.93 (9H, s, SiC(C*H*$_3$)$_3$), 0.08 (6H, s, Si(C*H*$_3$)$_2$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.2, 153.8, 139.6, 138.5, 131.9, 131.1, 129.2, 119.9, 113.8, 113.6, 74, 72.7, 65.1, 55.4, 40.1, 39.8, 27.2, 27, 26.1, 21.7, 20.7, 18.4, 18.3, 17.4, 13.3, -5.1 ppm; HRESIMS calcd. for $C_{38}H_{64}O_4Si_2Na^+$, $[M+Na]^+$ 663.4241 found 663.4226

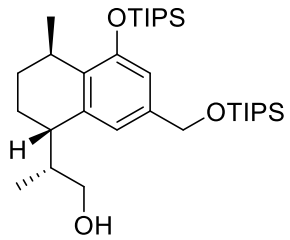


(5R, 8S)-8-((R)-1-hydroxypropan-2-yl)-5-methyl-4-((triisopropylsilyl)oxy)-5,6,7,8-tetrahydronaphthalene-2-carbaldehyde ***268***. To a rapidly stirred mixture of PMB ether **265** (41 mg, 64 μmol) in CH_2Cl_2 (4 mL) and pH 7 phosphate buffer solution (0.4 mL) at room temperature was added DDQ (60 mg; 0.26 mmol) and the resulting suspension stirred for 16 h. The reaction mixture was diluted with CH_2Cl_2 (5 mL), quenched by addition of $NaHCO_3$ (10 mL, sat. aq.) and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3×10 mL) and the combined organic layers washed with brine (10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (20% Et_2O/CH_2Cl_2) afforded the *title compound* **268** (21 mg, 80%) as a colourless oil. $[\alpha]^{20}_D$ −35.5 (*c* 0.87 in $CHCl_3$); IR ($CHCl_3$, cm^{-1}) 3379, 2945, 2868, 2727, 1697, 1598, 1574, 1464, 1430, 1385, 1370, 1341, 1283, 1205, 1177, 1140, 1067, 1034, 998, 923, 883, 847, 806, 729, 686 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.85 (1H, s, C*H*O), 7.26 (1H, s, Ar-*H*), 7.11 (1H, d, *J*=1.3 Hz, Ar-*H*), 3.55 (1H, dd, *J*=10.5, 4.7 Hz, CH_AH$_B$OH), 3.48 (1H, dd, *J*=10.5, 7.5 Hz, CH$_A$$H_B$OH), 3.28 (1H, p, *J*=6.6 Hz, C1*H*), 2.84 (1H, t, *J*=5.3 Hz, C4*H*), 2.10–2.02 (1H, m), 2.00–1.90 (1H, m), 1.89–1.76 (2H, m), 1.63–1.55 (1H, m), 1.36 (3H, hept, *J*=7.5 Hz, O*TIPS*), 1.18 (3H, d, *J*=7.0 Hz, C1C*H*$_3$), 1.13 (9H, d, *J*=7.5 Hz, O*TIPS*), 1.10 (9H, d, *J*=7.5 Hz, O*TIPS*), 0.97 (3H, d, *J*=6.9 Hz, C11C*H*$_3$), O*H* absent; ^{13}C NMR (150 MHz, $CDCl_3$) δ 192.4, 154.5, 141.5, 141, 134.3, 125.8, 114.1, 66.2, 42.1, 39.7, 27.8, 26.4, 21.2, 20, 18.22, 18.17, 16.7,

13.2 ppm; HRESIMS calcd. for $C_{24}H_{40}O_3SiNa^+$, $[M+Na]^+$ 427.2644 found 427.2642

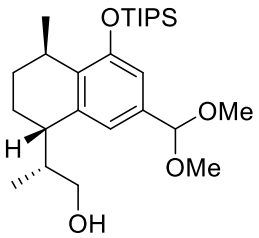


(3R,6S)-6-((R)-1-hydroxypropan-2-yl)-3-methyl-2-(2-(phenylselanyl)-1-((triisopropylsilyl)oxy)ethyl)-1-(3-((triisopropylsilyl)oxy)prop-1-yn-1-yl)cyclohexan-1-ol ***269***. To a vigorously stirred mixture of PMB ether **263*a*** (142 mg, 0.17 mmol) in CH_2Cl_2 (6 mL) and pH 7 phosphate buffer solution (0.7 mL) at room temperature was added DDQ (60 mg; 0.26 mmol) in portions and the resulting suspension stirred for 4 days. The reaction mixture was diluted with CH_2Cl_2 (10 mL), quenched by addition of $NaHCO_3$ (10 mL, sat. aq.) and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3×10 mL) and the combined organic layers washed with brine (10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (10% EtOAc/X4) afforded the *title compound* **269** (62 mg, 51%) as a colourless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.60–7.53 (2H, m), 7.29–7.22 (3H, m), 6.06 (1H, s), 4.89 (1H, d, *J*=9.7 Hz), 4.46 (2H, s), 4.35–4.21 (1H, m), 3.90–3.79 (1H, m), 3.39 (1H, t, *J*=10.8 Hz), 3.28–3.19 (1H, m), 3.07 (1H, dd, *J*=18.1, 6.8 Hz), 2.82–2.67 (1H, m), 1.98–1.90 (2H, m), 1.84 (1H, dd, *J*=13.2, 3.4 Hz), 1.72 (1H, s), 1.64–1.55 (1H, m), 1.49–1.40 (1H, m), 1.36 (1H, d, *J*=12.8 Hz), 1.17–1.04 (33H, m), 1.02–0.96 (9H, m), 0.93 (3H, d, *J*=5.8 Hz), 0.85 (3H, d, *J*=7.3 Hz). ^{13}C NMR (150 MHz, $CDCl_3$) δ 134.5, 132.1, 129.8, 129.2, 127.7, 114, 88.7, 85.8, 75.6, 72.2, 64.1, 53.8, 52.4, 50.8, 36, 35.6, 35.2, 29.6, 20.9, 19.7, 19.1, 18.6, 18.2, 12.9, 12.1 ppm.



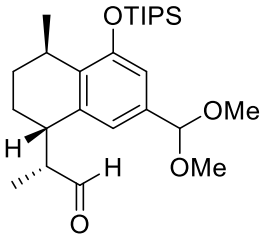
(R)-2-((1S,4R)-4-methyl-5-((triisopropylsilyl)oxy)-7-(((triisopropylsilyl)oxy)methyl)-1,2,3,4-tetrahydronaphthalen-1-yl)propan-1-ol ***266***. The selenoxide elimination was conducted according to a procedure by Engman.[139] To a stirred solution of phenylselenide **269** (399 mg, 0.54 mmol) in benzene (15 mL) at ~10 °C was added *m*CPBA (120 mg, 0.7 mmol) and the resulting solution stirred for 30 minutes. $NaHCO_3$ (30 mL, sat. aq.) and benzene (20 mL) were added and the biphasic mixture heated at 90 °C for 12 hours. The reaction mixture was allowed to cool to room temperature and the layers separated. The organic layer was washed with $NaHCO_3$ (20 mL) and brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude yellow enyne **270** was used without further purification.

The cycloisomerisation was conducted according to a procedure by March and Perkins.[138] To a stirred solution of crude enyne **270** (57 mg, 98 μmol) in 1, 2-dichloroethane (3 mL) at reflux was added $AgNO_3$ (1 mg, 6 mol%) and the resulting yellow solution heated at reflux overnight in darkness. The reaction mixture was allowed to cool to room temperature then diluted with CH_2Cl_2 (5 mL) and quenched by addition of $NaHCO_3$ (5 mL). The organic layer was separated and washed with brine (5 mL), dried (Na_2SO_4) and concentrated *in vacuo.* Column chromatography (5% EtOAc/X4) afforded multiple fractions with no observable products resembling the arene.

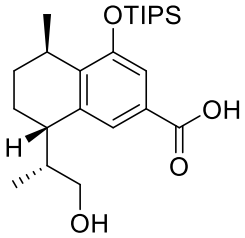


(R)-2-((1S,4R)-7-(dimethoxymethyl)-4-methyl-5-((triisopropylsilyl)oxy)-1,2,3,4-tetrahydronaphthalen-1-yl)propan-1-ol ***272***. To a stirred solution of aldehyde **268** (32 mg, 79 μmol) in MeOH (3 mL) was added $CH(OMe)_3$ (100 μL, 0.91 mmol) at room temperature. The mixture was cooled to 0 °C and Acetyl chloride (1 drop) added. The solution was stirred for 1.5 hours then quenched by addition of K_2CO_3 (40 mg, 0.29 mmol). The mixture was concentrated *in vacuo* then re-dissolved in $NaHCO_3$ (5 mL, sat. aq.) and CH_2Cl_2 (5 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (20% Et_2O/CH_2Cl_2, buffered SiO_2) afforded the *title compound* **272** (34 mg, 94%) as a colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.86–6.81 (1H, m, Ar-*H*), 6.72 (1H, d, *J*=1.6 Hz, Ar-*H*), 5.29 (1H, s, C*H*$(OMe)_2$), 3.56 (1H, dd, *J*=10.5, 4.9 Hz, CH_AH_BOH), 3.44 (1H, dd, *J*=10.5, 7.6 Hz, CH_AH_BOH), 3.29 (3H, s, OCH_3), 3.29 (3H, s, OCH_3), 3.24–3.18 (1H, m, C1*H*), 2.76–2.73 (1H, m, C4*H*), 2.08 (1H, dqd, *J*=12.0, 7.0, 5.0 Hz), 1.93 (1H, tdd, *J*=13.8, 6.3, 3.2 Hz), 1.82 (1H, tdd, *J*=13.7, 5.8, 3.0 Hz), 1.77–1.72 (1H, m), 1.67–1.60 (1H, m), 1.59–1.51 (1H, m), 1.31 (3H, hept, *J*=7.4 Hz, O*TIPS*), 1.16 (3H, d, *J*=6.9 Hz, C1CH_3), 1.12 (9H, d, *J*=7.5 Hz, O*TIPS*), 1.09 (9H, d, *J*=7.5 Hz, O*TIPS*), 0.96 (3H, d, *J*=6.9 Hz, C11CH_3), O*H* absent; ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.7, 139.7, 135.2, 133.5, 120.6, 113.9, 103.2, 66.6, 52.7, 52.6, 42.3, 39.8, 27.2, 27, 21.4, 20, 18.3, 18.2, 16.8, 13.2 ppm.



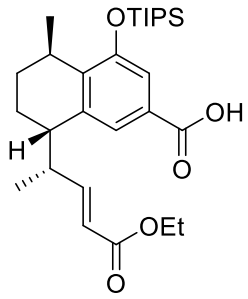
(R)-2-((1S,4R)-7-(dimethoxymethyl)-4-methyl-5-((triisopropylsilyl)oxy)-1,2,3,4-tetrahydronaphthalen-1-yl)propan-1-al **274**. The oxidation was conducted according to a procedure by Dess and Martin.[154] To a stirred solution of acetal **274** (31 mg, 69 μmol) in CH_2Cl_2 (2 mL) was added DMP (60 mg, 141 μmol) at room temperature and the resulting suspension stirred in darkness for 3 hours. The reaction mixture was diluted with Et_2O (5 mL), poured into $Na_2S_2O_3$ (2 g) in $NaHCO_3$ (5 mL, sat. aq.) and the biphasic mixture stirred for 1 hour. The layers were separated and the organic layer washed with $NaHCO_3$ (10 mL, sat. aq.), brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo.* Analysis of the crude ^{1}H NMR spectrum revealed multiple aldehyde signals indicating hydrolysis of the acetal had occurred.



*(5R, 8S)-8-((R)-1-hydroxypropan-2-yl)-5-methyl-4-((triisopropylsilyl)oxy)-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid **275***. The oxidation was conducted according to the procedure by Pinnick *et al.*[144] To a stirred solution of aldehyde **268** (61 mg, 150 μmol) and 2,3-dimethyl-2-butene (0.27 mL, 2.27 mmol) in *t*-BuOH (4 mL) at room temperature was added dropwise a solution of NaH_2PO_4 (181 mg, 1.51 mmol) and $NaClO_2$ (64 mg, 0.71 mmol) in H_2O (5 mL). The reaction mixture was stirred overnight at 30 °C, then concentrated *in vacuo*, diluted with EtOAc (10 mL) and HCl (1M, 10 mL) added. The layers were separated and the aqueous layer extracted with EtOAc (3×10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification through a plug of silica (40% Et_2O/CH_2Cl_2) afforded the *title compound* **275** (57 mg, 90%) as a colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.55–7.50 (1H, m, Ar-*H*), 7.37–7.31 (1H, m, Ar-*H*), 3.56 (1H, dd, *J*=10.5, 4.6 Hz, CH_AH$_B$OH), 3.48 (1H, dd, *J*=10.2, 8.0 Hz, CH$_A$$H_B$OH),

3.27 (1H, p, *J*=6.6 Hz, C1*H*), 2.81 (1H, t, *J*=5.2 Hz, C4*H*), 2.10–2.02 (1H, m), 1.98–1.90 (1H, m), 1.84 (1H, ddd, *J*=13.4, 9.6, 6.6 Hz), 1.81–1.76 (1H, m), 1.61–1.56 (1H, m), 1.40–1.32 (3H, m), 1.18 (3H, d, *J*=6.9 Hz, C1C*H*$_3$), 1.14 (9H, d, *J*=7.5 Hz, O*TIPS*), 1.10 (9H, d, *J*=7.5 Hz, O*TIPS*), 0.97 (3H, d, *J*=6.9 Hz, C11C*H*$_3$), 2×O*H* absent; ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.1, 153.8, 140.3, 140.2, 126.5, 124.4, 116.4, 66.3, 42.1, 39.7, 27.7, 26.5, 21.2, 20.0, 18.3, 18.2, 16.7, 13.1 ppm.

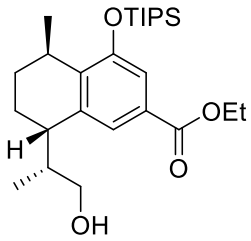


*(5R, 8S)-8-((S,E)-5-ethoxy-5-oxopent-3-en-2-yl)-5-methyl-4-((triisopropylsilyl)oxy)-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid **278**.* The oxidation/Wittig olefination was conducted according to a modified procedure by Tilve *et al.*[146] To a stirred suspension of alcohol **275** (29 mg, 69 μmol) and buffered SiO_2 (74 mg) in CH_2Cl_2 (4 mL) at room temperature was added PDC (74 mg, 0.2 mmol) and the resulting suspension stirred at room temperature for 5 hours. The reaction mixture was filtered through a pad of Celite, and the crude material carried through into the next reaction without further purification.

To a stirred solution of crude aldehyde **276** in CH_2Cl_2 (2 mL) at room temperature was added (Carbethoxymethylene)triphenylphosphorane **277** (56 mg, 0.16 mmol) and the solution stirred at room temperature overnight. The reaction mixture was concentrated *in vacuo* and purified through a plug of silica (CH_2Cl_2 then Et_2O) to afford the *title compound* **278** (10 mg, 30% over 2 steps) as a light yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.54 (1H, d, *J*=1.6 Hz, Ar-*H*), 7.37 (1H, d, *J*=1.6 Hz, Ar-*H*), 6.81 (1H, dd, *J*=15.7, 8.0 Hz, C*H*=CHCO$_2$Et), 5.64 (1H, dd, *J*=15.7, 1.2 Hz, CH=C*H*CO$_2$Et), 4.14 (2H, m, CO$_2$C*H*$_2$CH$_3$), 3.25 (1H, p, *J*=6.4 Hz, C1*H*), 2.81 (1H, t, *J*=5.7 Hz, C4*H*), 2.70 (1H, h, *J*=6.8 Hz, C11*H*), 1.90 (1H, tdd, *J*=13.4, 5.9, 2.9 Hz), 1.83 (1H, ddd, *J*=13.8, 5.6, 2.7 Hz), 1.79 – 1.73 (1H, m), 1.53–1.48 (1H, m), 1.41 – 1.30

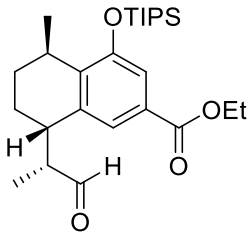
(3H, m), 1.25 (3H, t, *J*=7.1 Hz, $CO_2CH_2CH_3$), 1.18–1.13 (15H, m, C1CH_3, C11CH_3 and O*TIPS*), 1.11 (9H, d, *J*=7.5 Hz, O*TIPS*), O*H* absent; ^{13}C NMR (151 MHz, $CDCl_3$) δ 171.6, 166.7, 153.9, 152.4, 140.4, 139.6, 126.4, 124.7, 120.4, 116.7, 60.3, 42.8, 42.7, 29.9, 27.5, 26, 21.2, 19.3, 18.6, 18.3, 18.2, 14.4, 13.2 ppm.



Ethyl (5R, 8S)-8-((R)-1-hydroxypropan-2-yl)-5-methyl-4-((triisopropylsilyl)oxy)-5,6,7,8-tetrahydronaphthalene-2-carboxylate ***279***. The oxidation was conducted according to a procedure from Borhan *et al.*[147] To a stirred solution of aldehyde **268** (116 mg, 0.29 mmol) in EtOH (4 mL) at room temperature was added Oxone® (175 mg, 0.57 mmol) and the resulting mixture rapidly stirred for 16 hours. The precipitate was filtered and washed with ethanol, and the solution concentrated to ~1 mL *in vacuo*. The residue was taken up in EtOAc and H_2O, and layers separated. The aqueous layer was extracted with EtOAc (3×10 mL), washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification through a plug of silica (20% EtOAc/X4) afforded the *title compound* **279** (112 mg, 87%) as a colourless oil.

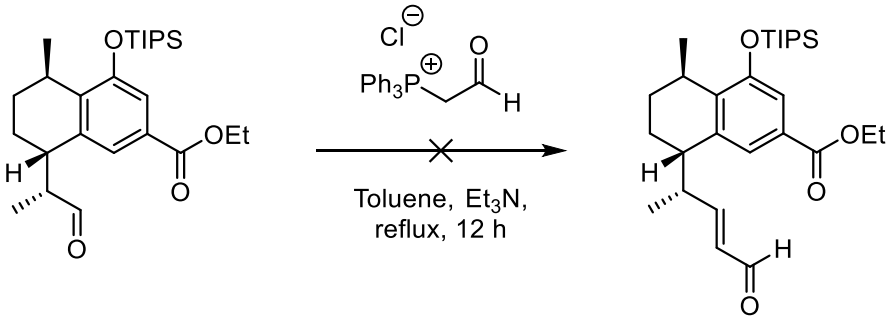
$[\alpha]^{20}_D$ −32.3 (*c* 0.99 in $CHCl_3$); IR ($CHCl_3$, cm^{-1}) 3427, 2945, 2868, 1718, 1603, 1575, 1464, 1421, 1368, 1341, 1289, 1228, 1174, 1111, 1065, 1035, 976, 922, 883, 848, 771, 685 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 (1H, d, *J*=1.6 Hz, Ar-*H*), 7.30 (1H, d, *J*=1.6 Hz, Ar-*H*), 4.38–4.27 (2H, m, $CO_2CH_2CH_3$), 3.54 (1H, dd, *J*=10.5, 4.7 Hz, CH_AH_BOH), 3.46 (1H, dd, *J*=10.5, 7.7 Hz, CH_AH_BOH), 3.26 (1H, p, *J*=6.6 Hz, C1*H*), 2.80 (1H, t, *J*=5.4 Hz, C4*H*), 2.11–2.03 (1H, m), 1.98–1.88 (1H, m), 1.86–1.75 (2H, m), 1.62–1.53 (2H, m), 1.37 (3H, t, *J*=7.1 Hz, $CO_2CH_2CH_3$), 1.37–1.29 (3H, m, O*TIPS*), 1.17 (3H, d, *J*=7.0 Hz, C1CH_3), 1.14 (9H, d, *J*=7.5 Hz, O*TIPS*), 1.10 (9H, d, *J*=7.5 Hz, O*TIPS*), 0.98 (3H, d, *J*=6.9 Hz, C11CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.0, 153.7, 140.2, 139.0, 127.7, 123.6, 116.1, 66.3, 60.9, 42.3, 39.8, 27.5, 26.6, 21.2, 19.8, 18.3, 18.2, 16.7, 14.5,

13.1 ppm; HRESIMS calcd. for $C_{26}H_{44}O_4SiNa^+$, $[M+Na]^+$ 471.2907 found 471.2899

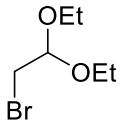


Ethyl (5R, 8S)-5-methyl-8-((R)-1-oxopropan-2-yl)-4-((triisopropylsilyl)oxy)-5,6,7,8-tetrahydronaphthalene-2-carboxylate ***280***. The oxidation was conducted according to a modified procedure by Mancuso and Swern.[48] To a stirred solution of DMSO (225 μL, 3.2 mmol) in CH_2Cl_2 (4.5 mL) at −78 °C was added oxalyl chloride (2.0M in CH_2Cl_2, 750 μL, 1.5 mmol) and the resulting solution stirred for 20 minutes. Alcohol **279** (157 mg, 0.35 mmol) in CH_2Cl_2 was added *via* cannula and the solution stirred for 1 hour at −78 °C. $^{i}Pr_2NEt$ (1.1 mL, 6.3 mmol) was added and the resulting solution stirred for a further hour at −78 °C. The reaction mixture was quenched through addition of NH_4Cl (5 mL, sat. aq.) and the biphasic mixture allowed to warm to room temperature. Layers were separated and the aqueous layer extracted with CH_2Cl_2 (3×10 mL), washed with brine (5 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (10% EtOAc/X4) afforded the *title compound* **280** (147 mg, 94%) as a colourless oil.

$[\alpha]^{20}_D$ −69.9 (*c* 0.83 in $CHCl_3$); IR ($CHCl_3$, cm^{-1}) 2945, 2868, 1720, 1576, 1495, 1452, 1422, 1332, 1291, 1229, 1050 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.53 (1H, d, *J*=1.7 Hz, C*H*O), 7.48 (1H, d, *J*=1.6 Hz, Ar-*H*), 7.35 (1H, d, *J*=1.6 Hz, Ar-*H*), 4.39–4.29 (2H, m, $CO_2CH_2CH_3$), 3.29–3.20 (1H, m, C*H*CH_3CHO), 3.18 (1H, t, *J*=6.3 Hz, C1*H*), 2.78 (1H, pd, *J*=6.9, 1.7 Hz, C4*H*), 2.04–1.96 (1H, m), 1.76–1.69 (2H, m), 1.59–1.55 (1H, m), 1.38 (3H, t, *J*=7.2 Hz, OCH_2CH_3), 1.36–1.30 (3H, m), 1.18 (3H, d, *J*=7.0 Hz, C1CH_3), 1.14 (9H, d, *J*=7.5 Hz, O*TIPS*), 1.10 (9H, d, *J*=7.5 Hz, O*TIPS*), 1.10 (3H, d, *J*=6.9 Hz, C11CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 204.9, 166.7, 154.0, 138.9, 138.1, 128.2, 123.4, 116.7, 61.0, 52.6, 39.5, 29.9, 27.4, 25.8, 21.1, 20.0, 18.3, 18.2, 14.5, 13.1, 12.8 ppm; HRESIMS calcd. for $C_{26}H_{42}O_4SiNa^+$, $[M+Na]^+$ 469.2750 found 469.2740

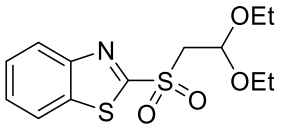


Ethyl (5R,8S)-5-methyl-8-((S,E)-5-oxopent-3-en-2-yl)-4-((triisopropylsilyl)oxy)-5,6,7,8-tetrahydronaphthalene-2-carboxylate **282**. To a stirred solution of aldehyde **280** (10 mg, 22 μmol) in toluene (2 mL) was added Et_3N (20 μL, 0.14 mmol) and (formylmethyl)triphenylphosphonium chloride (45 mg, 0.13 mmol). The resulting solution was heated at reflux for 12 hours, then cooled to room temperature and H_2O (5 mL) added. The two layers were separated and the aqueous layer extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography returned only the epimerised aldehyde **280**.



*Bromoacetaldehyde diethyl acetal **283***. To a stirred suspension of *N*-bromosuccinimide (5.13 g, 28.8 mmol) in CH_2Cl_2 (25 mL) was added EtOH (1.63 mL, 28 mmol). The resulting yellow solution was cooled to −20 °C and ethyl vinyl ether (3.5 mL, 36 mmol) added dropwise. The resulting colourless mixture was stirred for 2 hours then warmed to room temperature and filtered (CH_2Cl_2). The filtrate was concentrated *in vacuo* and the residue purified by column chromatography (buffered SiO_2, 5% Et_2O/X4) giving the *title compound* **283** (4.59 g, 83%) as a colourless liquid. NMR data matched the reported data from the literature.

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.67 (1H, t, *J*=5.5 Hz, C*H*$(OEt)_2$), 3.70 (2H, dq, *J*=9.3, 7.0 Hz, OC*H*$_2$CH$_3$), 3.58 (2H, dq, *J*=9.3, 7.0 Hz, OC*H*$_2$CH$_3$), 3.37 (2H, d, *J*=5.5 Hz, C*H*$_2$Br), 1.24 (6H, t, *J*=7.0 Hz, OCH$_2$C*H*$_3$). ^{13}C NMR (150 MHz, $CDCl_3$): δ 101.6, 62.6, 32.0, 15.3 ppm.

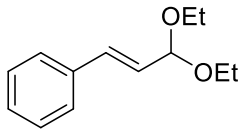


*2-((2,2-diethoxyethyl)sulfonyl)benzo[d]thiazole **285***. Alkylation of the benzothiazole was conducted according to a modified procedure by Zajc *et al.*[158] To a stirred solution of 2-mercaptobenzothiazole **284** (2.37 g, 14.2 mmol) in THF (25 mL) and DMF (8 mL) at 0 °C was added NaH (510 mg, 21.3 mmol) portionwise. The suspension was stirred for 30 minutes at 0 °C, then bromoacetaldehyde diethyl acetal **283** (2.14 g, 10.9 mmol) added *via* cannulation (THF). The reaction mixture was stirred for 30 minutes at 0 °C then warmed to room temperature. The reaction mixture was heated at 60 °C for 24 hours, then cooled to room temperature. The mixture was poured into H_2O (15 mL) and extracted with Et_2O (3×20 mL). The combined organic layers were washed with NaOH (1M, 30 mL), H_2O (2×30 mL) and brine (30 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was passed through a plug of buffered silica (20% EtOAc/X4) and used directly in the next reaction.

Oxidation of the crude sulfide was conducted according to a procedure by To a stirred solution of the sulfide (2.76 g, 9.7 mmol) in MeOH/H_2O (1:1, 200 mL) was added Oxone® (7.49 g, 24.4 mmol) and the resulting suspension stirred for 12 hours at room

temperature. The suspension was filtered, concentrated *in vacuo* to remove MeOH, and the aqueous layer extracted with EtOAc (3×50 mL). The combined organic layers were washed with H_2O (50 mL), brine (50 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (buffered SiO_2, 20% EtOAc/X4) afforded the *title compound* **285** (2.67 g, 78% over 2 steps) as light yellow needles.

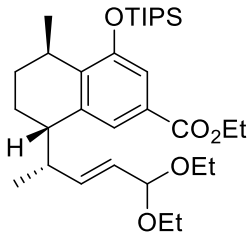
Mp: 89–91.5 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.22 (1H, ddd, *J*=8.3, 1.3, 0.7 Hz, Ar-*H*), 8.01 (1H, ddd, *J*=8.0, 1.3, 0.7 Hz, Ar-*H*), 7.63 (1H, ddd, *J*=8.3, 7.2, 1.3 Hz, Ar-*H*), 7.58 (1H, ddd, *J*=8.3, 7.2, 1.3 Hz, Ar-*H*), 5.11 (1H, t, *J*=5.4 Hz, C*H*$(OEt)_2$), 3.87 (2H, d, *J*=5.4 Hz, SO_2CH_2), 3.58 (2H, dq, *J*=9.2, 7.0 Hz, OCH_2CH_3), 3.49 (2H, dq, *J*=9.2, 7.1 Hz, OCH_2CH_3), 0.98 (6H, t, *J*=7.0 Hz, OCH_2CH_3); ^{13}C NMR (150 MHz, $CDCl_3$): δ 166.4, 152.8, 137.0, 128.1, 127.7, 125.6, 122.3, 97.4, 62.6, 58.2, 14.9 ppm.



*(E)-(3,3-diethoxyprop-1-en-1-yl)benzene **287**.* The olefination reaction was conducted according to a modified procedure by Pospisil and Marko.[150] To a stirred solution of benzaldehyde **286** (67 mg, 0.63 mmol) and sulfone **285** (270 mg, 0.86 mmol, 1.4 equiv.), in THF (5 mL) at −78 °C was added LiHMDS (0.94 mL, 0.94 mmol, 1.1 equiv.) dropwise over 5 minutes. The resulting orange solution was maintained at −78 °C for 30 minutes then allowed to warm to −40 °C over 1 hour. The reaction mixture was warmed to room temperature and quenched through addition of H_2O (10 mL). The layers were separated and the aqueous layer extracted with Et_2O (3×10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (buffered SiO_2, 10% EtOAc/X4) afforded the *title compound* **287** (100 mg, 77%, 77/23 *E/Z*) as a colourless oil.

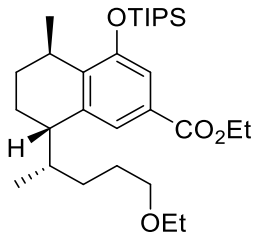
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.43–7.38 (2H, m, Ar-*H*), 7.37–7.30 (2H, m, Ar-*H*), 7.29–7.23 (1H, m, Ar-*H*), 6.71 (0.77H, d, *J*=16.1 Hz, (*E*)-PhC*H*=CH), 6.67 (0.23H, d, *J*=11.9 Hz, (*Z*)-PhC*H*=CH), 6.21 (0.77H, dd, *J*=16.1, 5.2 Hz, (*E*)-PhCH=C*H*), 5.79 (0.23H, dd, *J*=11.9, 7.4 Hz, (*Z*)-PhCH=C*H*), 5.23 (0.23H, dd, *J*=7.4, 1.1 Hz, (*Z*)-C*H*$(OEt)_2$), 5.07 (0.77H, dd, *J*=5.2, 1.2 Hz, (*E*)-C*H*$(OEt)_2$), 3.74–3.65 (2H, m, OCH_2CH_3), 3.60–3.53 (2H, m, OCH_2CH_3), 1.26 (4.6H, t, *J*=7.1 Hz, (*E*)-OCH_2CH_3), 1.23 (1.4H, t, *J*=7.1 Hz, (*Z*)-OCH_2CH_3). ^{13}C NMR (151 MHz, $CDCl_3$): δ 136.40,

136.35, 133.1, 133, 129.3, 129.2, 128.7, 128.4, 128.1, 127.7, 126.9, 126.8, 101.7, 98.1, 61.2, 60.7, 15.5, 15.4 ppm.



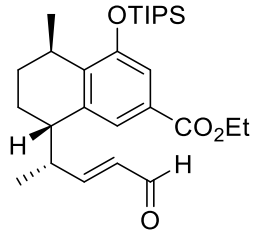
Ethyl (5R,8S)-8-((S,E)-5,5-diethoxypent-3-en-2-yl)-5-methyl-4-((triisopropylsilyl)oxy)-5,6,7,8-tetrahydronaphthalene-2-carboxylate ***289***. The olefination reaction was conducted according to a modified procedure by Pospisil and Marko.[150] To a stirred solution of aldehyde **280** (55.6 mg, 0.124 mmol) and sulfone **285** (70.7 mg, 0.22 mmol, 1.8 equiv.) in THF (5 mL) at −78 °C was added LiHMDS (0.25 mL, 0.25 mmol) dropwise over 5 minutes. The resulting orange solution was maintained at −78 °C for 1 hour then allowed to warm to −10 °C over 3 hours. The reaction mixture was warmed to room temperature and quenched through addition of NH_4Cl (10 mL, sat. aq.). The layers were separated and the aqueous layer extracted with Et_2O (3×10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (buffered SiO_2, 5% Et_2O/X4) afforded the *title compound* **289** (48 mg, 71%, 83/17 E/Z) as a colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.46 (0.18H, s), 7.40 (0.71 H, s), 7.30 (1H, s), 5.63 (0.20H, dd, *J*=15.8, 7.3 Hz), 5.52 (0.79H, t, *J*=10.9 Hz), 5.43 (0.74H dd, *J*=11.3, 6.8 Hz), 5.36 (0.19H, dd, *J*=15.8, 5.4 Hz), 5.05 (0.72H, d, *J*=6.8 Hz), 4.76 (0.18H, d, *J*=5.4 Hz), 4.39–4.27 (2H, m), 3.56 (2H, ddq, *J*=13.9, 9.7, 7.1 Hz), 3.50–3.43 (1H, m), 3.42–3.33 (1H, m), 3.23 (1H, p, *J*=6.9 Hz), 2.81–2.67 (1H, m), 2.61–2.53 (1H, m), 2.05–1.95 (1H, m), 1.93–1.74 (2H, m), 1.51 (1H, d, *J*=13.6 Hz), 1.37 (6H, t, *J*=7.4 Hz), 1.19–1.15 (9H, m), 1.14 (9H, d, *J*=7.6 Hz), 1.11 (9H, d, *J*=7.5 Hz), 0.98 (3H, d, *J*=6.7 Hz). ^{13}C NMR (151 MHz, $CDCl_3$) δ 167, 153.8, 153.6, 140.1, 139.6, 139.4, 139.1, 138.90, 138.86, 138.3, 127.5, 127, 126.8, 126.7, 124.7, 123.9, 123.4, 116.7, 116.2, 116, 101.9, 98, 61, 60.9, 60.81, 60.78, 60.2, 52.6, 43.3, 42.6, 42, 39.5, 37.8, 27.7, 27.5, 27.4, 26, 25.80, 25.78, 21.5, 21.3, 21.1, 20.4, 20.3, 19.3, 19, 18.28, 18.27, 18.25, 18.23, 15.43, 15.38, 14.5, 13.1 ppm.



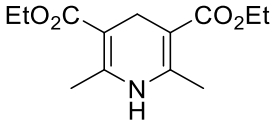
*Ethyl (5R,8S)-8-((S)-5-ethoxypentan-2-yl)-5-methyl-4-((triisopropylsilyl)oxy)-5,6,7,8-tetrahydronaphthalene-2-carboxylate **291***. To a stirred solution of alkene **289** (39 mg, 72 μmol) in EtOH (2 mL) at room temperature was added Pd/C (6 mg) and the heterogeneous mixture vigorously stirred under a H_2 atmosphere (balloon) for 2 hours. The mixture was passed through a plug of buffered silica (Et_2O) and concentrated *in vacuo* to give compound 2**91** as a colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.44 (1H, d, *J*=1.2 Hz, Ar-*H*), 7.29 (1H, d, *J*=1.6 Hz, Ar-*H*), 4.38–4.28 (2H, m, $CO_2CH_2CH_3$), 3.39 (2H, qd, *J*=7.0, 4.7 Hz, CH_2OEt), 3.33–3.21 (3H, m, $CH_2OCH_2CH_3$ and C1*H*), 2.69–2.64 (1H, m, C4*H*), 1.94–1.82 (3H, m), 1.79–1.73 (1H, m), 1.68–1.58 (1H, m), 1.55–1.49 (1H, m), 1.37 (6H, t, *J*=7.1 Hz, $CO_2CH_2CH_3$ and $CH_2OCH_2CH_3$), 1.37–1.30 (3H, m, O*TIPS*), 1.16 (3H, d, *J*=7.0 Hz, C1CH_3), 1.14 (9H, d, *J*=7.5 Hz, O*TIPS*), 1.14 (3H, t, *J*=7.0 Hz, $CH_2OCH_2CH_3$), 1.10 (9H, d, *J*=7.5 Hz, O*TIPS*), 0.95 (3H, d, *J*=6.8 Hz, C11CH_3). ^{13}C NMR (150 MHz, $CDCl_3$): δ 167.1, 153.6, 141.1, 139.3, 127.5, 123.5, 115.8, 71.0, 66.1, 60.8, 42.5, 39.1, 30.1, 28.3, 27.6, 26.9, 21.3, 19.4, 19.0, 18.3, 18.2, 15.3, 14.5, 13.1 ppm.

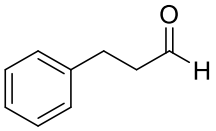


*Ethyl (5R,8S)-5-methyl-8-((S,E)-5-oxopent-3-en-2-yl)-4-((triisopropylsilyl)oxy)-5,6,7,8-tetrahydronaphthalene-2-carboxylate **296***. The transacetalisation was conducted according to a procedure by Quinn *et al.*[159] To a stirred solution of diethyl acetal **289** (8 mg, 15 μmol) in acetone (1 mL) at room temperature was added $InCl_3$ (1 mg, 4.5 μmol) and the resulting solution stirred for 2 hours. The reaction mixture was concentrated *in vacuo* and filtered through a plug of buffered silica (Et_2O/CH_2Cl_2). The *title compound* **296** (7 mg, quant.) was isolated as a colourless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.73 (0.81H, d, *J*=8.2 Hz), 9.38 (0.19 H, d, *J*=8.0 Hz), 7.49 (0.2H, s), 7.44 (0.8H, d, *J*=1.6 Hz), 7.35 (0.2H, d, *J*=1.6 Hz), 7.32 (0.8H, d, *J*=1.7 Hz), 6.64 (0.2H, dd,

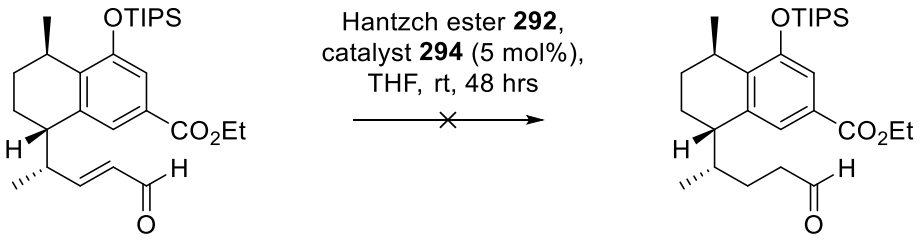
J=15.8, 6.5 Hz), 6.49 (0.8H, t, *J*=11.3 Hz), 5.98 (0.2H, dd, *J*=15.8, 7.8 Hz), 5.87 (0.8H, dd, *J*=11.3, 8.1 Hz), 4.42–4.28 (2H, m), 3.45 (1H, dq, *J*=12.5, 7.0 Hz), 3.24 (1H, p, *J*=6.9 Hz), 2.97–2.85 (1H, m), 2.75 (1H, t, *J*=6.4 Hz), 2.05–1.70 (3H, m), 1.42–1.30 (6H, m), 1.19–1.16 (3H, m), 1.15–1.12 (9H, m), 1.12–1.08 (12H, m)



diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate ***292***. The Hantzsch ester was synthesised according to a procedure from Eey and Lear.[152] A stirred suspension of paraformaldehyde (323 mg, 10.8 mmol), ethyl acetoacetate (5.1 mL, 40.3 mmol) and NH_4OAc (1.65 g, 21.4 mmol) in H_2O (25 mL) was heated at reflux for 2.5 hours. The mixture was cooled to room temperature and filtered. The precipitate was washed with H_2O (3×10 mL) and dried *in vacuo* to give the *title compound* **292** (3.99 g, 74%) as a yellow fluffy solid. NMR data were in agreement with the literature.
^{1}H NMR (600 MHz, $CDCl_3$) δ 5.11 (1H, s, N*H*), 4.17 (4H, q, *J*=7.1 Hz, $CO_2CH_2CH_3$), 3.26 (2H, s, =C(CO_2Et)C*H*), 2.19 (6H, s, =CCH_3), 1.28 (6H, t, *J*=7.1 Hz, $CO_2CH_2CH_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.2, 144.8, 99.7, 59.8, 24.9, 19.4, 14.6 ppm.

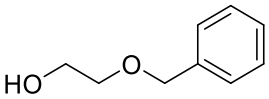


3-phenylpropanal ***295***. The Organocatalytic Transfer Hydrogenation was conducted according to a procedure by List *et al.*[151] To a stirred solution of cinnamaldehyde **293** (65 mg, 0.49 mmol) and Hantzsch ester **292** (137 mg, 0.54 mmol) in THF (3 mL) at room temperature was added dibenzylammonium trifluoroacetate **294** (9 mg, 29 μmol, 6 mol%) and the resulting solution stirred for 24 hours. The mixture was concentrated *in vacuo* and purified by column chromatography (30% EtOAc/X4) to give the *title compound* **295** (41 mg, 62%) as a colourless liquid. ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.83 (1H, t, *J*=1.5 Hz, C*H*O), 7.33–7.28 (2H, m, Ar-*H*), 7.24–7.18 (3H, m, Ar-*H*), 2.97 (2H, t, *J*=7.6 Hz, CH_2Ph), 2.79 (2H, td, *J*=7.6, 1.4 Hz, CH_2CHO).



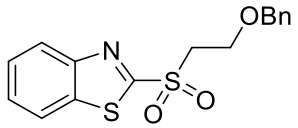
296 **297**

*Ethyl (5R,8S)-5-methyl-8-((S)-5-oxopentan-2-yl)-4-((triisopropylsilyl)oxy)-5,6,7,8-tetrahydronaphthalene-2-carboxylate **297***. The Organocatalytic Transfer Hydrogenation was conducted according to a procedure by List *et al.*[151] To a stirred solution of enal **296** (36 mg, 74 μmol) and Hantzsch ester **292** (25 mg, 99 μmol) in THF (3 mL) was added dibenzylammonium trifluoroacetate **294** (1.2 mg, 3.9 μmol, 5 mol%) at room temperature and the resulting solution stirred for 48 hours. The mixture was concentrated *in vacuo* and purified by column chromatography (30% EtOAc/X4). A 50/50 mixture of *E/Z* isomers of enal **296** was obtained with no observable product **297**.



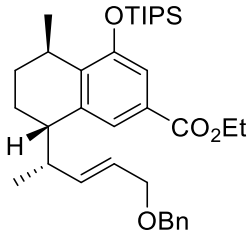
*2-(benzyloxy)ethan-1-ol **298***. To a stirred solution of ethylene glycol (3 mL, 53.7 mmol) in THF (30 mL) at 0 °C was added NaH (0.76 g, 60% dispersion in mineral oil) portionwise. The resulting suspension was warmed to room temperature and stirred for 30 minutes. Benzyl bromide (1.94 mL, 16.3 mmol) was added dropwise followed by $^{n}Bu_4N^{+}I^{-}$ (0.66 g, 1.79 mmol) and the resulting mixture heated at reflux overnight. The reaction mixture was cooled to room temperature and quenched through slow addition of NH_4Cl (30 mL, sat. aq.). Layers were separated and the aqueous layer extracted with Et_2O (3×30 mL). The combined organic layers were washed with brine (2×30 mL), dried (Na_2SO_4) and concentrated *in vacu*o. Purification by column chromatography (40% EtOAc/ X4) afforded the *title compound* **298** (2.26 g, 91%) as a colourless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.39–7.33 (4H, m, Ar-*H*), 7.32–7.27 (1H, m, Ar-*H*), 4.57 (2H, s, C*H*$_2$Ph), 3.76 (2H, q, *J*=4.7 Hz, C*H*$_2$OBn), 3.60 (2H, t, *J*=4.6 Hz, C*H*$_2$OH), 2.10 (1H, s, O*H*). ^{13}C NMR (150 MHz, $CDCl_3$): δ 138.1, 128.6, 127.9, 127.9, 73.4, 71.5, 62 ppm.



2-((2-(benzyloxy)ethyl)sulfonyl)benzo[d]thiazole ***299***. To a stirred solution of benzyl ether **298** (2.25 g, 14.8 mmol), PPh_3 (5.8 g, 22.1 mmol) and 2-mercaptobenzothiazole **284** (5.1 g, 30.5 mmol) in THF (80 mL) at 0 °C was added DIAD (5.1 mL, 25.9 mmol) dropwise. The reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was quenched through addition of H_2O, layers separated and the aqueous layer extracted with EtOAc (3×20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to give the crude sulfide (3.87 g, 87%) as a light yellow oil. To a stirred solution of the crude sulfide (3.87 g, 12.8 mmol) in THF/H_2O/MeOH (1:1:1, 300 mL) at room temperature was added Oxone® (9.2 g, 30 mmol) and the resulting mixture stirred for 24 hours at room temperature. The reaction mixture was filtered (Et_2O), THF and MeOH removed *in vacuo*, and the aqueous layer extracted with EtOAc (3×50 mL). The combined organic layers were washed with H_2O (30 mL) and brine (30 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude residue was recrystallised from Et_2O attaining separation of the dimeric by-product and the *title compound* **299** (2.1 g, 49%) as white needles.

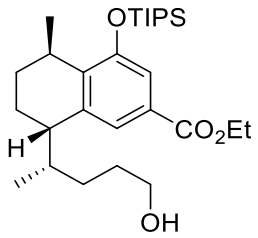
Mp 89.6–91.1 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.20 (1H, ddd, *J*=8.3, 1.2, 0.7 Hz, Ar-*H*), 7.94 (1H, ddd, *J*=8.1, 1.3, 0.7 Hz, Ar-*H*), 7.62 (1H, ddd, *J*=8.3, 7.2, 1.3 Hz, Ar-*H*), 7.57 (1H, ddd, *J*=8.3, 7.2, 1.2 Hz, Ar-*H*), 7.21–7.09 (3H, m, OCH_2Ph-*H*), 7.01–6.97 (2H, m, OCH_2Ph-*H*), 4.39 (2H, s, OCH_2Ph), 4.00 (2H, t, *J*=5.8 Hz), 3.85 (2H, t, *J*=5.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.5, 152.8, 137.0, 137.0, 128.3, 128.0, 127.8, 127.7, 127.4, 125.6, 122.4, 73.4, 63.4, 55.2 ppm; HRESIMS calcd. for $C_{16}H_{15}NO_3S_2Na^+$, $[M+Na]^+$ 356.0391 found 356.0393



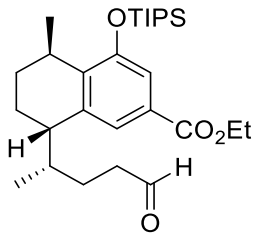
Ethyl (5R, 8S)-8-((S, E)-5-(benzyloxy)pent-3-en-2-yl)-5-methyl-4-((triisopropylsilyl)oxy)-5,6,7,8-tetrahydronaphthalene-2-carboxylate ***300***.

The olefination was conducted according to a modified procedure by Pospisil and Marko.[150] To a stirred solution of aldehyde **280** (48 mg, 0.11 mmol) and benzyl sulfone **299** (78 mg, 0.23 mmol) in THF (5 mL) at −78 °C was added LiHMDS (1M, 0.25 mL, 0.25 mmol) dropwise over 5 minutes. The resulting red solution was allowed to stir at −78 °C for 1 hour before warming to room temperature and quenching through addition of NH_4Cl (10 mL, sat. aq.). The layers were separated and the aqueous layer extracted with Et_2O (3×10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (5% EtOAc/X4) gave the *title compound* **300** (54 mg, 89%) as a colourless oil and 1:1 mixture of *E*/*Z* isomers.

IR ($CHCl_3$, cm^{-1}) 2944, 2867, 1718, 1575, 1494, 1454, 1421, 1368, 1289, 1228, 1066 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.47 (0.45H, d, *J*=1.6 Hz, Ar-*H*), 7.43 (0.53H, d, *J*=1.6 Hz, Ar-*H*), 7.36–7.23 (6H, m, Ar-*H*), 5.57–5.38 (2H, m, C*H*=C*H*), 4.49-4.26 (4H, m, $CO_2CH_2CH_3$ and OCH_2Ph), 3.95–3.87 (1.4H, m, CH_2OBn), 3.64-3.62 (0.6H, m, CH_2OBn), 3.21 (1H, dp, *J*=12.5, 6.2, 5.7 Hz, C1*H*), 2.73–2.65 (1H, m, C4*H*), 2.65–2.53 (1H, m, C11*H*), 1.96–1.77 (3H, m), 1.51–1.44 (1H, m), 1.37 (3H, t, *J*=7.1 Hz, $CO_2CH_2CH_3$), 1.34 (3H, hept. of d, *J*=7.5, 1.9 Hz), 1.28–1.23 (1H, m), 1.16 (1.7H, d, *J*=7.0 Hz, C1CH_3), 1.15–1.13 (12H, m, O*TIPS* and C1CH_3), 1.12–1.09 (9H, m, O*TIPS* and C11CH_3), 1.02 (1.6H, d, *J*=6.7 Hz, C11CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.99, 166.94, 153.70, 153.66, 140.24, 139.85, 139.16, 139.02, 138.58, 138.47, 138.26, 137.94, 128.47, 128.44, 127.89, 127.87, 127.66, 127.64, 127.45, 127.19, 125.80, 125.49, 124.60, 123.96, 116.15, 116.11, 72.30, 71.89, 71.09, 66.19, 60.80, 43.29, 42.66, 42.21, 38.01, 27.59, 27.57, 26.09, 26.02, 21.43, 21.35, 20.55, 19.75, 19.37, 19.20, 18.27, 18.25, 18.23, 18.21, 14.49, 13.08 ppm; HRESIMS calcd. for $C_{35}H_{52}O_4SiNa^+$, $[M+Na]^+$ 587.3501 found 587.3517

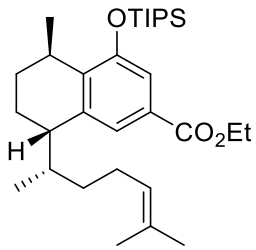


Ethyl (5R, 8S)-8-((S)-5-hydroxypentan-2-yl)-5-methyl-4-((triisopropylsilyl)oxy)-5,6,7,8-tetrahydronaphthalene-2-carboxylate ***301***. To a stirred solution of alkene **300** (38 mg, 67 μmol) in EtOH (3 mL) at room temperature was added 10% Pd/C (11 mg, 10 μmol) and the heterogeneous mixture stirred under a H_2 atmosphere (balloon) overnight. The mixture was filtered through celite (EtOAc) and concentrated *in vacuo*. Purification by gradient elution chromatography (X4 then 10% EtOAc/X4) afforded the *title compound* ***301*** (22 mg, 70%) as a colourless oil. $[\alpha]^{20}_{D}$ −40.7 (*c* 0.98 in $CHCl_3$); IR ($CHCl_3$, cm^{-1}) 3446, 2942, 2868, 1719, 1575, 1494, 1464, 1368 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 (1H, s, Ar-*H*), 7.29 (1H, d, *J*=1.6 Hz, Ar-*H*), 4.33 (2H, qd, *J*=7.1, 3.8 Hz, $CO_2CH_2CH_3$), 3.58–3.47 (2H, m, CH_2OH), 3.30–3.21 (1H, m, C1*H*), 2.71–2.66 (1H, m, C4*H*), 1.94–1.83 (2H, m), 1.77–1.72 (1H, m), 1.66–1.50 (3H, m), 1.37 (3H, t, *J*=7.1 Hz, $CO_2CH_2CH_3$), 1.36–1.31 (4H, m), 1.29–1.24 (2H, m), 1.16 (3H, d, *J*=7.0 Hz, C1CH_3), 1.14 (9H, d, *J*=7.5 Hz, O*TIPS*), 1.10 (9H, d, *J*=7.5 Hz, O*TIPS*), 0.97 (3H, d, *J*=6.8 Hz, C11CH_3), O*H* absent; ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.1, 153.6, 141.1, 139.4, 127.5, 123.2, 115.9, 63.3, 60.8, 42.5, 38.9, 31.3, 29.6, 27.7, 27.1, 21.3, 19.3, 19.1, 18.3, 18.2, 14.5, 13.1 ppm; HRESIMS calcd. for $C_{28}H_{48}O_4SiNa^+$, $[M+Na]^+$ 499.3220 found 499.3213



4.2.14 ethyl (5R, 8S)-5-methyl-8-((S)-5-oxopentan-2-yl)-4-((triisopropylsilyl)oxy)-5,6,7,8-tetrahydronaphthalene-2-carboxylate ***302***. To a stirred solution of alcohol **301** (78 mg, 0.16 mmol) in CH_2Cl_2 (3 mL) at room temperature was added finely ground PDC (95 mg, 0.25 mmol) and the resulting suspension stirred for 6 hours. The reaction mixture was filtered through celite

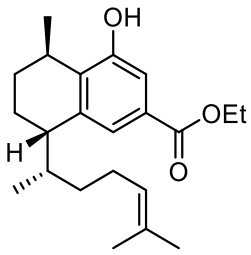
(CH_2Cl_2), concentrated *in vacuo* and passed through a plug of silica gel (10% EtOAc/X4) to give the *title compound* **302** (70 mg, 90%) as a colourless oil. $[\alpha]^{20}_D$ −57.2 (*c* 0.83 in $CHCl_3$). IR (CHCl3, cm^{-1}): 2927, 2868, 2715, 1721, 1575, 1464, 1368, 1341, 1289, 1227, 1065 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 9.64 (1H, t, *J*=1.8 Hz, C*H*O), 7.43 (1H, s, Ar-*H*), 7.30 (1H, d, *J*=1.6 Hz, Ar-*H*), 4.39–4.27 (2H, m, $CO_2CH_2CH_3$), 3.32–3.21 (1H, m, C1*H*), 2.73–2.67 (1H, m, C4*H*), 2.41 (1H, dddd, *J*=17.1, 9.9, 5.4, 1.7 Hz, CH_AH_BCHO), 2.24 (1H, dddd, *J*=17.2, 9.7, 6.1, 2.1 Hz, CH_AH_BCHO), 1.97–1.83 (3H, m), 1.65–1.51 (4H, m), 1.37 (3H, t, *J*=7.2 Hz, $CO_2CH_2CH_3$), 1.35–1.31 (3H, m, O*TIPS*), 1.17 (3H, d, *J*=7.0 Hz, C1HCH_3), 1.14 (9H, d, *J*=7.5 Hz, O*TIPS*), 1.10 (9H, d, *J*=7.5 Hz, O*TIPS*), 0.96 (3H, d, *J*=6.8 Hz, C11CH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.8, 167, 153.7, 140.5, 139.3, 127.7, 123.2, 116, 60.9, 42.7, 42.3, 38.9, 29.9, 27.6, 27, 25.8, 21.2, 19.1, 18.9, 18.3, 18.2, 14.5, 13.1 ppm; HRESIMS calcd. for $C_{28}H_{46}O_4SiNa^+$, $[M+Na]^+$ 497.3063 found 497.3050



Ethyl (5R, 8S)-5-methyl-8-((S)-6-methylhept-5-en-2-yl)-4-((triisopropylsilyl)oxy)-5,6,7,8-tetrahydronaphthalene-2-carboxylate ***303***. To a stirred solution of isopropyltriphenylphosphonium iodide (83 mg, 0.19 mmol) in THF (1 mL) at 0 °C was added *n*-BuLi (2.0M in cyclohexane, 90 μL, 0.18 mmol) dropwise. The deep red solution was stirred for 30 minutes at 0 °C then aldehyde **302** (40 mg, 84 μmol) was added *via* cannulation (THF). The reaction mixture was stirred at 0 °C for 1 hour, then allowed to warm to room temperature and quenched through addition of NH_4Cl (5 mL, sat. aq.). The layers were separated and the aqueous layer extracted with pentane (3×10 mL). The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (40% CH_2Cl_2/X4) afforded the *title compound* **303** (40 mg, 95%) as a colourless oil.

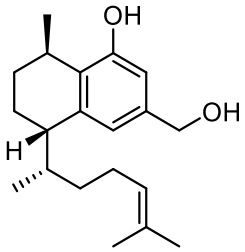
$[\alpha]^{20}_D$ −42.7 (*c* 0.98 in $CHCl_3$); IR ($CHCl_3$, cm^{-1}) 2926, 2867, 1721, 1606, 1575, 1494, 1453, 1421, 1288, 1226, 1065, 882 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ

7.45 (1H, d, *J*=1.4 Hz, Ar-*H*), 7.29 (1H, d, *J*=1.6 Hz, Ar-*H*), 4.99–4.91 (1H, m, C*H*=C(CH$_3$)$_2$), 4.33 (2H, qd, *J*=7.1, 3.3 Hz, CO$_2$C*H*$_2$CH$_3$), 3.30–3.20 (1H, m, C1*H*), 2.70–2.64 (1H, m, C4*H*), 1.97 (1H, ddd, *J*=14.7, 8.4, 4.0 Hz), 1.92–1.83 (3H, m), 1.82–1.69 (2H, m), 1.63 (3H, d, *J*=1.3 Hz, CH=C(C*H*$_3$)$_A$(CH$_3$)$_B$), 1.52 (3H, s, CH=C(CH$_3$)$_A$(C*H*$_3$)$_B$), 1.51–1.49 (1H, m), 1.42–1.30 (6H, m), 1.29–1.19 (1H, m), 1.16 (3H, d, *J*=7.0 Hz, C1C*H*$_3$), 1.14 (9H, d, *J*=7.5 Hz, O*TIPS*), 1.14–1.08 (1H, m), 1.10 (9H, d, *J*=7.5 Hz, O*TIPS*), 0.96 (3H, d, *J*=6.8 Hz, C11C*H*$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 167.1, 153.5, 141.2, 139.3, 131.3, 127.5, 124.9, 123.4, 115.8, 60.7, 42.5, 38.8, 33.8, 27.7, 27.0, 26.5, 25.8, 21.3, 19.3, 19.0, 18.3, 18.2, 17.7, 14.5, 13.1 ppm.



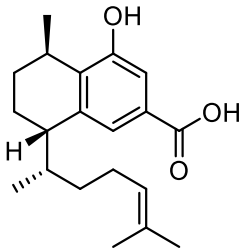
*Ethyl (5R, 8S)-4-hydroxy-5-methyl-8-((S)-6-methylhept-5-en-2-yl)-5,6,7,8-tetrahydronaphthalene-2-carboxylate **304***. To a stirred solution of **303** (19 mg, 38 μmol) in THF (1 mL) at room temperature was added TBAF (1M in THF, 0.4 mL) dropwise. The reaction mixture was stirred at room temperature for 1.5 hours, then diluted with EtOAc (10 mL) and NH$_4$Cl (1 mL, sat. aq.) added. The layers were separated and the organic layer washed with H$_2$O (3 mL) and brine (3 mL). The organic layer was dried (Na$_2$SO$_4$) and concentrated *in vacuo*. Purification by column chromatography (buffered SiO$_2$, CH$_2$Cl$_2$) afforded the *title compound* **304** (12 mg, 91%) as a colourless oil. [α]$^{20}_D$ −62.8 (*c* 0.61 in CHCl$_3$); IR (CHCl$_3$, cm^{-1}) 3436, 2957, 2925, 2856, 1718, 1694, 1608, 1582, 1494, 1452, 1423, 1372, 1293, 1235, 1051, 824 cm^{-1}; ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.46 (1H, d, *J*=1.6 Hz, Ar-*H*), 7.31 (1H, d, *J*=1.3 Hz, Ar-*H*), 5.24 (1H, s, O*H*), 5.00–4.92 (1H, m, C*H*=C(CH$_3$)$_2$), 4.41–4.29 (2H, m, CO$_2$C*H*$_2$CH$_3$), 3.18 (1H, pd, *J*=6.9, 2.3 Hz, C1*H*), 2.66 (1H, td, *J*=5.7, 2.7 Hz, C4*H*), 2.03–1.83 (3H, m), 1.83–1.73 (2H, m), 1.66–1.60 (1H, m), 1.63 (3H, s, C*H*=C(C*H*$_3$)$_A$(CH$_3$)$_B$), 1.54 (3H, s, C*H*=C(CH$_3$)$_A$(C*H*$_3$)$_B$), 1.55–1.51 (1H, m), 1.38 (3H, t, *J*=7.1 Hz, CO$_2$CH$_2$C*H*$_3$), 1.30–1.21 (1H, m), 1.21 (3H, d, *J*=7.0 Hz, C1C*H*$_3$), 1.10 (1H, dtd, *J*=13.4, 9.7, 5.1 Hz), 0.97 (3H, d, *J*=6.8 Hz, C11C*H*$_3$); ^{13}C NMR (150 MHz,

$CDCl_3$) δ 167.1, 153.4, 141.6, 135.4, 131.4, 127.8, 124.9, 123.4, 113, 61, 42.6, 38.3, 33.6, 27.3, 27.1, 26.4, 25.8, 21, 19.3, 18.8, 17.8, 14.5 ppm.



(5S, 8R)-3-(hydroxymethyl)-8-methyl-5-((S)-6-methylhept-5-en-2-yl)-5,6,7,8-tetrahydronaphthalen-1-ol ***147***. To a stirred solution of **304** (5 mg, 15 μmol) in CH_2Cl_2 (1 mL) at −78 °C was added DIBAL (1M in toluene, 50 μL, 50 μmol) dropwise and the resulting solution stirred at −78 °C for 2 hours. The reaction mixture was warmed to 0 °C and quenched through addition of H_2O dropwise. 1M HCl (5 mL) was added and the biphasic mixture diluted with CH_2Cl_2 (5 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (20% Et_2O/CH_2Cl_2) afforded the *title compound* **147** (3 mg, 68%) as a colourless oil.

$[\alpha]^{20}_D$ −46.5 (*c* 0.19 in MeOH); IR (MeOH, cm^{-1}) 3368, 3018, 2925, 2861, 1709, 1610, 1494, 1452, 1430, 1377, 1051, 825 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.74 (1H, s, Ar-*H*), 6.63 (1H, d, *J*=1.6 Hz, Ar-*H*), 4.98 (1H, t, *J*=7.1 Hz, C*H*=C$(CH_3)_2$), 4.85 (1H, s, O*H*), 4.59 (2H, s, CH_2OH), 3.10 (1H, pd, *J*=6.8, 2.4 Hz, C1*H*), 2.61 (1H, td, *J*=5.6, 2.8 Hz, C4*H*), 2.04–1.91 (2H, m), 1.91–1.70 (4H, m), 1.65 (3H, s, C*H*=C(CH_3)$_A$(CH_3)$_B$), 1.55 (3H, s, C*H*=C(CH_3)$_A$(CH_3)$_B$), 1.51 (1H, dq, *J*=10.3, 2.6 Hz), 1.33–1.23 (1H, m), 1.20 (3H, d, *J*=7.0 Hz, C1CH_3), 1.09 (1H, dtd, *J*=13.3, 9.7, 5.1 Hz), 0.96 (3H, d, *J*=6.8 Hz, C11CH_3), O*H* absent; ^{13}C NMR (151 MHz, $CDCl_3$) δ 153.6, 141.7, 138.4, 131.4, 129, 125, 120.5, 111.2, 65.5, 42.7, 38.2, 33.6, 27.5, 26.9, 26.4, 25.8, 21.20, 19.5, 18.9, 17.8 ppm.



*(5R, 8S)-4-hydroxy-5-methyl-8-((S)-6-methylhept-5-en-2-yl)-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid (**147**).* To a stirred solution of **304** (4 mg, 12 μmol) in THF (2 mL) was added 1M NaOH (1 mL) and the resulting biphasic mixture heated under reflux for 40 hours. The reaction mixture was allowed to cool to room temperature and acidified with 1M HCl to ~pH 2. The layers were separated and the aqueous layer extracted with EtOAc (3×5 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (20% Et_2O/CH_2Cl_2, 1% Et_3N) afforded the *title compound **147*** (1.9 mg, 52%) as a colourless oil.

IR (thin film, cm^{-1}) 3400, 2925, 2859, 1688, 1608, 1582, 1494, 1452, 1425, 1404, 1051, 875 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.53 (1H, s, Ar-*H*), 7.27 (1H, s, Ar-*H*), 5.00–4.94 (1H, m, C*H*=C$(CH_3)_2$), 3.18 (1H, dtd, *J*=13.3, 6.6, 1.8 Hz, C1*H*), 2.72–2.63 (1H, m, C4*H*), 2.05–1.84 (4H, m), 1.84–1.72 (2H, m), 1.64 (3H, s, C*H*=C(CH_3)$_A$(CH_3)$_B$), 1.56–1.52 (1H, m), 1.54 (3H, s, C*H*=C(CH_3)$_A$(CH_3)$_B$), 1.28–1.22 (1H, m), 1.22 (3H, d, *J*=7.0 Hz, C1CH_3), 1.10 (1H, dtd, *J*=13.5, 9.6, 5.0 Hz), 0.97 (3H, d, *J*=6.8 Hz, C11CH_3), 2×O*H* absent; ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.1, 153.3, 141.8, 136.5, 131.6, 126.5, 124.8, 124.24, 113.4, 42.6, 38.2, 33.6, 29.9, 27.4, 27.1, 26.4, 25.8, 21, 19.4, 18.8, 17.8 ppm.

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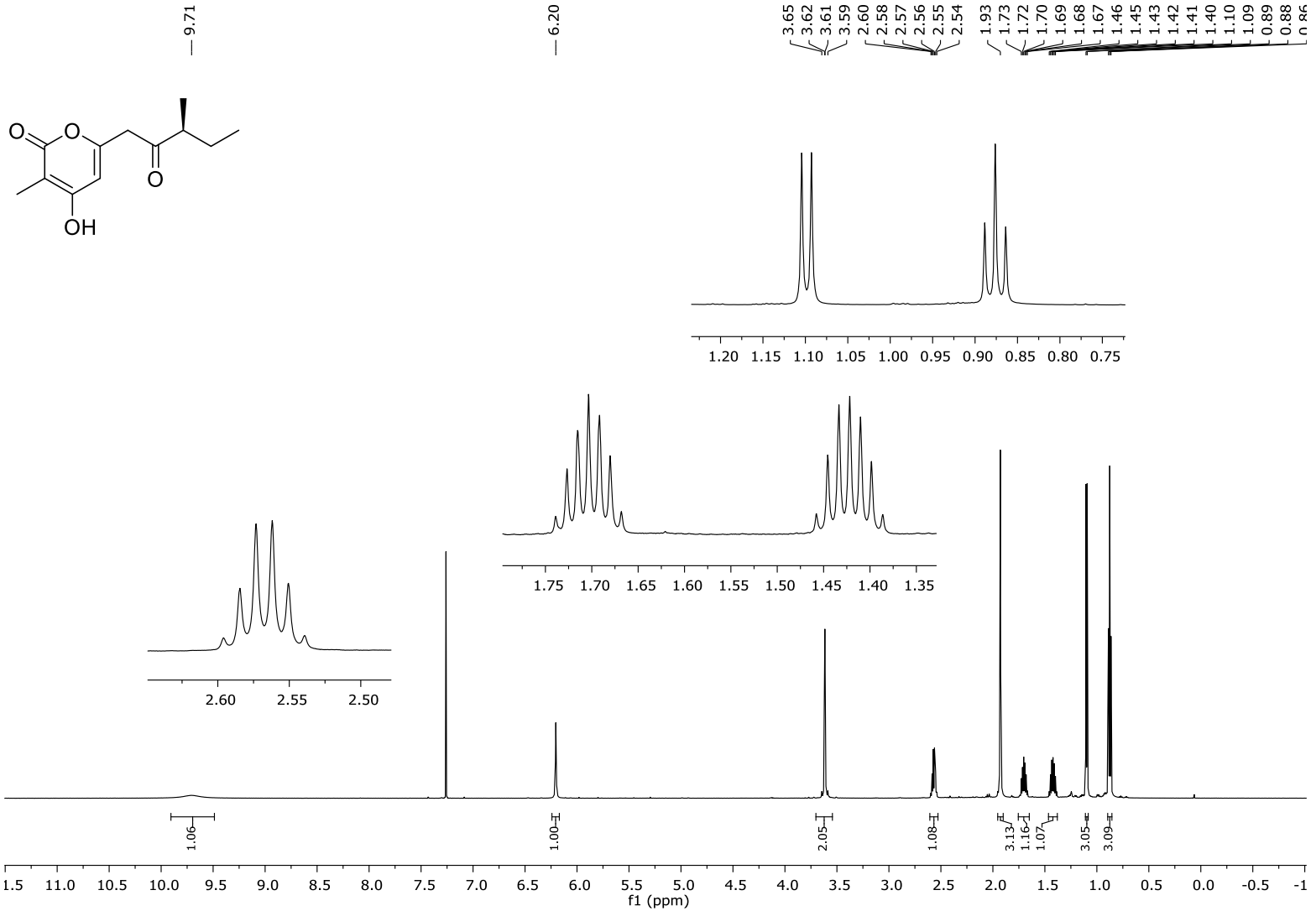
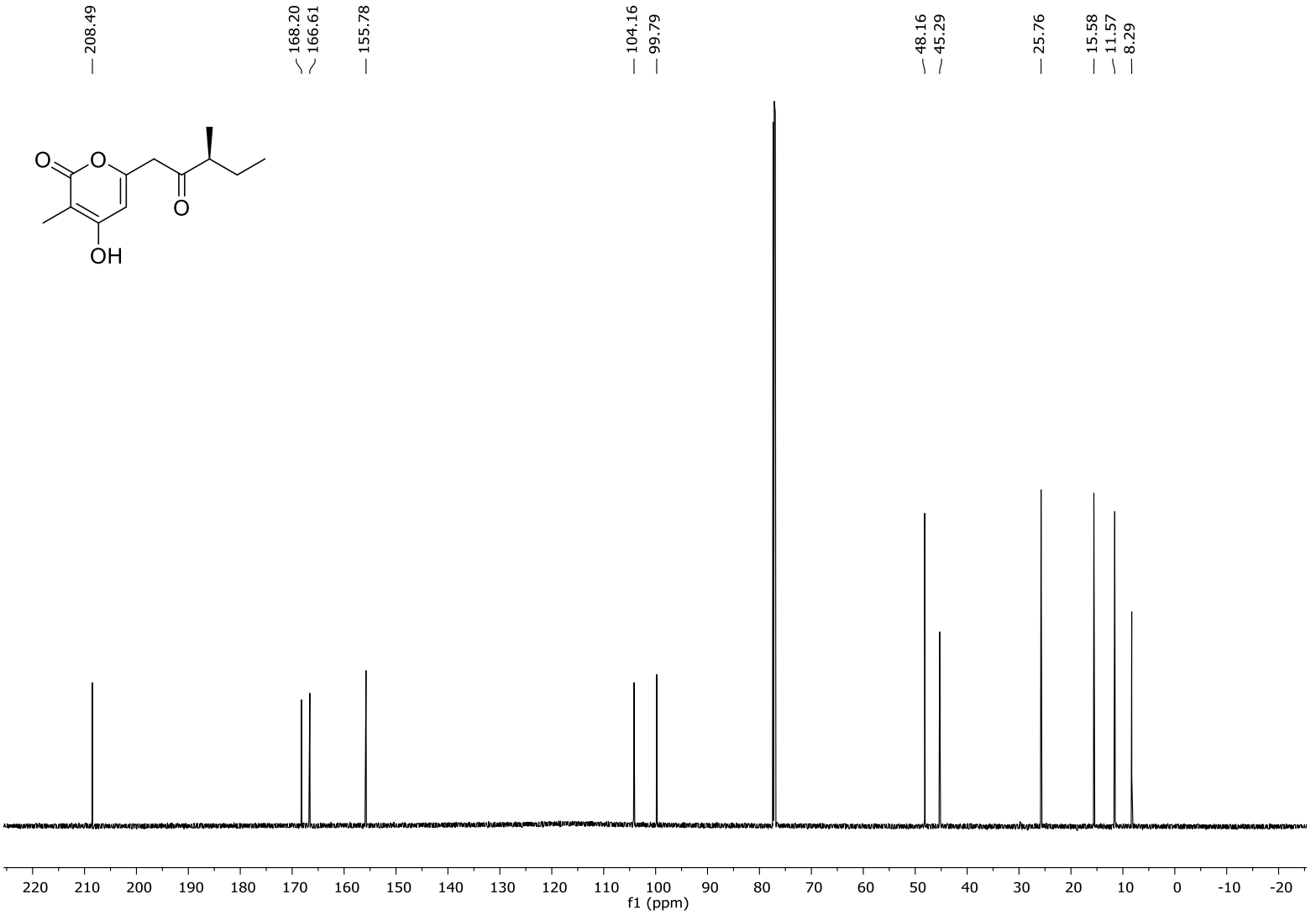
Appendices
Selected 1D and 2D NMR spectra for chapters 2-4

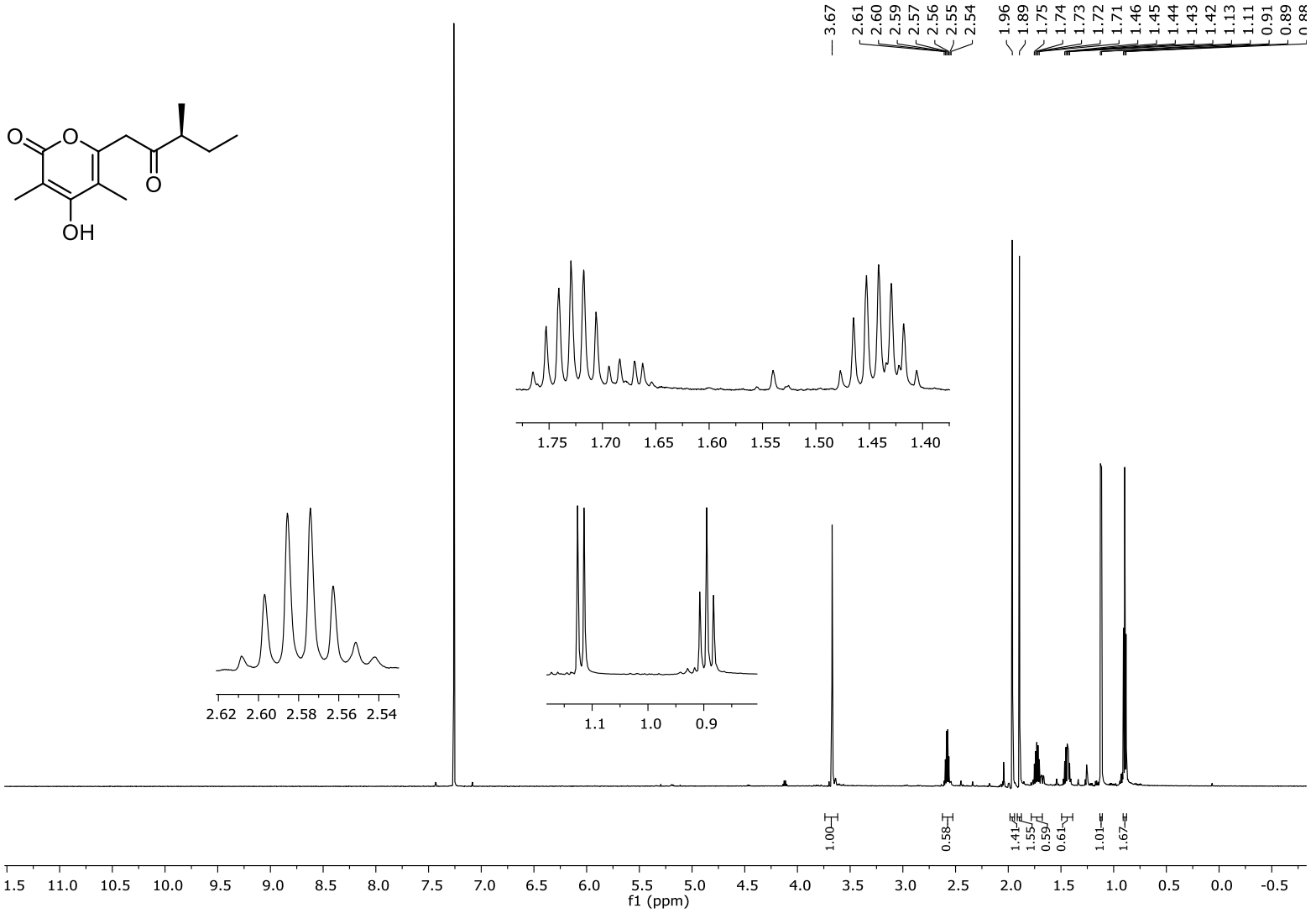
76: ^{1}H NMR (600 MHz, $CDCl_3$)



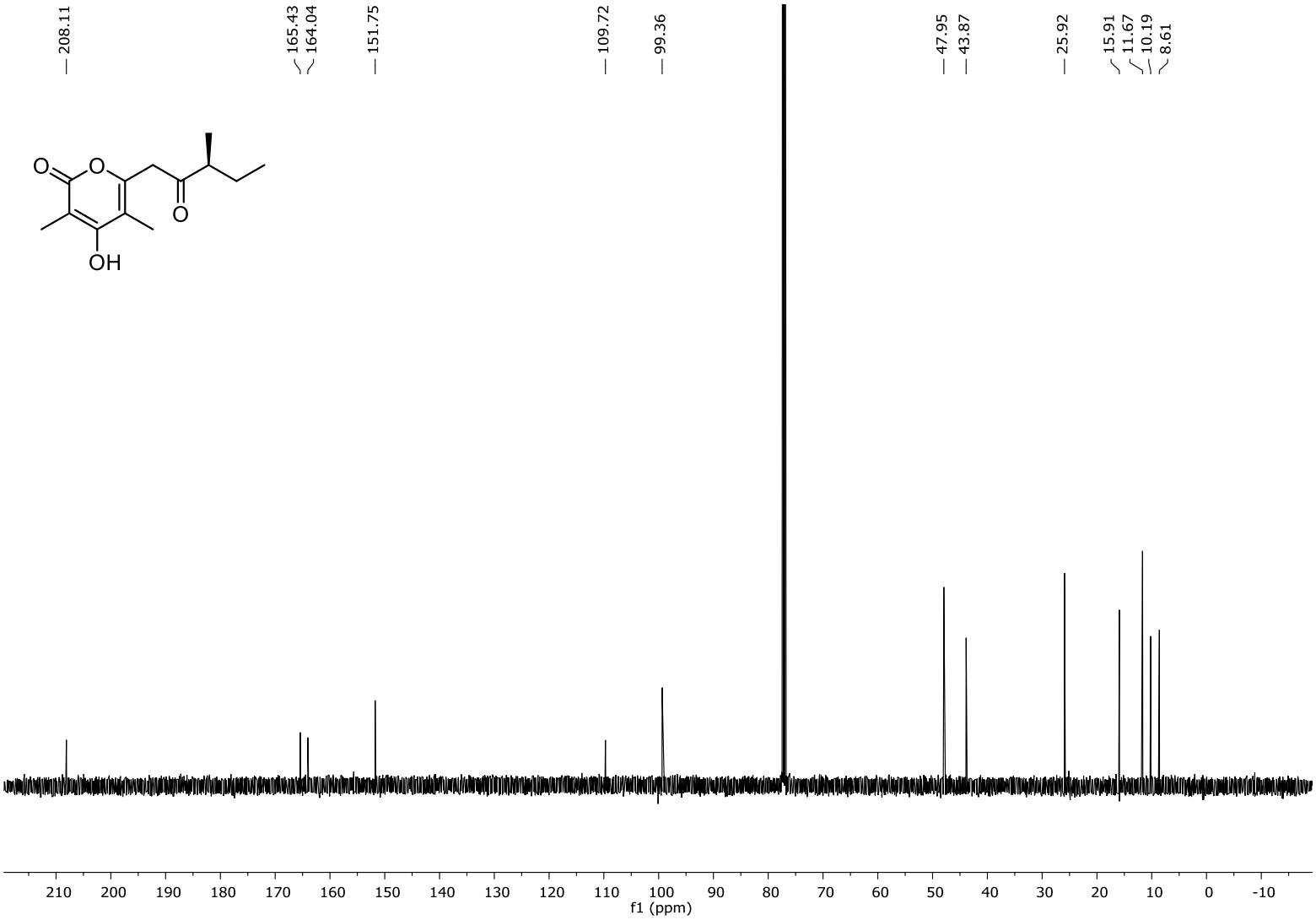
76: ^{13}C NMR (150 MHz, $CDCl_3$)



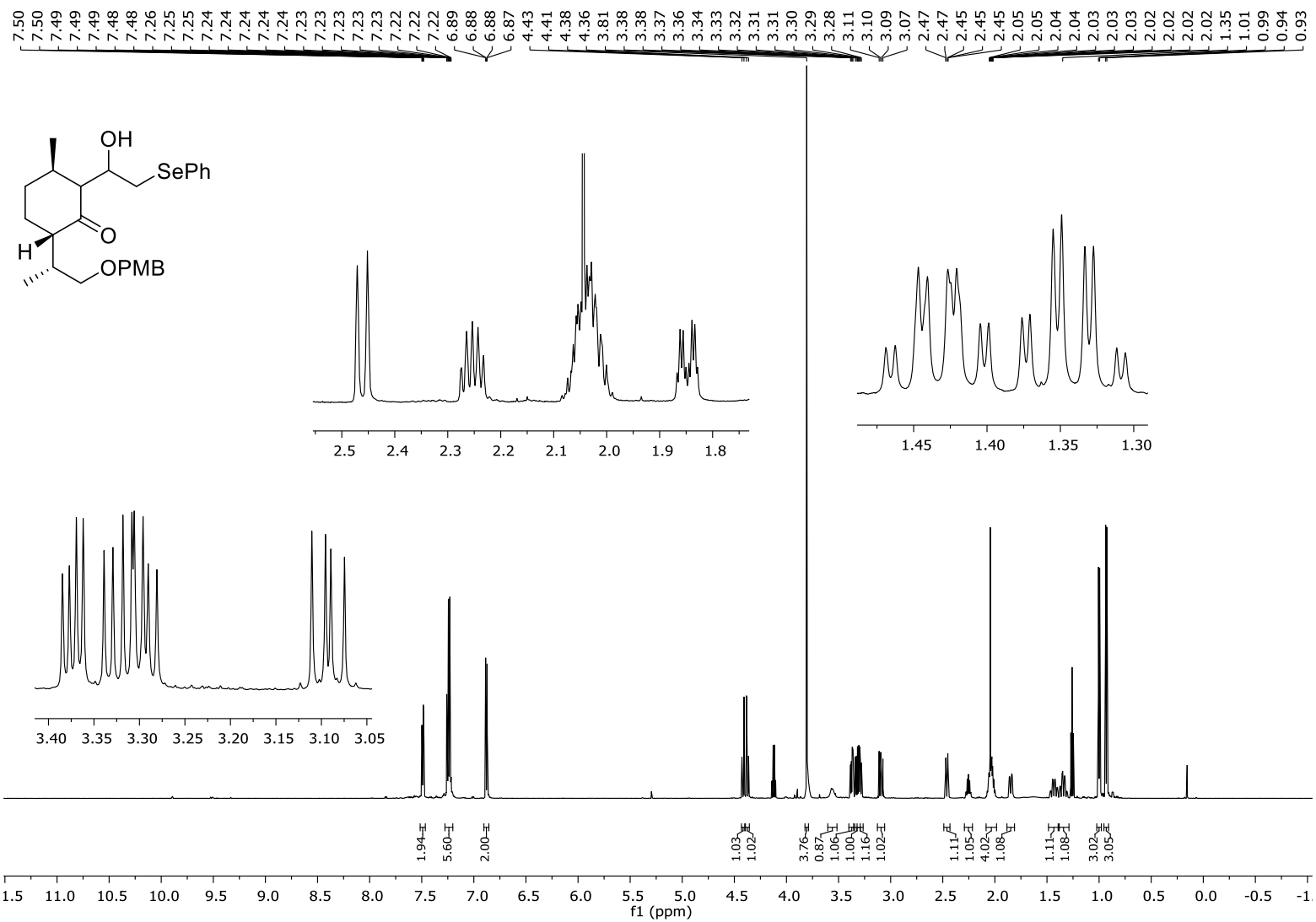
78: ^{1}H NMR (600 MHz, $CDCl_3$)



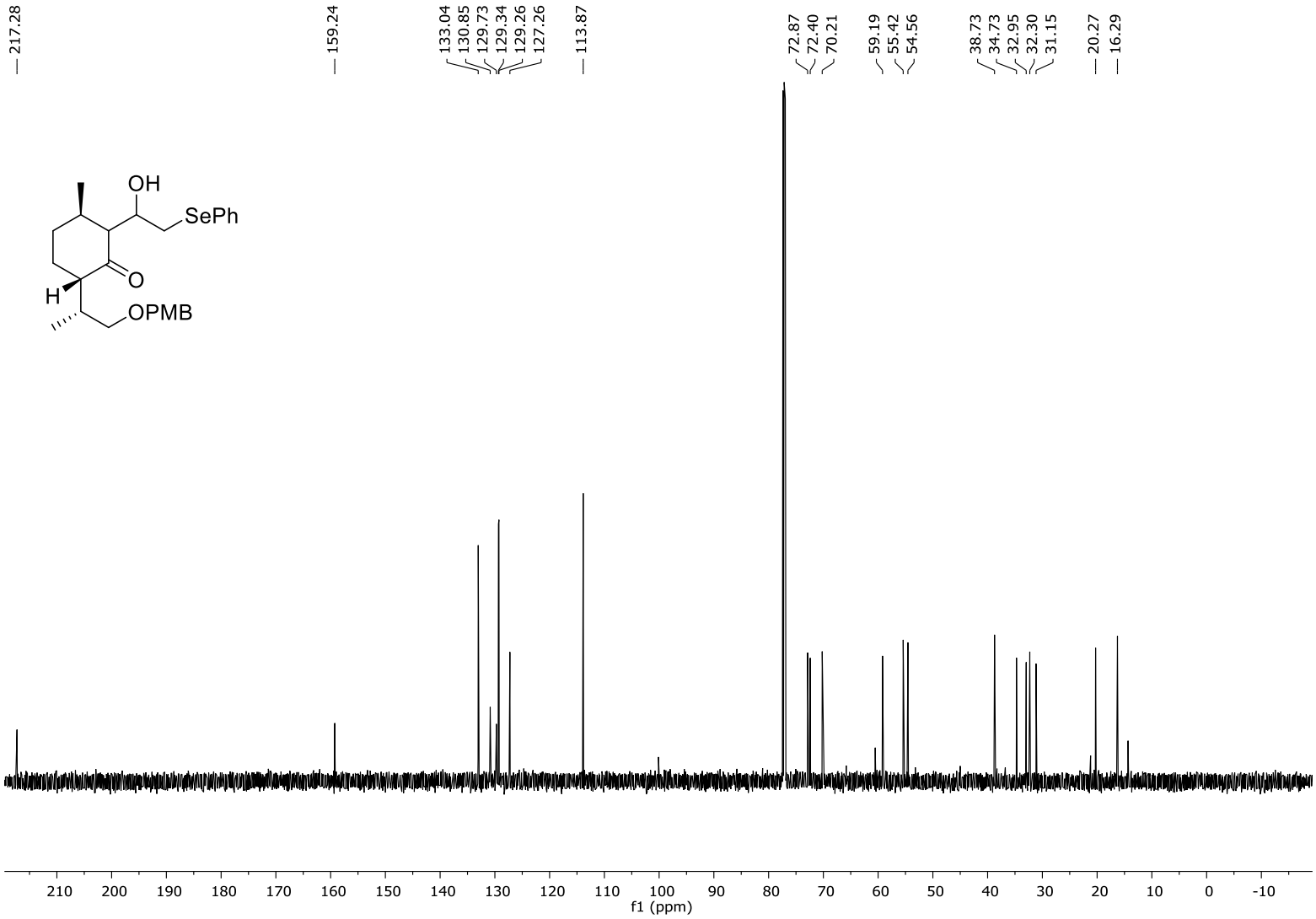
78: ^{13}C NMR (150 MHz, $CDCl_3$)



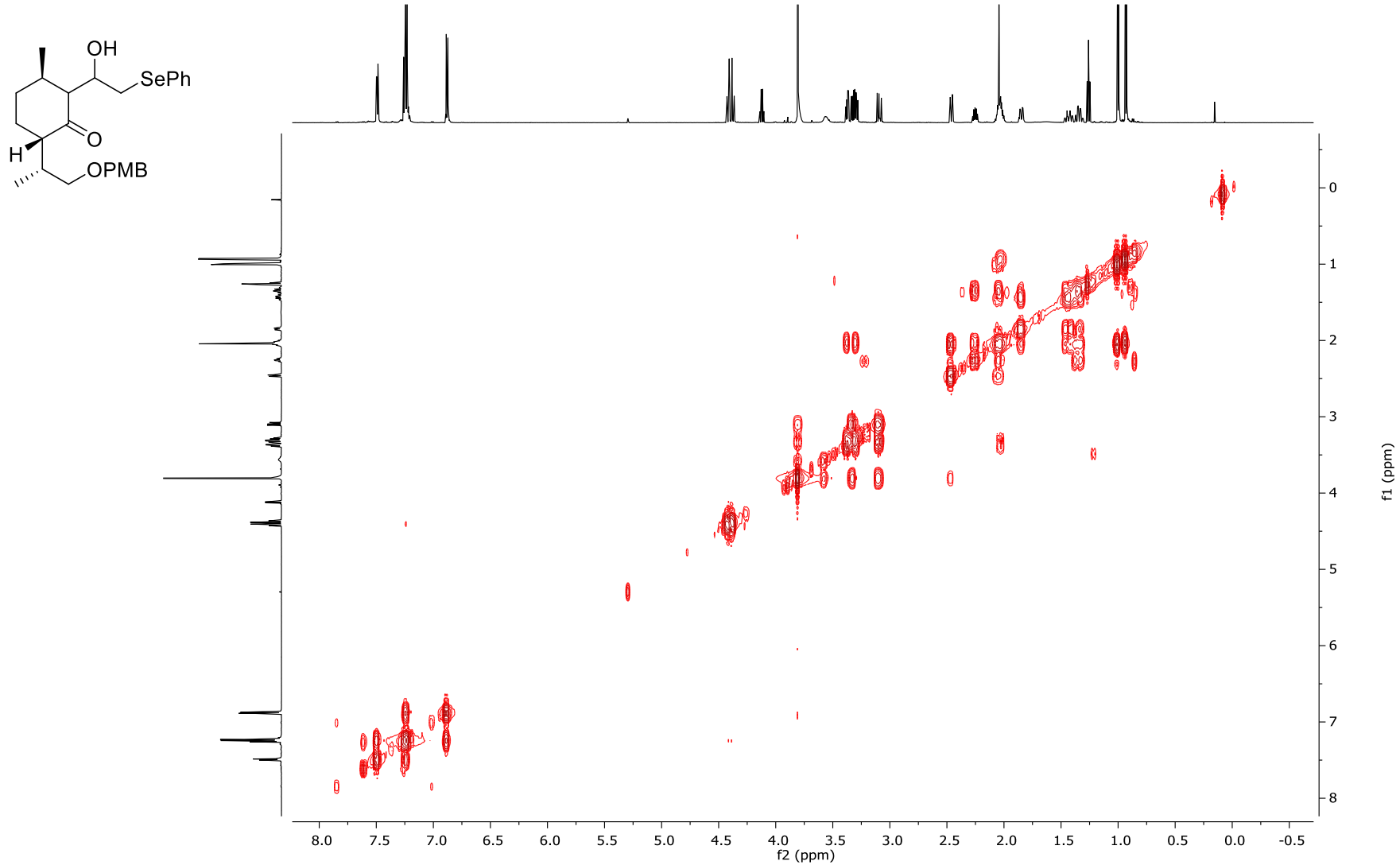
261: ^{1}H NMR (600 MHz, $CDCl_3$)



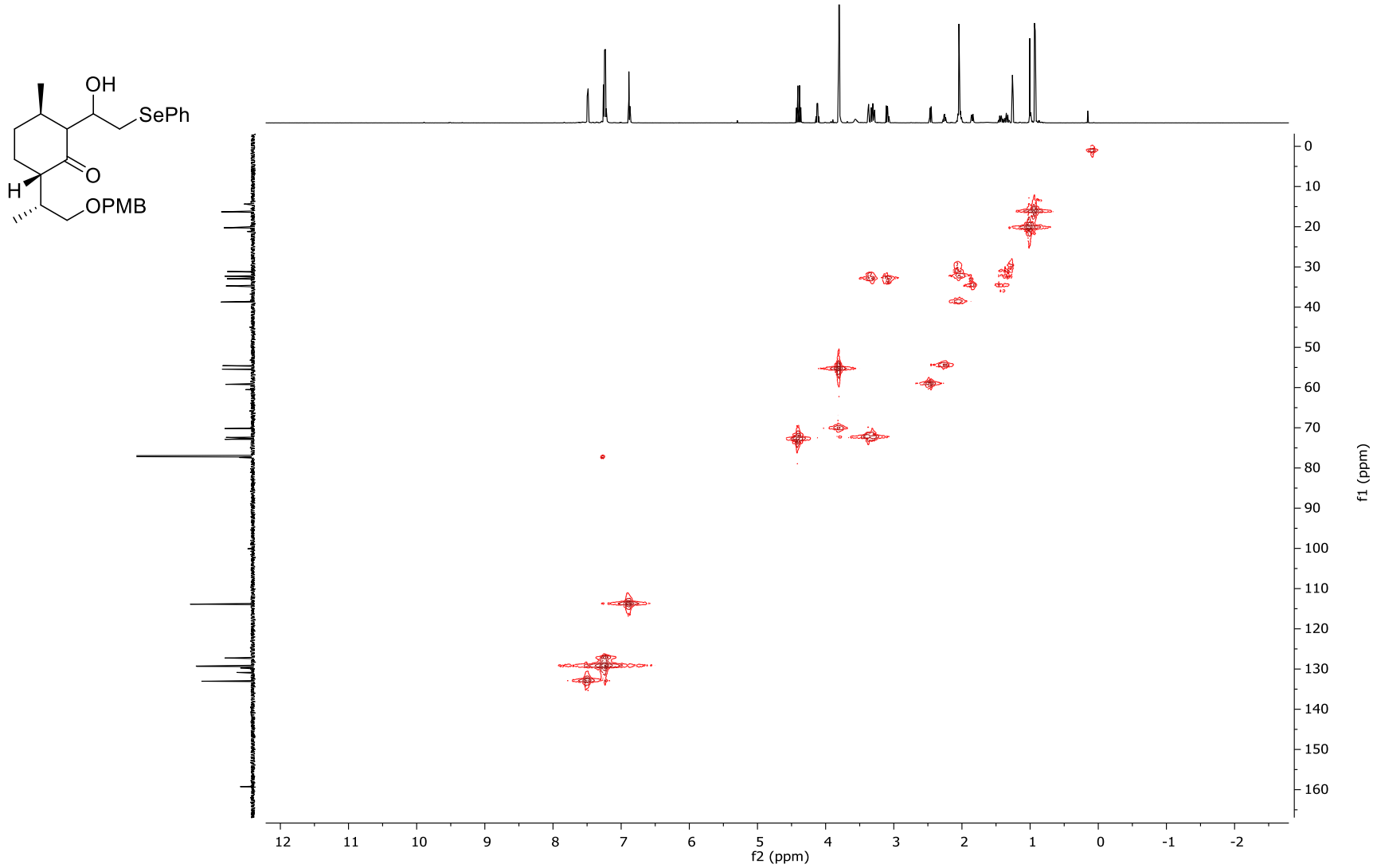
261:^{13}C NMR (150 MHz, $CDCl_3$)



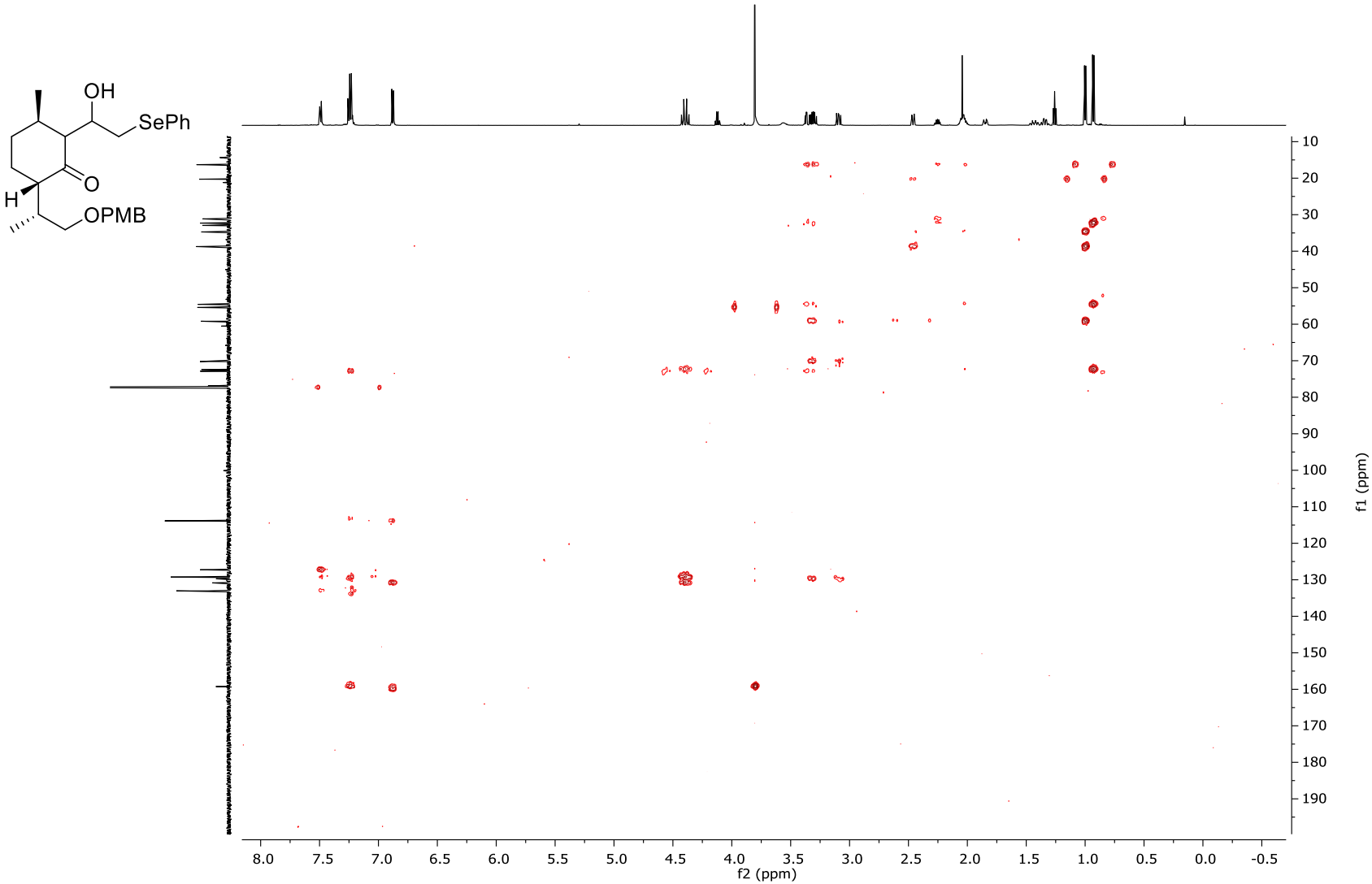
261: COSY (600 × 600 MHz, $CDCl_3$)



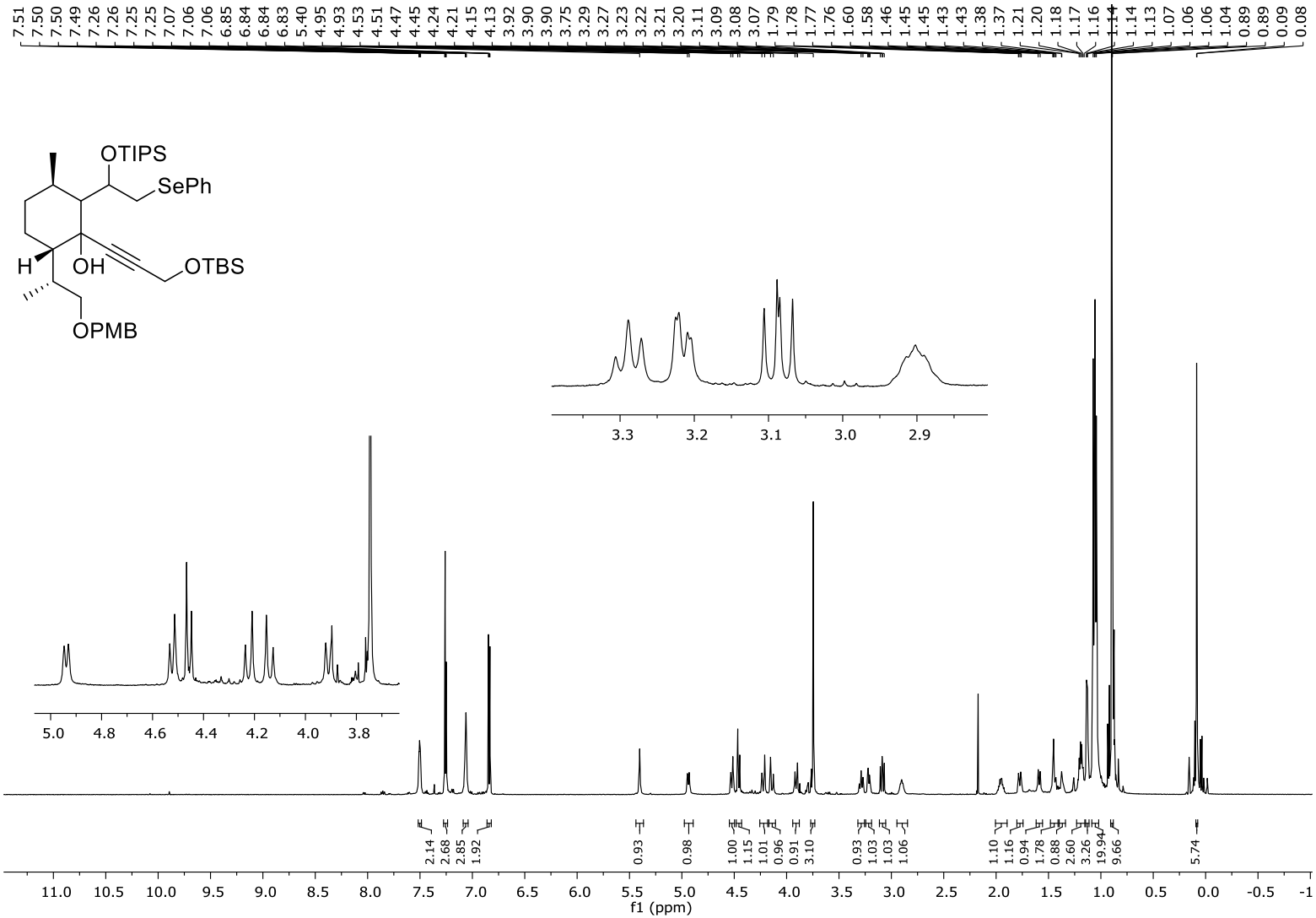
261: HMQC (400 × 100 MHz, $CDCl_3$)



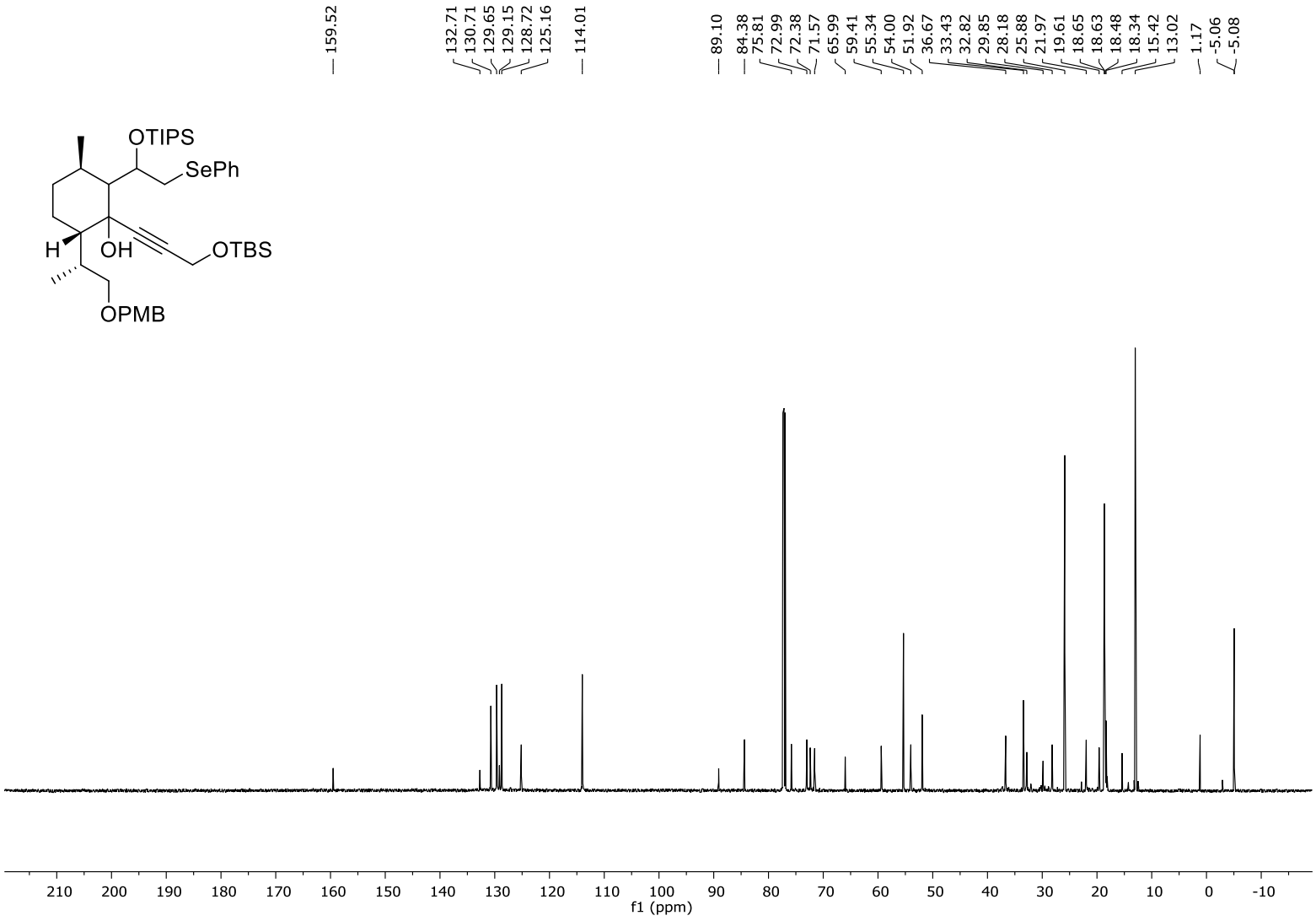
261: HMBC (400 × 100 MHz, $CDCl_3$)



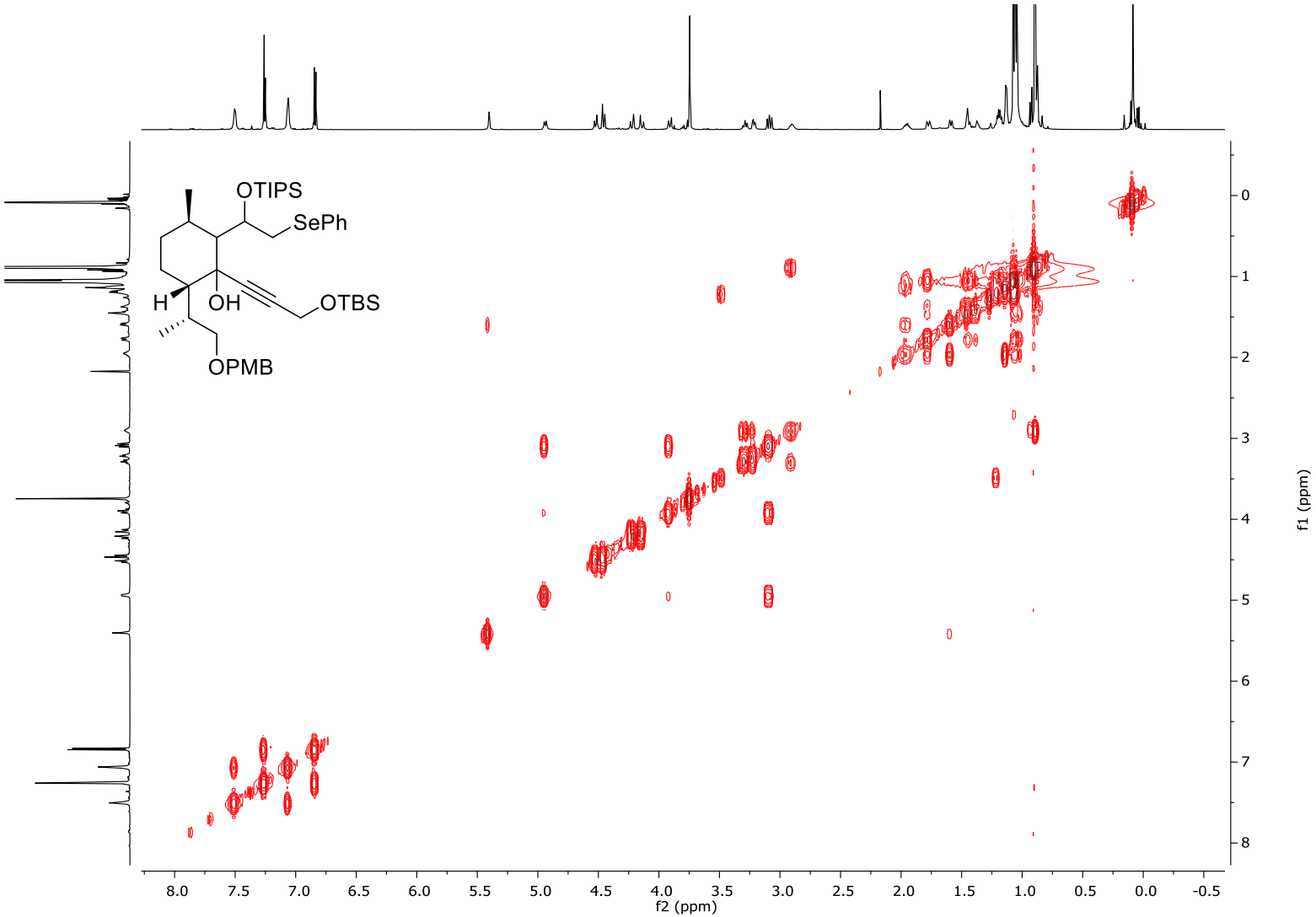
263*b*: ^{1}H NMR (600 MHz, $CDCl_3$)



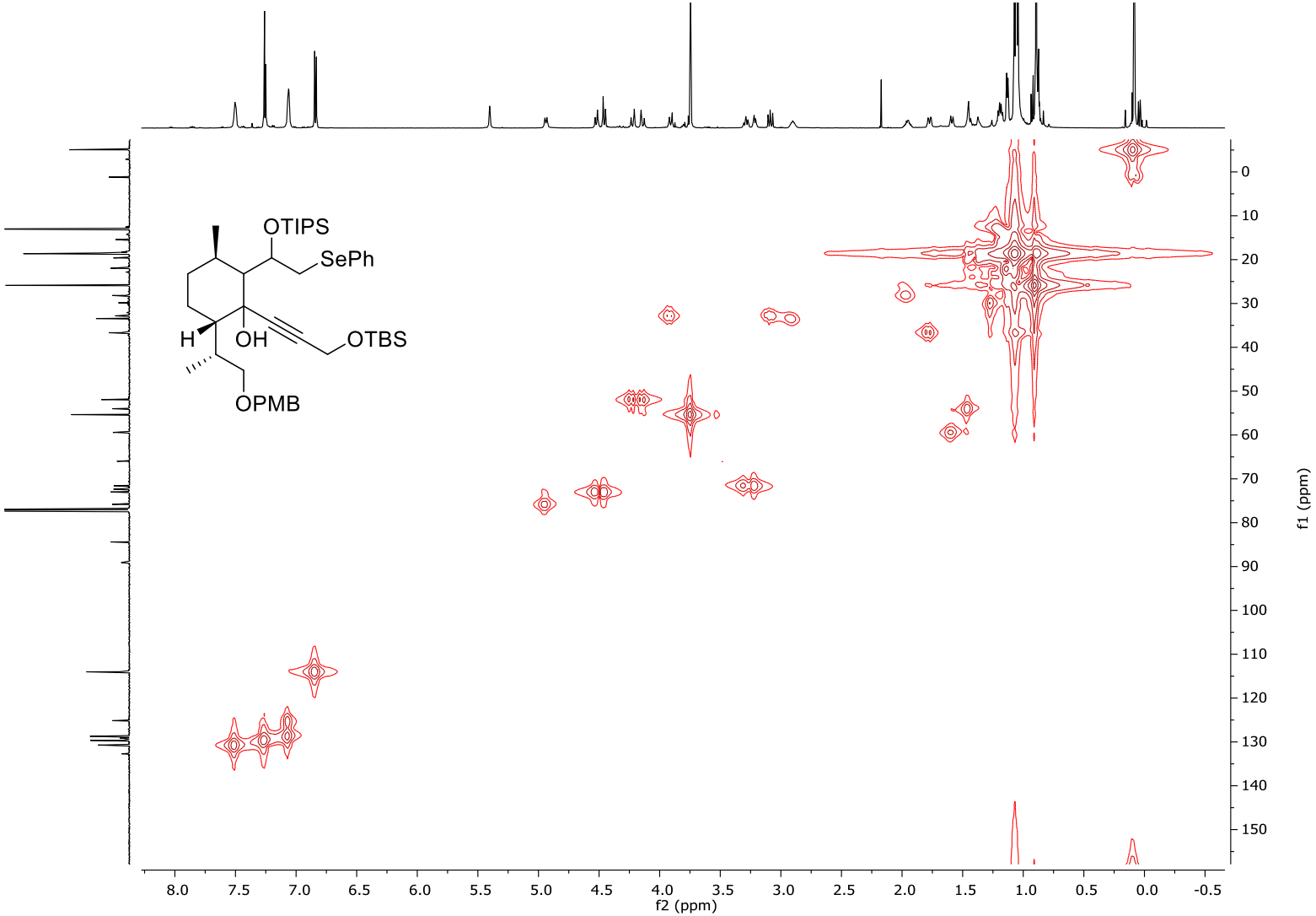
263*b*: ^{13}C NMR (150 MHz, $CDCl_3$)



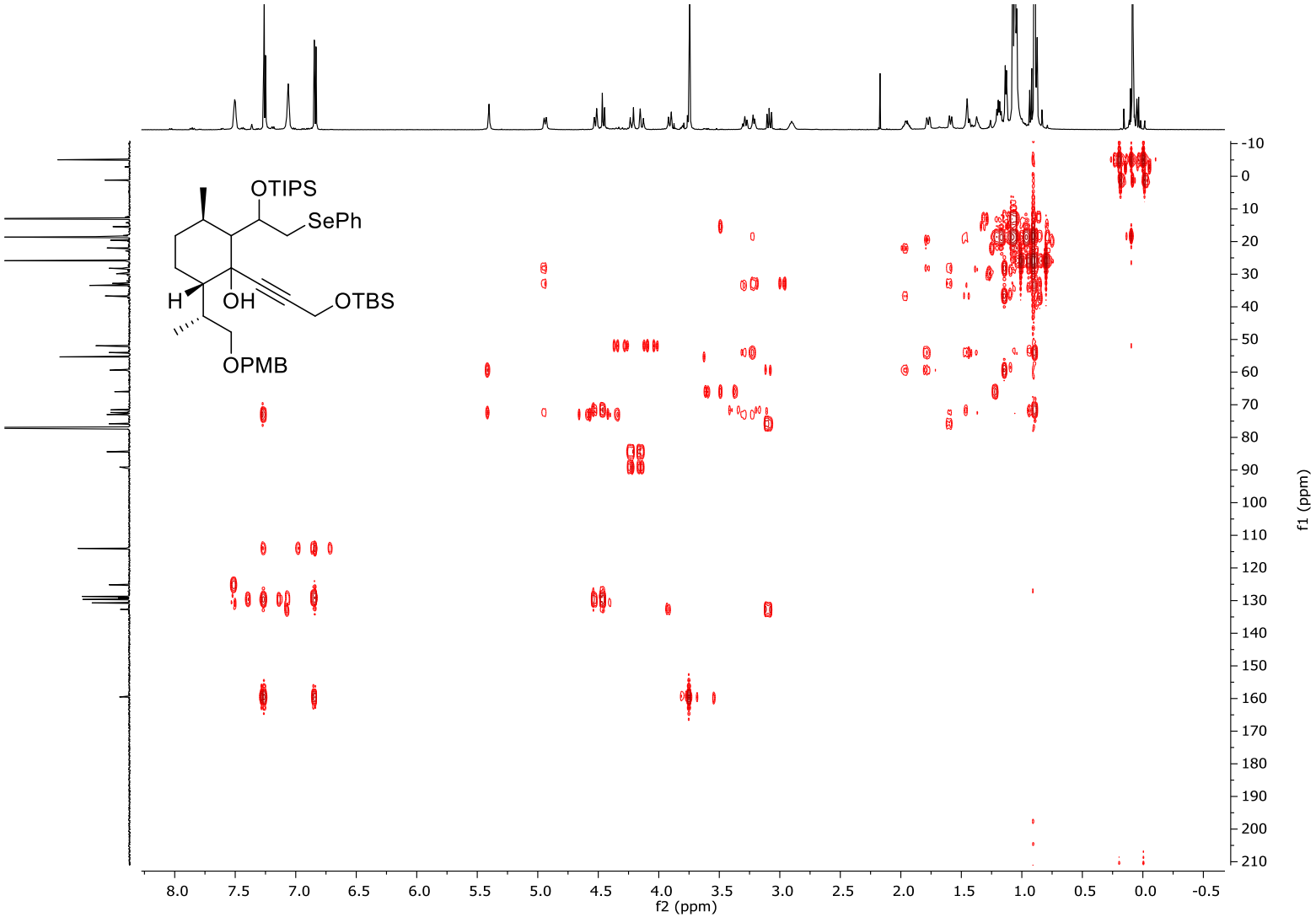
263*b*: COSY (600 × 600 MHz, $CDCl_3$)



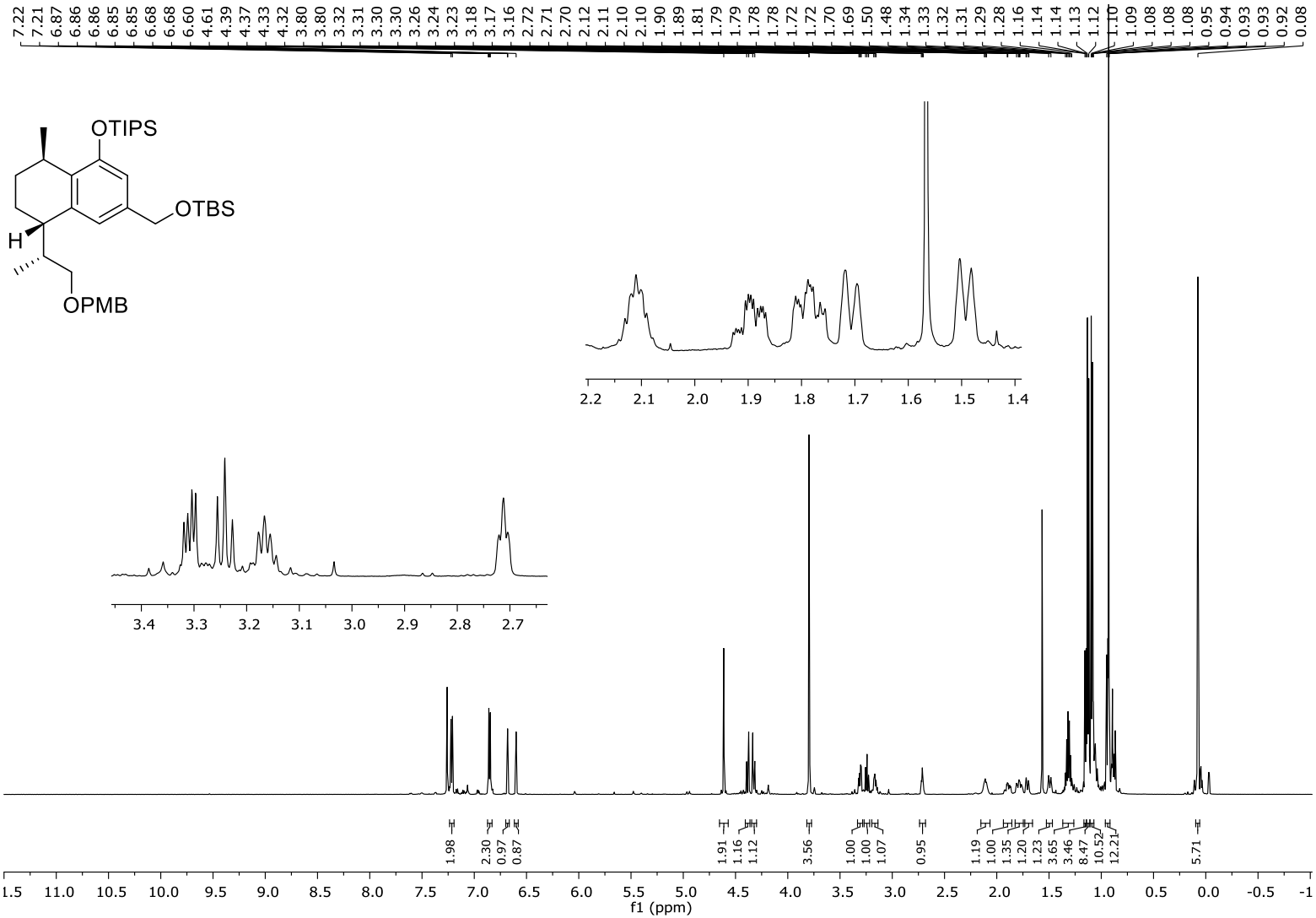
263*b*: HMQC (600 × 150 MHz, $CDCl_3$)



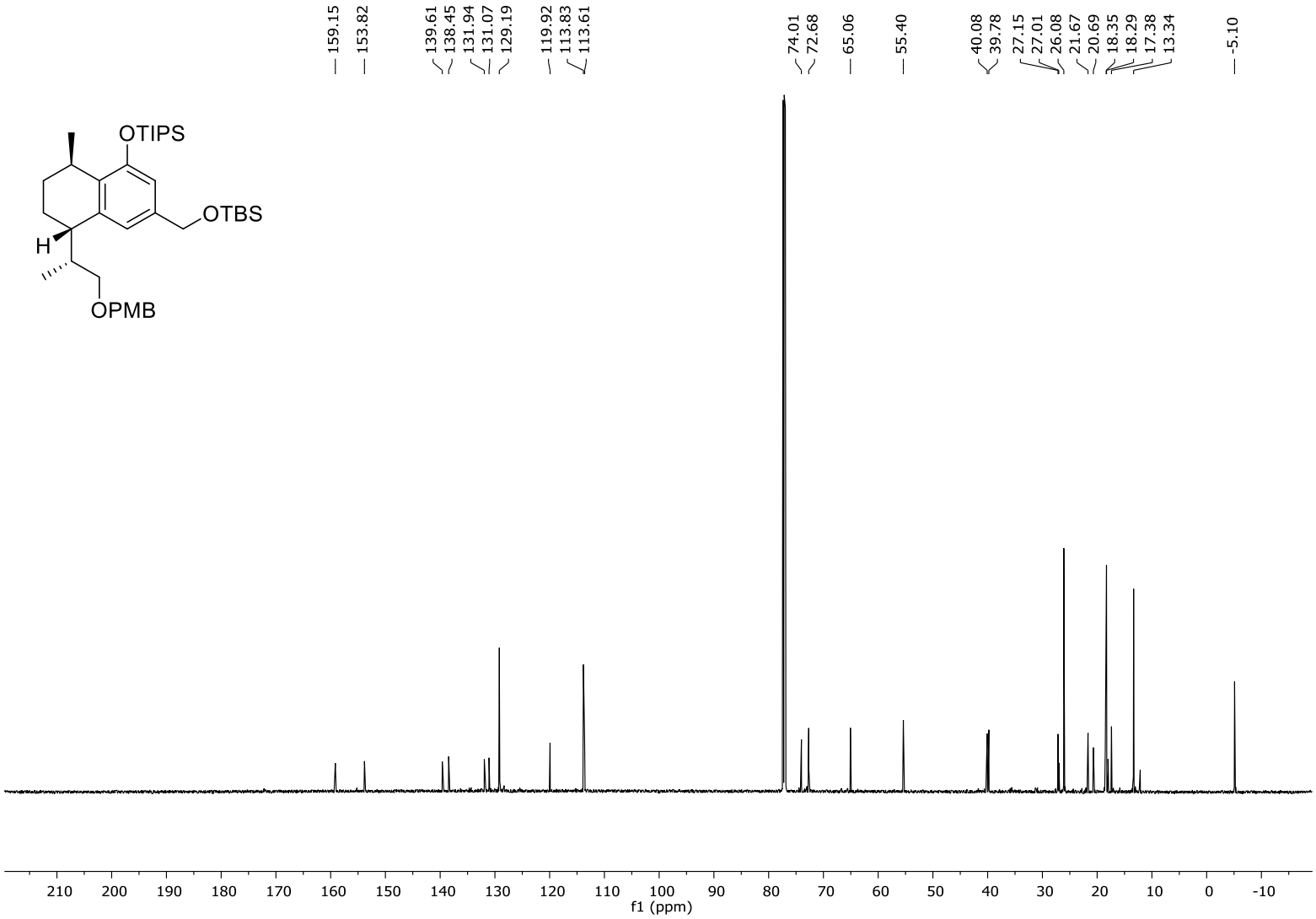
263*b*: HMBC (600 × 150 MHz, $CDCl_3$)



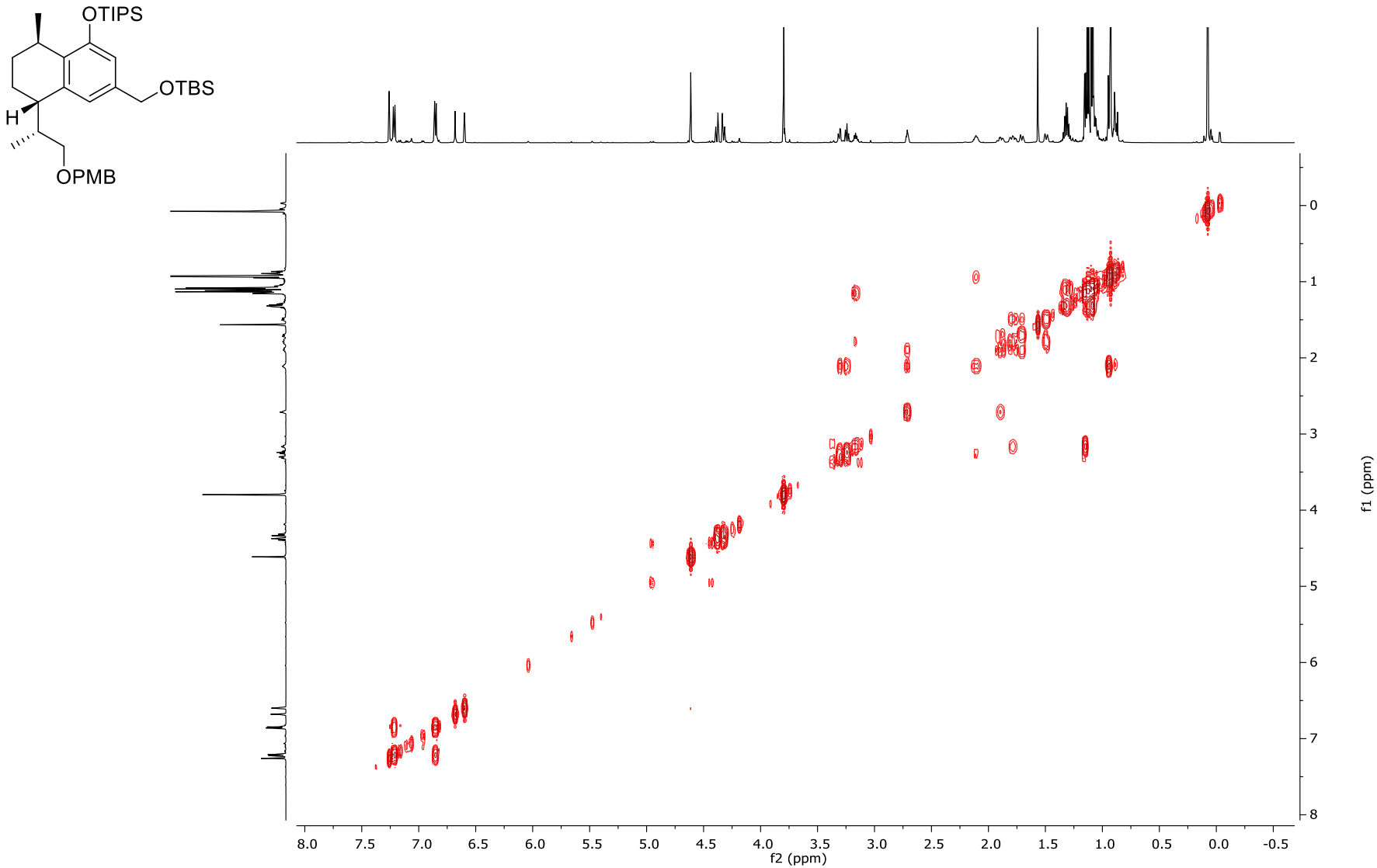
265: ^{1}H NMR (600 MHz, $CDCl_3$)



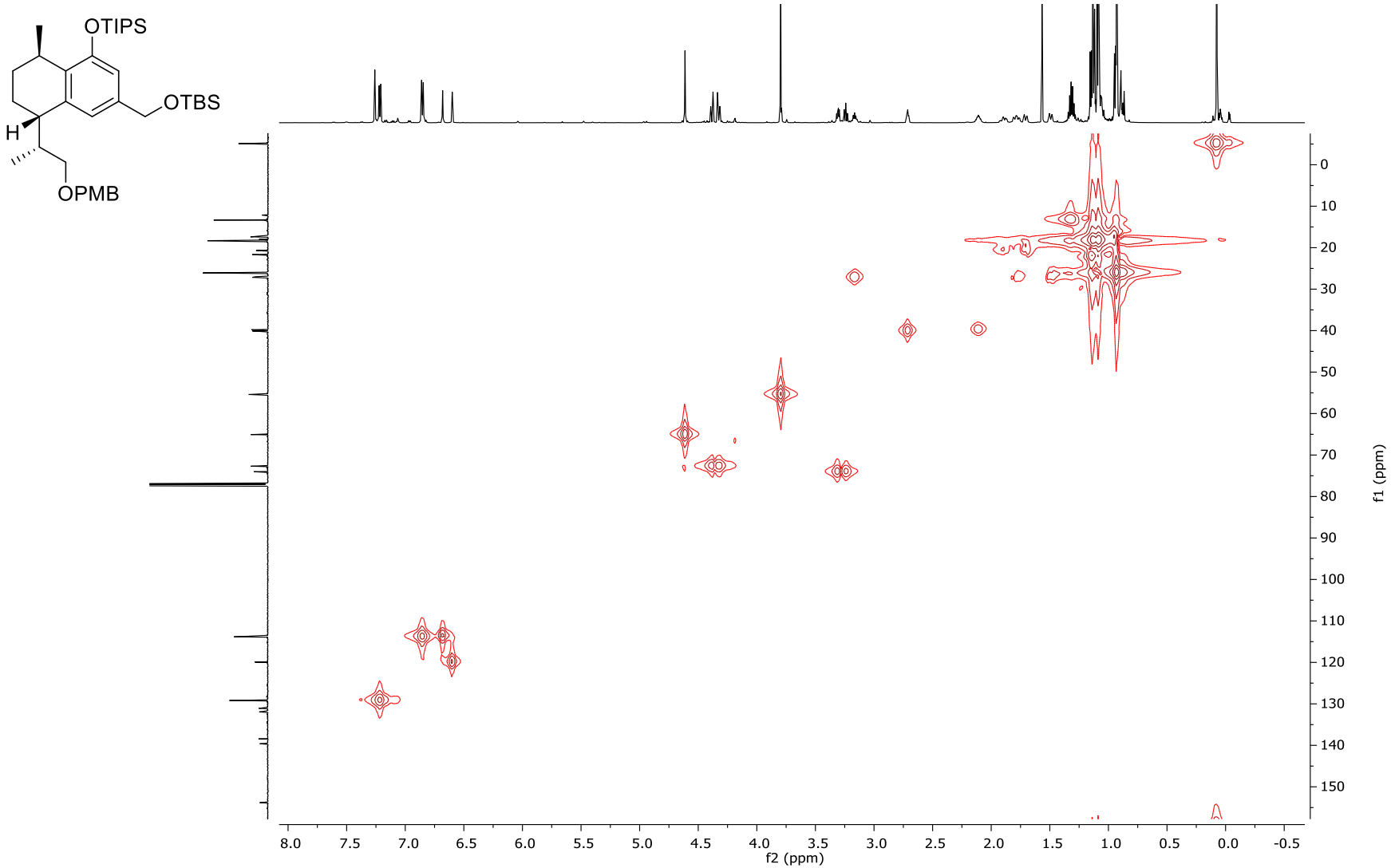
265: ^{13}C NMR (150 MHz, $CDCl_3$)



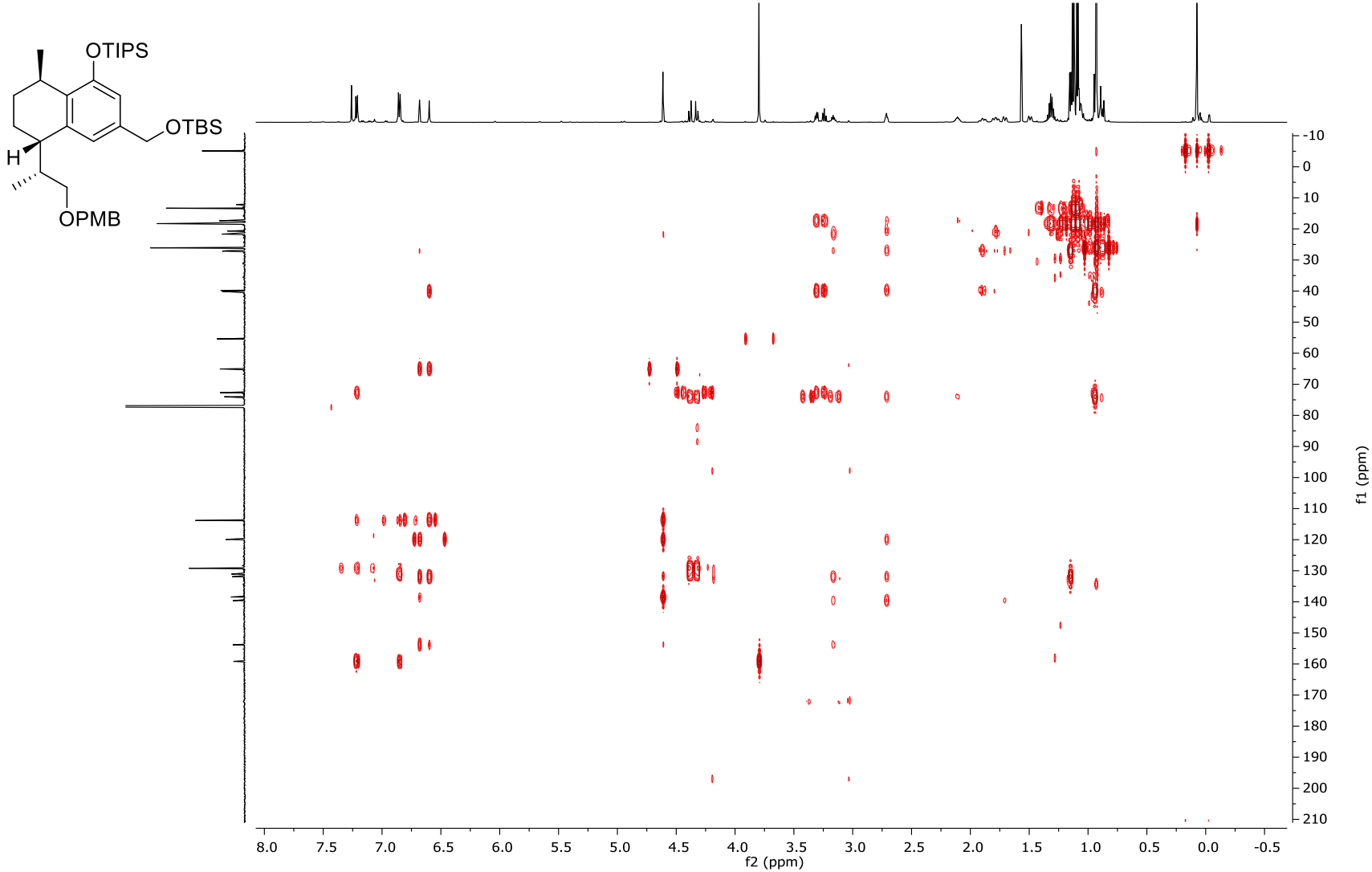
265: COSY (600 × 600 MHz, $CDCl_3$)



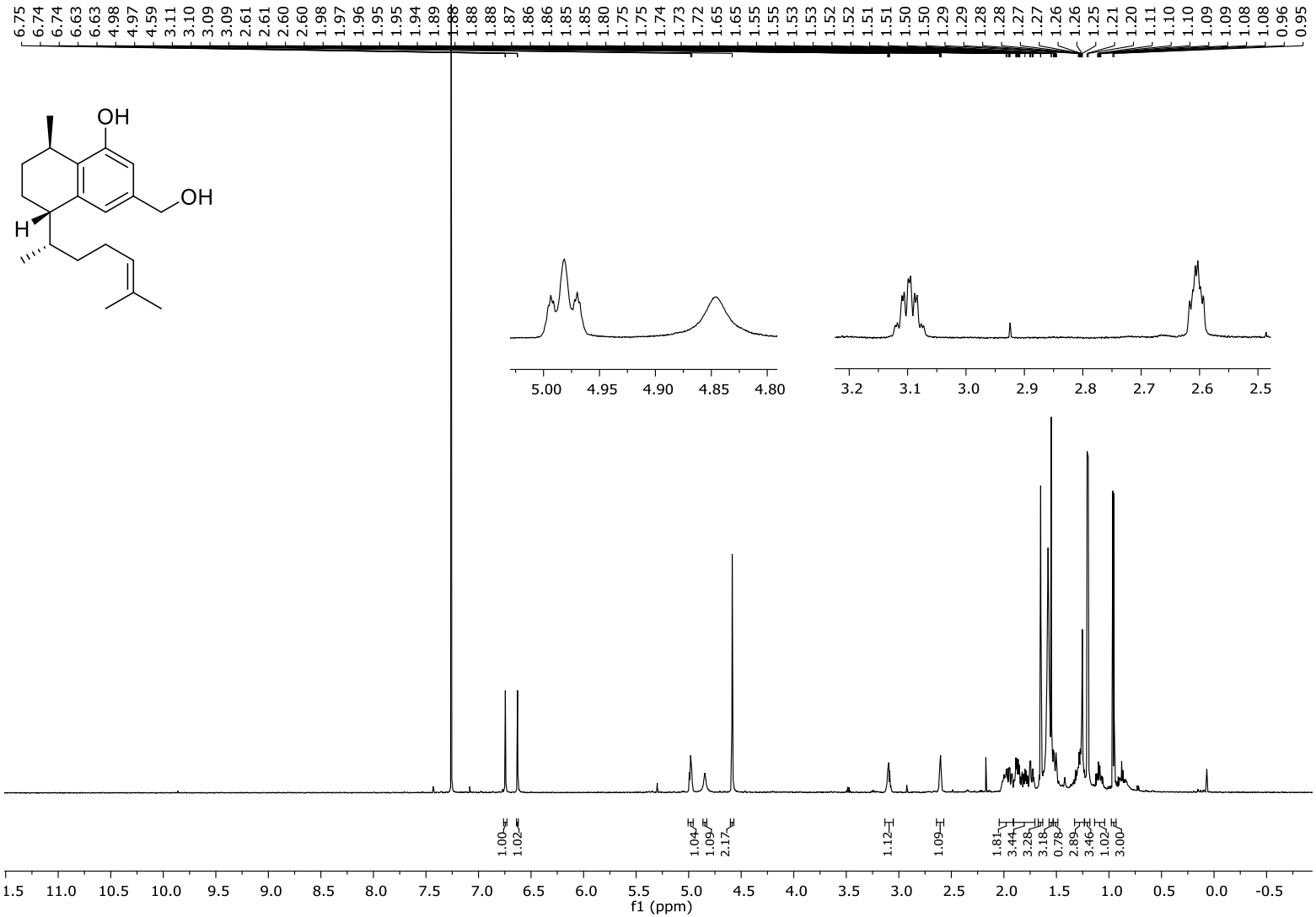
265: HMQC (600 × 150 MHz, $CDCl_3$)



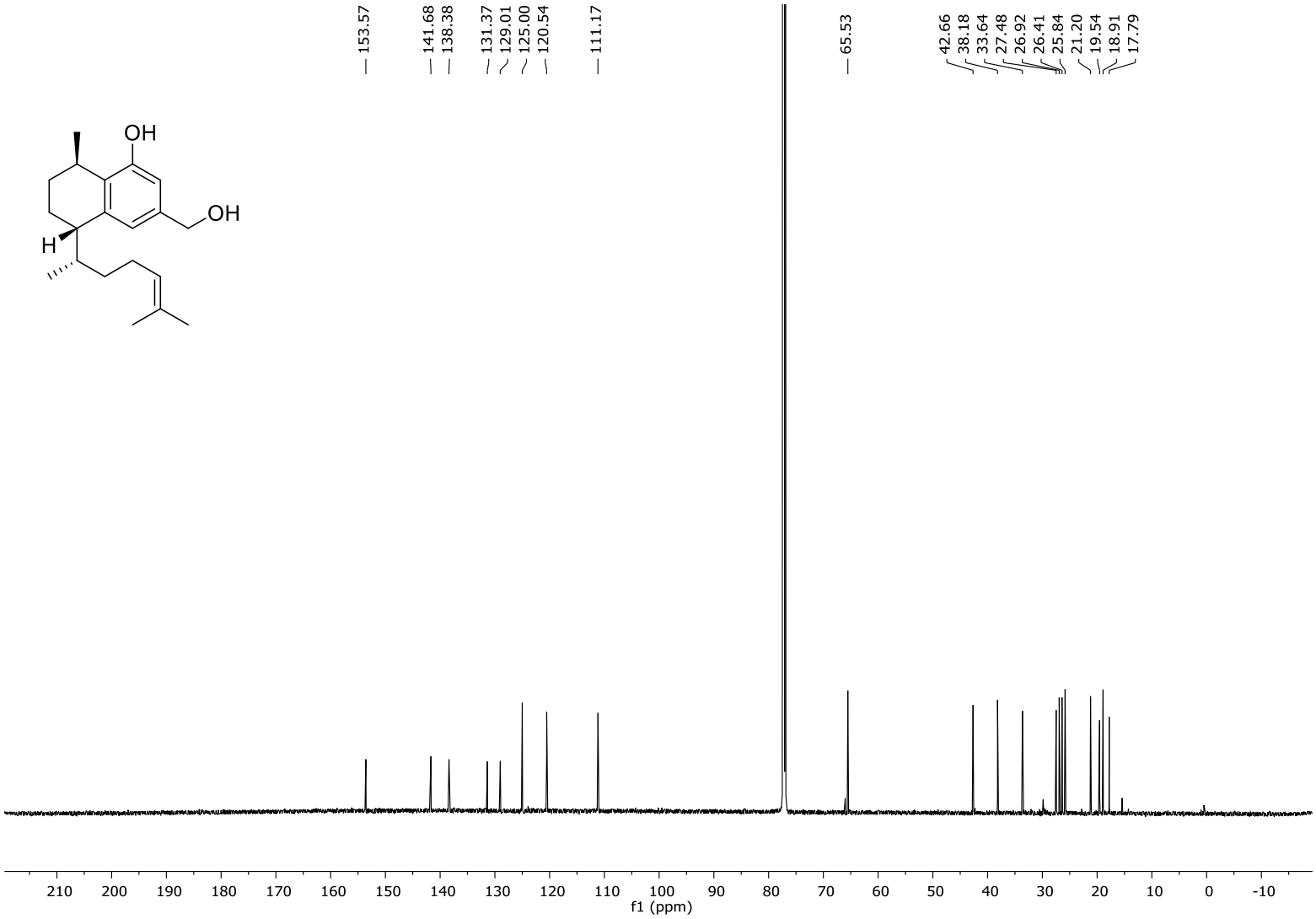
265: HMBC (600 × 150 MHz, $CDCl_3$)



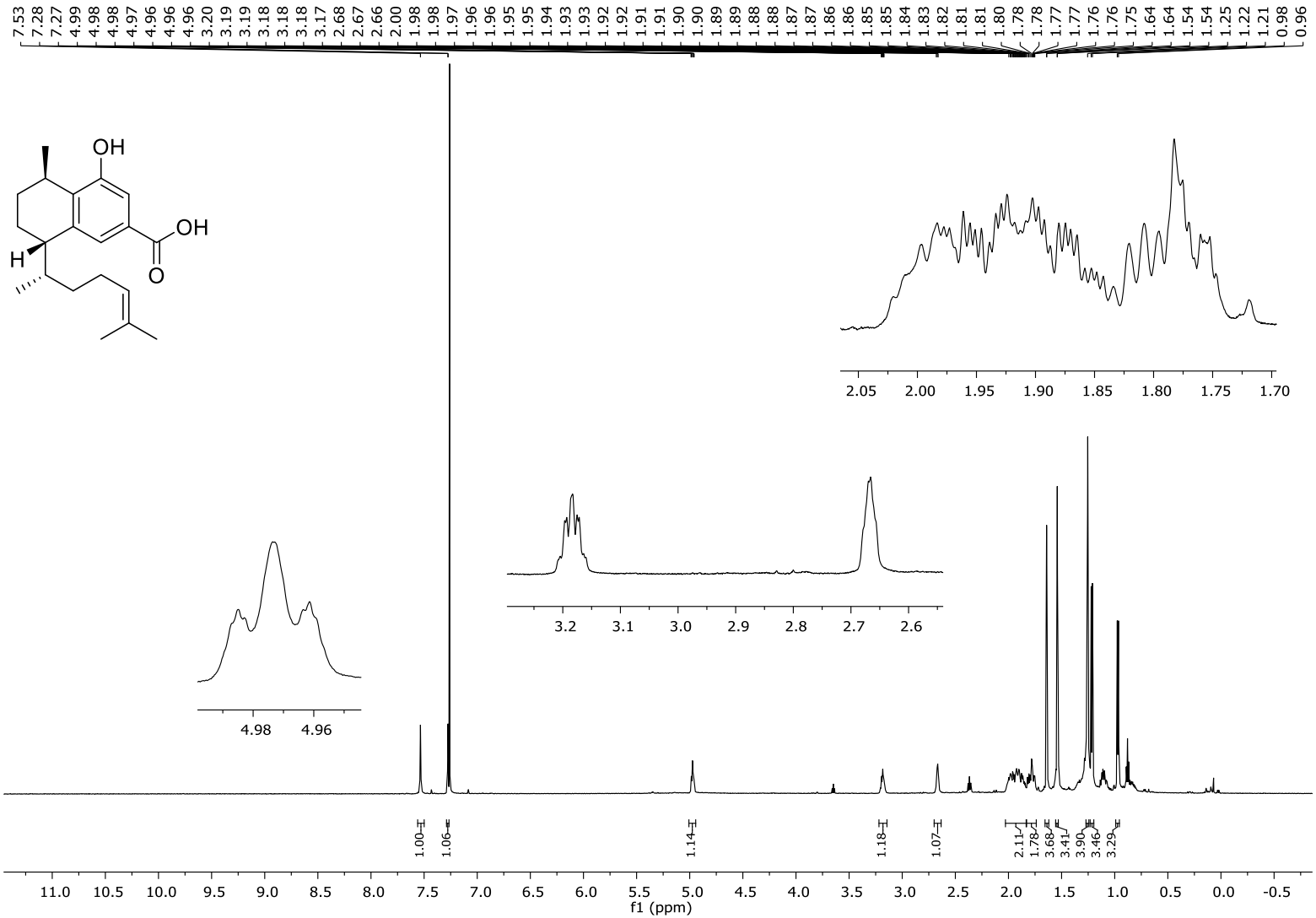
146: ^{1}H NMR (600 MHz, $CDCl_3$)



146: ^{13}C NMR (150 MHz, $CDCl_3$)



147: ^{1}H NMR (600 MHz, $CDCl_3$)



147: ^{13}C NMR (150 MHz, $CDCl_3$)