UNIVERSITY OF SOUTHAMPTON

FACULTY OF NATURAL & ENVIRONMENTAL SCIENCES

Department of Chemistry

Studies Directed Towards the Natural Product Nominine

by

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Thesis for the degree of Doctor of Philosophy

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ABSTRACT

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Natural product synthesis is a highly regarded and essential aspect of organic chemistry. Its challenging nature requires a wide spectrum of reactions to be performed with a broad set of skills being developed throughout each project. This thesis describes studies towards the total synthesis of nominine, an indole diterpenoid which exhibits antiinsectant properties. Synthesis of this natural product could provide entry into this family of indole diterpenoids allowing several natural products to be accessed.

Chapter 1 introduces this natural product and its proposed synthetic route. Two total syntheses, by Bonjoch and Nicolaou published after this project had ceased, are also presented.

Chapter 2 discusses the methods of constructing key intermediate enone **1.1** and describes its successful efficient synthesis on a multigram scale. The synthesis of natural products dehydrofukinone and fukinone using this key intermediate follows in chapter 3.

Chapter 4 details the challenges and successes of the investigations towards the total synthesis of nominine. Future work for its completion and other possible related indole diterpenoids are described in chapter 5. A conclusion to the project and a chapter containing experimental details conclude this thesis.

Contents

DECLARATION OF AUTHORSHIP

I, Wendy Yee Lee Goh,

declare that the thesis entitled

"Studies Directed Towards the Natural Product Nominine"

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

- this work was done wholly or mainly while in candidature for a research degree at this University;
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- None of this work has been published before submission.

Signed:

Date:

In memory of my father, Siak Chua Goh

(1947-2012).

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ABBREVIATIONS

Ac	Acetyl
ADME	Adsorption, distribution, metabolism, excretion
aq	aqueous
bp	boiling point
CIMS	chemical ionization mass spectrometry
cm^{-1}	wavenumbers
COSHH	Control of Substances Hazardous to Health
d	doublet
DBU	1, 8-diazabicyclo[5.4.0]undec-7-ene
dd	double doublet
DDQ	2,3-dichloro-5,6-dicyano-p-benzoquinone
DEAD	diethyl azodicarboxylate
DEPT	distortionless enhancement by polarisation transfer
DIBAL	Diisobutylaluminium hydride
DMAP	4-(N,N-dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	Dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	Dimethyl sulfoxide
EI	Electron impact
EPSRC	Engineering and Physical Sciences Research Council
Eq.	Molar equivalent
ESI	Electrospray ionisation
Et	Ethyl
g	grams
GLC	Gas liquid chromatography
HPLC	high pressure liquid chromatography
hr	Hour(s)
IR	Infra-red
Hz	Hertz
IPA	Isopropanol
J	Coupling constant
L	litre(s)
LCMS	liquid chromatography mass spectrometry
m	multiplet
M	molar
M+	Parent molecular ion
MCPBA	Meta-chloroperbenzoic acid (3-chloroperoxybenzoic acid)
Me	Methyl
min	minutes
mol	moles
MOMCl	methyl chloromethyl ether
MS	Mass Spectra
MVK	Methyl Vinyl Ketone
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser effect spectroscopy
Oxone®	Potassium peroxymonosulfate

PCC	Pyridinium chlorochromate
ppm	Parts per millions
PPTS	Pyridinium *p*-toluenesulfonate
PTC	Phase transfer catalyst
R_f	Retention factor
rt	Room temperature
s	Singlet
t	triplet
TBDMS	tert-butyldimethylsilyl
TEA	triethylamine
TEMPO	2,2,6,6-Tetramethylpiperidine 1-oxyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
Ts	*para*-toluenesulphonyl
UV	ultraviolet

Chapter 1. Introduction

1.1. Natural products and their syntheses

Natural product synthesis is a vital aspect of organic chemistry in which molecules of nature are recreated in the laboratory for a whole host of applications. For example, the true structure of a natural product may only be fully elucidated through its total synthesis.[1]

Some natural products which are found to have biological activity are only isolated in minute quantities, therefore there is a need to synthesise the compound for extensive biological testing or medicinal applications.[2] The activity of biologically active natural compounds can be investigated by manipulating the synthetic route to construct analogues of the natural product to form more potent or selective compounds with improved ADME properties for therapeutic purposes. Total synthesis has also been used to construct analogues to probe mechanistic aspects of biological systems and determine how they interact with nature.[3]

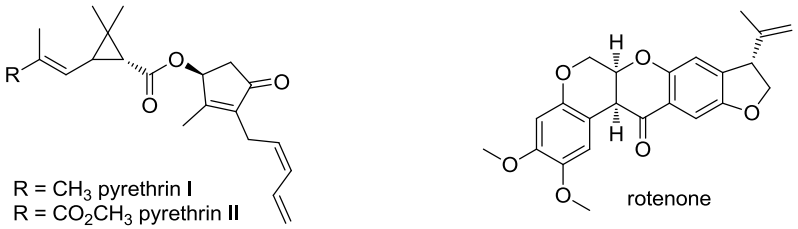
The journey which is undertaken is often fraught with unexpected problems and surprises, leading to the discovery of new methodology, strategies and novel compounds which have increased the capabilities and power of synthetic chemistry.[4] These are just a few of the reasons why natural product synthesis is such an active and important discipline.

It has been estimated that at least 60% of approximately 860 new therapeutic agents, for the treatment of human diseases, introduced worldwide over the last 20 years up to 2003 have had their origins in natural products chemistry.[5] Particularly noteworthy, in the area of cancer, from the 1940s to date, 47% of small molecule drugs were actually either natural products or directly derived from them.[6] Natural products continue to be an important source of leads for drug discovery[7] and interest in total synthesis continues to be strong as evident by the numerous total synthesis papers that are published each year.

The use of natural products in developing pesticides is not as well acknowledged or recognised compared to the use of natural products in human therapeutics, however pesticides are an essential part of modern agriculture. Where pests and disease are not systematically controlled, an estimated one-third of a typical crop is lost. Over the past half century, much of the increase in agricultural productivity has been due to the control of these pests with chemical pesticides.[8]

There are several examples of the use of natural products in crop protection as discussed in a review by Copping and Duke.[9] Two examples of well known natural products used as insecticides in agriculture are the pyrethrins and rotenone (*figure 1*).

Figure 1: Structure of well known insecticides; the pyrethrins and rotenone.



The pyrethrins were isolated from the seeds of *Chrysanthemum cinerariaefolium* and *Tanacetum cinerariaefolium* (pyrethrum) as plant extracts and have been used since the end of the 19th century against various insect pests.[10] They have been shown to be toxic in low doses and degrade quickly therefore they do not persist in the environment. Pyrethrins act as contact poisons affecting the central nervous system of insects. For doses too low to kill the insects, pyrethrins can act as an insect repellent.

Rotenone has been isolated from a variety of sources including *Cracca virginiana*, *Deiris elliptica* and *Lonchocarpus nicou* from the bean family.[11] Rotenone and related substances have been used for centuries as a piscicide and pesticide. Rotenone was found to be toxic against a wide range of pests but did not affect mammals when ingested by mouth. It is biodegradable and breaks down within six days. Its toxic effect on pests is due to its inhibitory effect on cellular respiration.

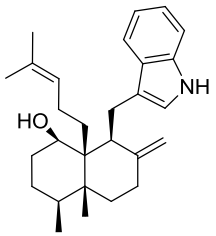
However, resistance has been developing to current insecticides and there is a growing awareness of the negative environmental impact of the long term use of certain synthetic compounds. Therefore there is a vital interest in discovering new insecticides to which there is no resistance and with fewer environmental and toxicological risks.[12] In the search to discover new prototype insecticides, one of the methods is to use natural products themselves or as a model. For example, natural products obtained from marine sources covering many structurally diverse scaffolds, have been tested for insecticidal activity.[13] Chinese medicinal plants traditionally used for human ailments has also been investigated as a source of possible antiinsectant compounds.[14] These types of compounds have been postulated to be environmentally friendly as they are naturally occurring as well as providing the opportunity to investigate new modes of action.

1.2. Nominine

Nominine was first isolated and characterized by the Gloer group in 1989.[15] This indole diterpenoid alkaloid was isolated from hexane extracts of the sclerotia of the fungus *Aspergillus nomius*. Sclerotia are reproductive masses produced by some fungi as a mechanism for survival and propagation of the species. They often contain unique antiinsectant metabolites that can help to protect them from predation. Many compounds isolated from fungal sclerotia have shown antiinsectant activity.[16]

The structure of nominine was elucidated through various spectroscopic techniques and comparison of spectral data with aflavinine derivatives isolated from *Aspergillus flavus*, which is closely related to *Aspergillus nomius*. The absolute stereochemistry was not determined at this point. Nominine consists of a congested bicyclic system with five contiguous *cis* stereocentres, two of which are quaternary carbons at ring junctions (*figure 2*).

Figure 2: Nominine.



Nominine was found to exhibit potent antiinsectant activity against *Heliothis zea* (corn earworm)[17] which is a severe pest in field corn of the southern states of the United States of America. *Heliothis zea* also feeds on other crops such as cotton, green beans, soybean and peppers. Nominine was found to cause 38% mortality at a dietary concentration of 25 ppm, and for those insects which survived after seven days on the test diet, the average weight was found to be 3% of the bodyweight of the control insects. This indicated nominine to be substantially more active than the standard broad spectrum insecticide rotenone. At the time this project commenced, a total synthesis had yet to be reported for nominine*.

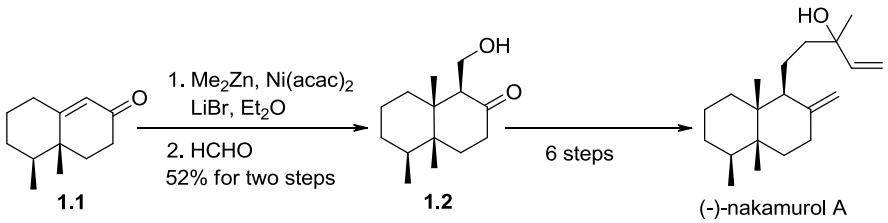
* It should be noted that another natural product exists by the name of nominine. This unrelated hetisine-type aconite alkaloid was first isolated in 1959[18] and its first total synthesis was reported by Muratake and Natsume in 2004.[19]

1.3. Proposed synthetic route to nominine

The proposed synthetic route to nominine was initially based on research by Bonjoch[20] during their total synthesis of (-)-nakamurol A. This marine sponge diterpenoid contains a similar scaffold to nominine with the same contiguous *cis* stereochemistry.

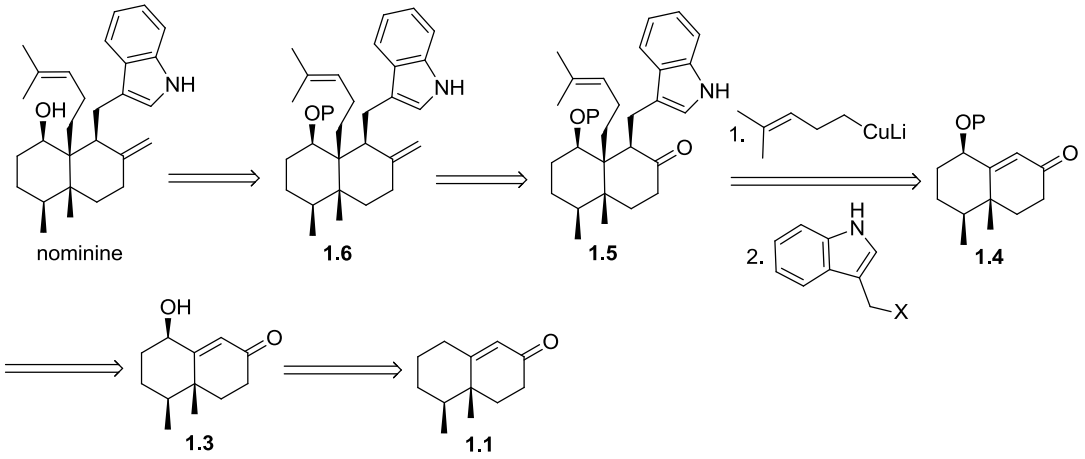
Bonjoch's synthetic plan was based on the use of the enantiopure bicyclic enone (**1.1**) as a synthetic intermediate. This would provide stereocontrol in the subsequent 1,4-conjugate addition and enolate trapping with formaldehyde, which attaches the relevant side chains (*Scheme 1.1*). Compound **1.2** was then elaborated further to give (-)-nakamurol A after six steps.

Scheme 1.1: Initial steps in the synthesis of (-)-nakamurol A by Bonjoch et al.



Using a similar concept, it was proposed that the key step would consist of the alkylation of compound **1.1** with the alkene moiety under copper catalysed conditions and the enolate trapped with a halogenated indole moiety which may require protection (*scheme 1.2*). However, as nominine contains an additional hydroxy group on the central ring system, this functionality would have to be incorporated before the 1,4-conjugate addition. This alcohol **1.3** would require protection **1.4** before the 1,4-conjugate addition with the alkyl cuprate followed by trapping of the enolate with a halogenated indole moiety **1.5**. It was proposed that the oxygen could chelate to the copper facilitating a facial specific reaction thus ensuring *cis* alkylation. A Wittig olefination with methyltriphenylphsophonium bromide would then transform the carbonyl into the required alkene **1.6**, followed by the final deprotection of the alcohol to afford the natural product nominine.

*Scheme 1.2: Retrosynthetic route to nominine based on the use of the bicyclic enone **1.1**.*



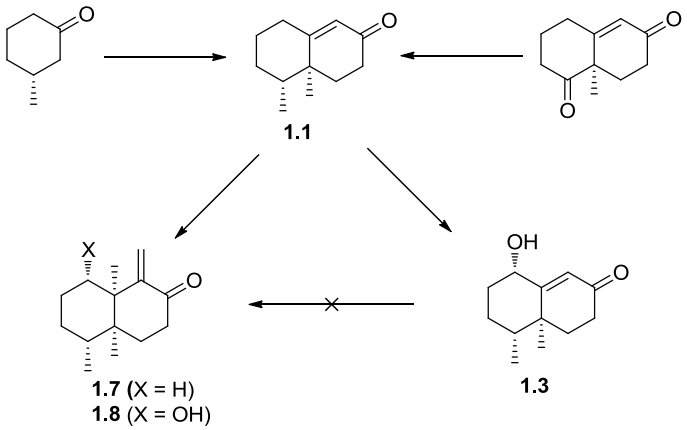
1.4. 1st Total synthesis of ent-anominine by Bonjoch et al.

During the course of the PhD, Bonjoch published a paper detailing his attempts towards the total synthesis of nominine (which he renamed anominine).[21] This was followed by a full paper detailing the first total synthesis of *ent*-anominine in 2010,[22] a year after practical work had ceased on this project.

Bonjoch has published a number of natural product syntheses, for example (+)-xylarenal A,[23] (-)-nakamurol A,[20] aeruginosin 298-A[24] and (-)-strychnine.[25] Bonjoch first expressed an interest in nominine in 1999 when a stereoselective synthesis of enone **1.1** from (*R*)-(+)-3-methylcyclohexanone was published by his group, stating that this could be an appropriate chiral building block for the total synthesis of nominine.

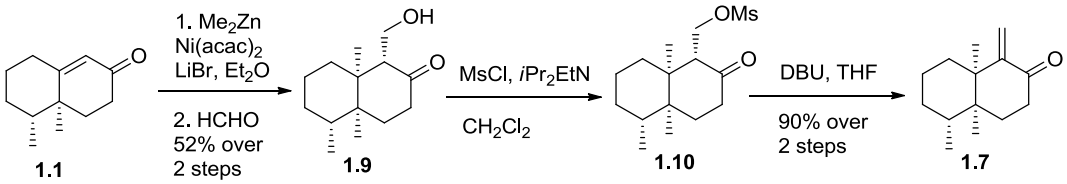
In the first generation synthesis, compound **1.8** was identified as a key synthetic intermediate which was proposed to be synthesised from enone **1.1** (*scheme 1.3*). Bonjoch utilized his previously published procedure to compound **1.7** from (*R*)-(+)-3-methylcyclohexanone.[20] However this procedure did not allow for the introduction of the hydroxyl group. A subsequent paper detailed the synthesis of **1.3**[23] with the synthesis of enone **1.1** starting from the Wieland-Miescher ketone (Paquette's procedure).[26] However, they were unable to affect the required 1,4-addition of **1.3** with various organometallics to afford compound **1.8**.

*Scheme 1.3: Bonjoch's first generation synthesis towards nominine based on key intermediate **1.8**.*



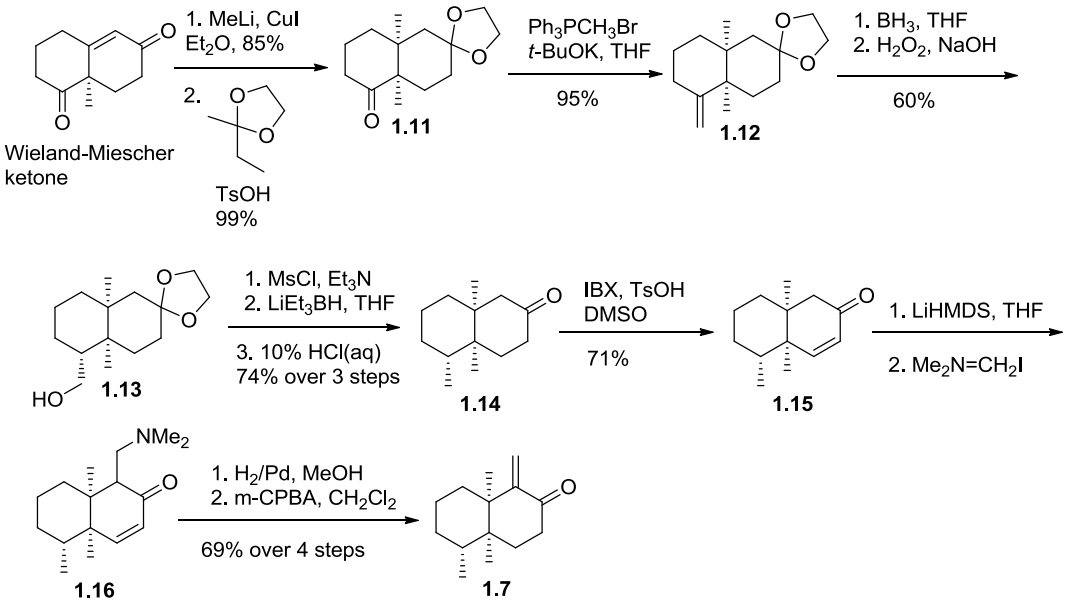
In the first generation synthesis of compound **1.7**, Bonjoch installed the methyl group in the quaternary position via 1,4-addition of methylzinc to enone **1.1** in the presence of nickel acetylacetonate, and trapping of the enolate with formaldehyde to give the alcohol **1.9** as a single diastereoisomer. Mesylation and subsequent elimination afforded the desired compound **1.7** in 11 steps with an overall yield of 12% from (*R*)-(+)-3-methylcyclohexanone (*scheme 1.4*).

*Scheme 1.4: Key steps of Bonjoch's first generation synthesis of intermediate **1.7**.*



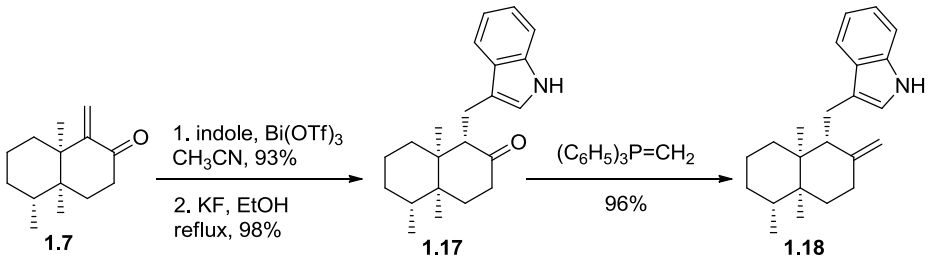
A second generation synthesis of **1.7** was developed starting from racemic Wieland-Miescher ketone (*scheme 1.5*). The second quaternary methyl group was once again installed via a 1,4-addition although this time using organocopper reagents. Protection of the less hindered carbonyl group afforded compound **1.11**. Initial attempts to hydrogenate the Wittig product **1.12** resulted in a majority of the undesired *trans* diastereoisomer. Therefore compound **1.12** was subjected to hydroboration followed by reduction to give the alcohol **1.13**, which was eliminated via the mesylate to afford **1.14**. Oxidation with *o*-iodoxybenzoic acid formed the enone **1.15.** This allowed for the regiospecific alkylation via the lithium enolate with Eschenmoser's salt to afford the amine **1.16**. Hydrogenation and subsequent oxidation with *m*-CPBA generated the exocyclic enone **1.7** in 11 steps (from Wieland-Miescher ketone) with an overall yield of 18%. Including the synthetic steps towards the formation of the Wieland-Miescher ketone, this second generation synthesis is no more efficient nor higher yielding than the previous synthesis. The installation of the required hydroxyl group to form the desired **1.8** was not detailed.

*Scheme 1.5: Second generation synthesis to intermediate **1.7**.*



Nevertheless, Bonjoch utilised intermediate **1.7** to build up the polycyclic skeleton of nominine. Conjugate addition of indole to the exocyclic enone **1.7** gave **1.17** as a 1:2 mixture of diastereoisomers with the *trans* product favoured, however this epimer was isomerised to the desired *cis* product using KF in refluxing EtOH. The subsequent Wittig reaction furnished the polycyclic framework of nominine **1.18** (*scheme 1.6*).

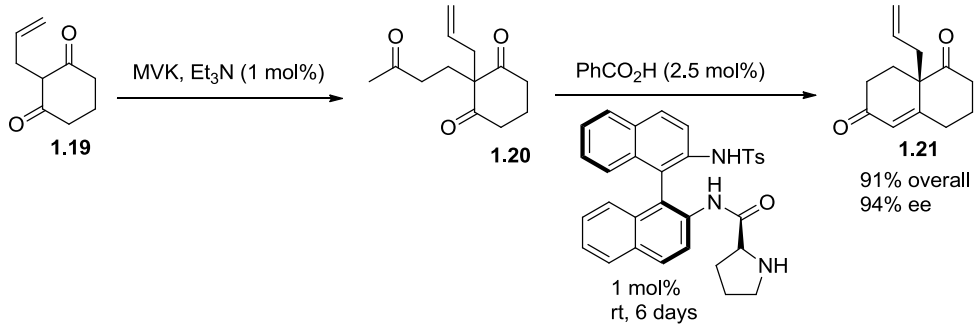
*Scheme 1.6: Formation of the polycyclic framework of nominine **1.18**.*



In the final successful total synthesis of *ent*-anominine,[22] Bonjoch modified his route once more to develop the third generation synthesis based on a Wieland-Miescher ketone analogue **1.21**. This was synthesised using methodology his group had recently developed for highly efficient and enantioselective synthesis of Wieland-Miescher ketone and analogues.[27] After screening many conditions and organocatalysts for the Robinson annulation, the optimum procedure for the Michael addition of **1.19** and MVK was found to be with the use of 1 mol% Et_3N to give the triketone **1.20** followed by the aldol condensation in the presence of 2.5 mol% benzoic acid and 1 mol% of N-Ts-(S_a)-binam-L-Pro (*scheme 1.7*). Both steps were achieved

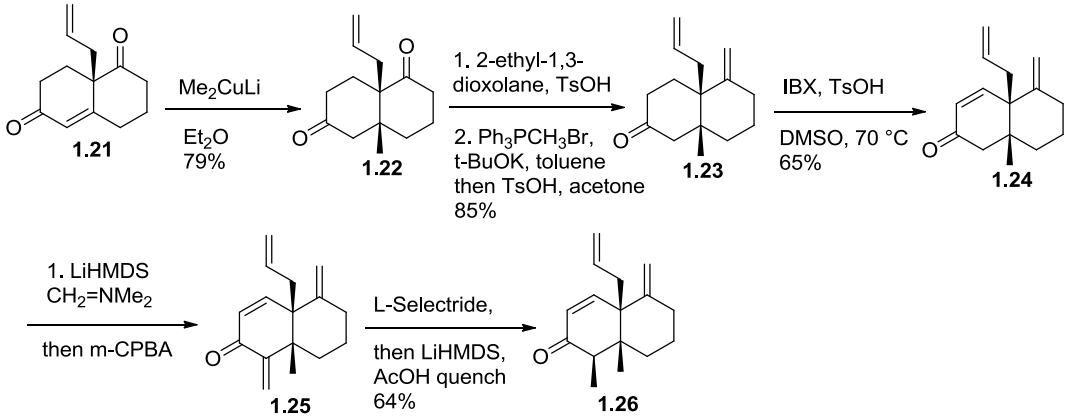
without the use of solvent although the aldol condensation required six days at room temperature to afford a 91% yield with 94% ee of (*R*)-**1.21**.

*Scheme 1.7: Synthesis of key Wieland-Miescher ketone analogue **1.21**.*



A second quaternary centre was achieved by conjugate addition with dimethyllithium cuprate to afford **1.22**. The less hindered carbonyl was protected which allowed for the regioselective Wittig methylenation followed by removal of the protecting group to give **1.23**. Oxidation of **1.23** with IBX in the presence of TsOH afforded the enone **1.24** which ensured alkylation with Eschenmoser's salt of the lithium anion occurred at the desired position. This was followed by oxidation of the β-aminoketone with m-CPBA and elimination to afford the exocyclic ketone **1.25**. Reduction with L-Selectride afforded the *cis* dimethyl compound **1.26** after equilibration (*scheme 1.8*).

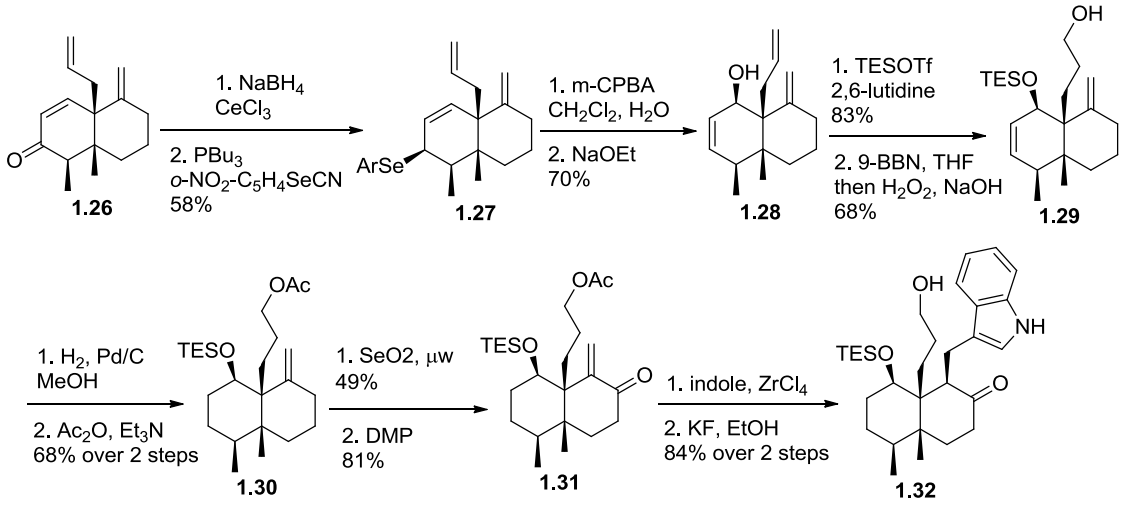
*Scheme 1.8: Installation of the two required cis methyl groups to give **1.26**.*



The next task was to install the hydroxyl moiety. Compound **1.26** was reduced to the alcohol and subsequently converted to the allylic selenide **1.27** by Grieco's protocol. This compound underwent [2,3]-sigmatropic rearrangement in the presence of water and subsequently afforded the allylic alcohol **1.28**. After protecting the alcohol, hydroboration occurred selectively at the allyl side chain due to steric hindrance of the congested bicyclic to give

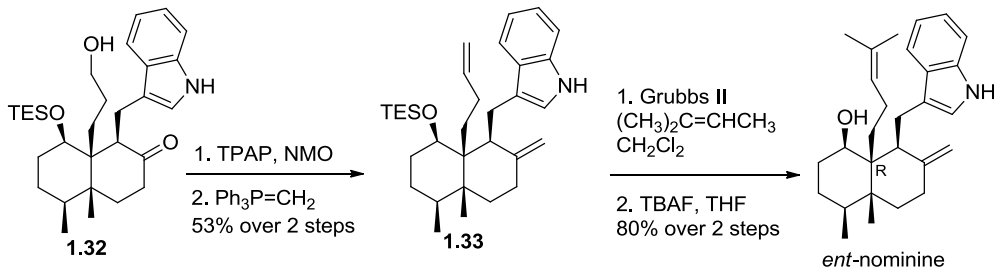
alcohol **1.29**. Hydrogenation reduced the endo methylene selectively as the exo methylene was protected by the bulk of the folded molecule. Protection of the alcohol then afforded **1.30** which underwent allylic oxidation followed by Dess-Martin oxidation to give exocyclic enone **1.31**. Coupling of indole with **1.31** in the presence of Lewis acid catalyst zirconium tetrachloride afforded **1.32** after deprotection (*scheme 1.9*).

*Scheme 1.9: Installation of the remaining cis stereocentres to afford **1.32**.*



Oxidation of the alcohol with Ley's perruthenate to give the aldehyde followed by a Wittig reaction converted both carbonyl groups into methylene groups to afford compound **1.33**. Selective alkene cross-metathesis using Grubbs 2nd generation catalyst followed by deprotection of the alcohol afforded *ent*-anominine ($[\alpha]_D$ −21.0 (c 0.3, MeOH)) in 24 steps from the Wieland-Miescher ketone analogue **1.19** (*scheme 1.10*). Compound **1.19** is not commercially available and the procedure for its synthesis was not included in the experimental so the overall yield cannot be calculated. This total synthesis resulted in the assignment of the absolute stereochemistry of nominine ($[\alpha]_D^{25}$ +23.6 (MeOH, c 0.85)).

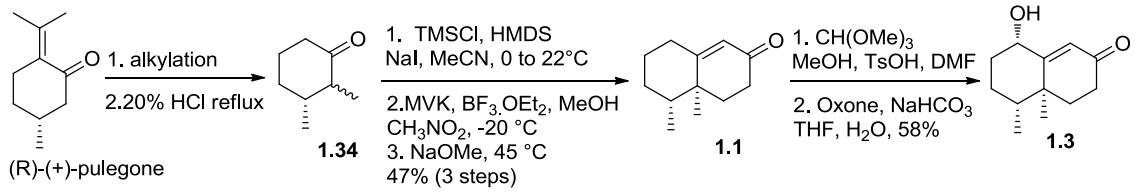
Scheme 1.10: Final steps of total synthesis of ent-anominine by Bonjoch et al.



1.5. 2nd Total synthesis of anominine by Nicolaou et al.

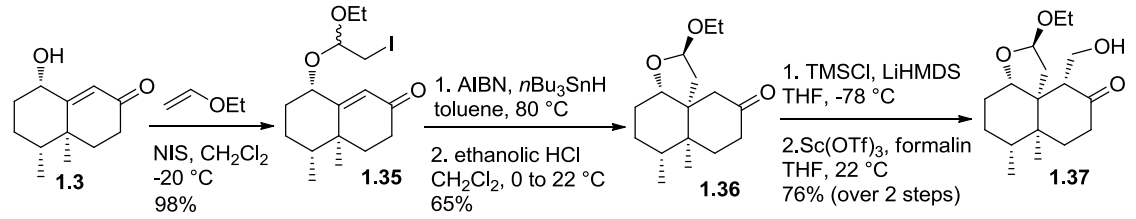
A 2nd total synthesis was recently achieved by Nicolaou *et al*. in 2012, along with the first total synthesis of tubingensin A, another member of this indole diterpenoid family.[28] Starting from the natural product (*R*)-(+)-pulegone, alkylation followed by an acid catalysed retro-aldol reaction afforded compound **1.34**.[29] Duhamel's method for a selective Mukaiyama-Michael addition followed by a Robinson annulation allowed compound **1.34** (after TMS enol ether formation) to be transformed into Bicyclic enone **1.1**.[30] Installation of the hydroxy group was accomplished via the dienol ether to give compound **1.3** (*Scheme 1.11)*.[23]

*Scheme 1.11: Nicolaou's route to compound **1.3***



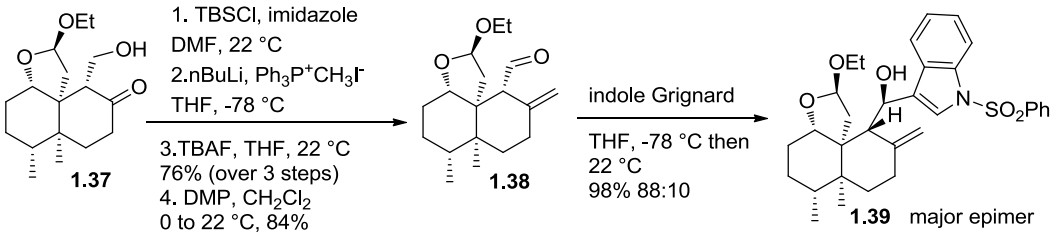
The iodoacetal **1.35**, formed using N-iodosuccinimide and ethyl vinylether, underwent an Ueno-Stork radical cyclisation to afford the tricyclic ketone **1.36**. Deprotonation of compound **1.36** was found to be regioselective with LiHMDS and the enolate trapped with TMSCl. This silyl enol ether was subjected to $Sc(OTf)_3$ mediated aqueous Mukaiyama aldol conditions to afford the alcohol **1.37** in which all the stereogenic centres of anominine core had been installed (*scheme 1.12*).

Scheme 1.12: Installation of remaining stereogenic centres for anominine core



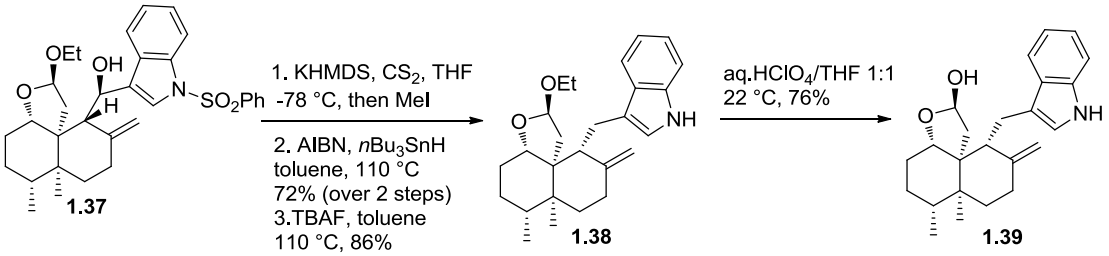
Compound **1.37** was subjected to the necessary protection, Wittig reaction, deprotection and oxidation to give compound **1.38** which allowed for the installation of the indole group via a Gignard reaction to afford intermediate **1.39** as the major epimer in 88% yield (*scheme 1.13*).

*Scheme 1.13: Formation of intermediate **1.39***



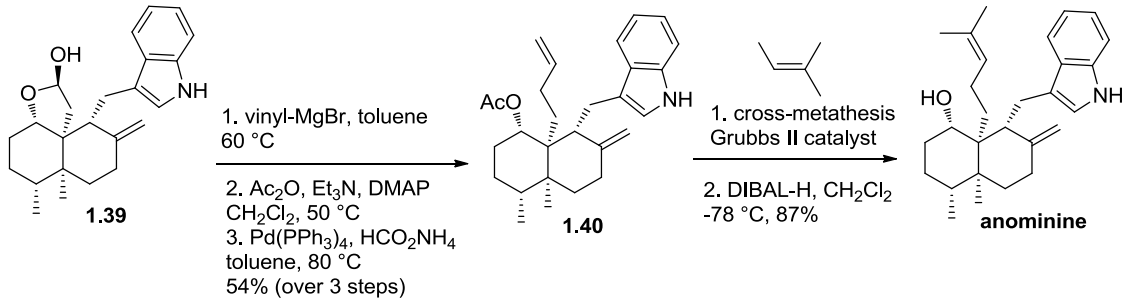
Xanthate formation followed by radical deoxygenation cleaved off the superfluous hydroxy group and indole deprotection afforded compound **1.38**. Acid hydrolysis with perchloric acid revealed lactol **1.39** (*scheme 1.14*).

*Scheme 1.14: Removal of superfluous OH and acidic hydrolysis to reveal lactol **1.39***



The lactol was ring opened with the Grignard reagent vinylmagnesium bromide and the diol immediately taken on to be bisacetylated. The allylic acetate was selectively cleaved using Tsuji's reduction conditions employing $Pd(PPh_3)_4$ and ammonium formate to give compound **1.40**.[31] A cross-metathesis with 2-methyl-2-butene and Hoveyda-Grubbs II catalyst completed the side chain and cleavage of the acetyl group furnished anominine in 26 steps from (*R*)-(+)-pulegone (*scheme 1.15*). Experimental was not published for every compound so an overall yield could not be calculated.

Scheme 1.15: Final steps of 2nd total synthesis of anominine



1.6. Conclusion to chapter 1.

New natural product targets set out a challenge to organic chemists to synthesis it in as few steps as possible, utilising the broad array of reactions available in the most efficient manner. Often, novel methodology is developed to suit each strategy. Analogues of natural products are essential in research & development work with a developed total synthesis route allowing for specific modifications as necessary.

Nominine is part of a family of indole diterpenoids which have shown potent biological properties. Nominine was chosen for this project due to its interest as an antiinsectant and a total synthesis had yet to be achieved in 2005. In addition, the total synthesis of nominine could lead to the synthesis of other members of the family by replicating the biosynthetic pathway linking the family of compounds.

The key step in the proposed route to nominine consists of a 1,4-addition to key intermediate **1.3** followed by trapping of the enolate in the indole moiety. This would allow for the installation of two side chains in one step in a stereoselective manner due to the conformation of the bicyclic rings.

At the commencement of this project, the total synthesis of (a)nominine had yet to be achieved. However, a year after practical work had ceased on this project, Bonjoch *et al.* published the first total synthesis of ent-anominine in 2010, followed by a 2nd total synthesis in 2012 by Nicolaou *et al*.

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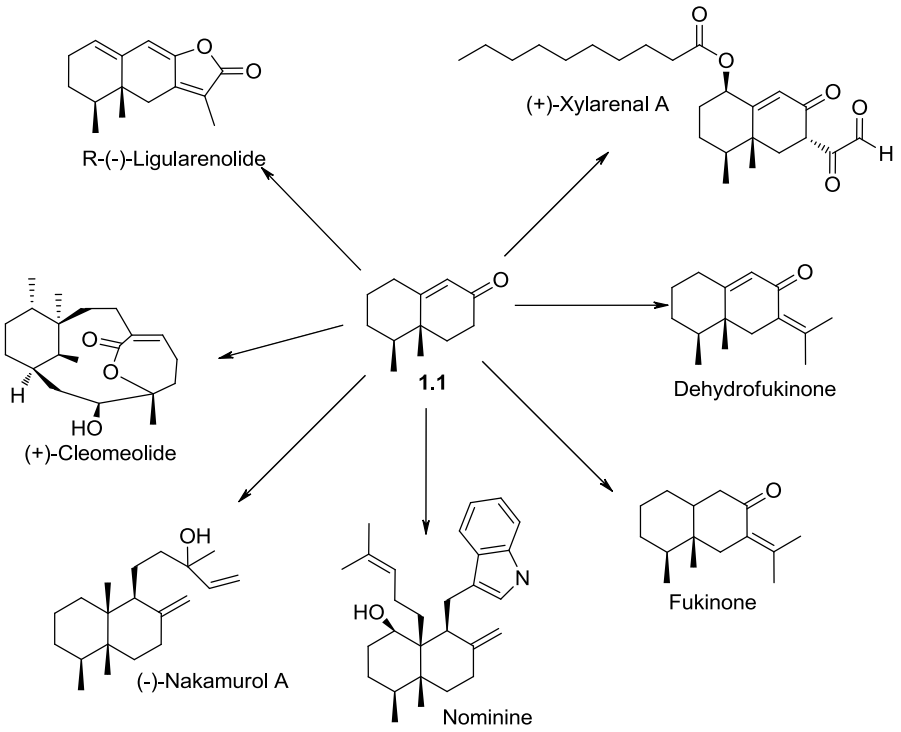
Chapter 2. Bicyclic enone intermediate 1.1

Bicyclic enone **1.1** is a versatile intermediate that has been used in several natural product syntheses, for example, (+)-xylarenal A,[1] *R*-(-)-ligularenolide,[2] (+)-cleomeolide,[3] (-)-nakamurol A,[4] fukinone[5] and dehydrofukinone[6] (*scheme 2.1*).

*Scheme 2.1: Examples of natural products synthesised from bicyclic enone **1.1***



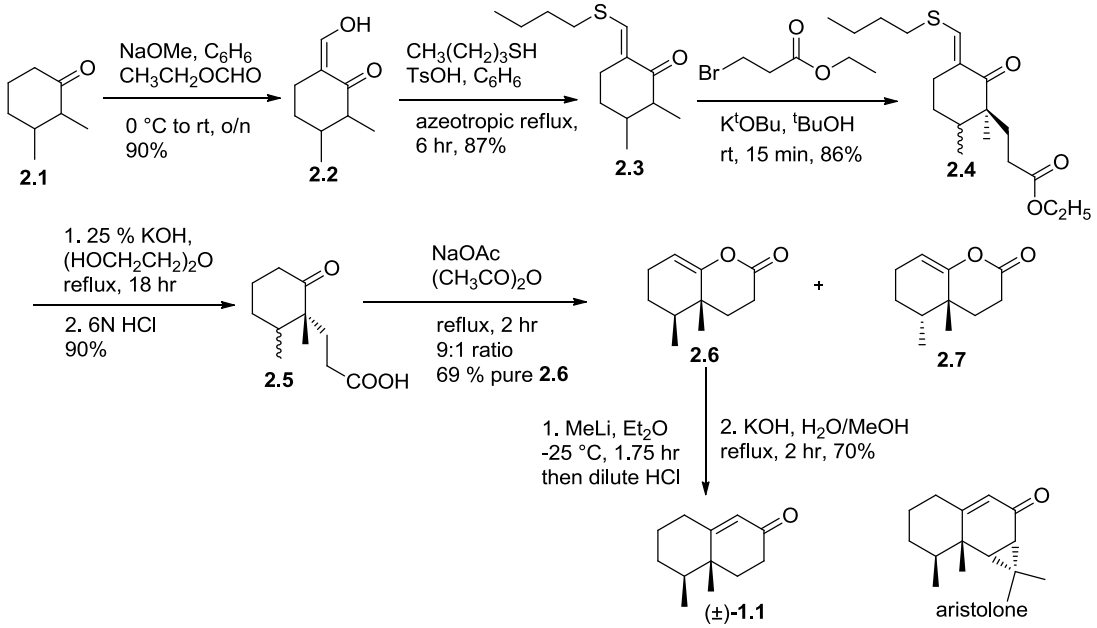
2.1. Literature review

Bicyclic enone **1.1** was considered to be a vital intermediate in our proposed synthetic route to nominine. Nine previous routes to enone **1.1** are discussed in section 2.1 in chronological order. Literature which influenced our work is discussed in section 2.2.

Piers, Britton & De Waal (1969)

Enone **1.1** was used to synthetically prove the relative stereochemistry of aristolone by Piers, Britton and De Waal in 1969.[7] In their synthesis of enone **1.1**, the n-butylthiomethylene fragment was utilised as a blocking group[8] to ensure alkylation at the desired C2 position of 2,3-dimethylcyclohexanone **2.1**. This was installed via the hydroxymethylene compound **2.2**.[9] Alkylation with ethyl 3-bromopropionate was carried out to form the keto-esters **2.4**. Removal of the blocking group under basic conditions followed by the hydrolysis of the ester group gave keto-acids **2.5**. Annulation occurred under refluxing acetic anhydride and sodium acetate to form the enol lactones **2.6** and **2.7** in a 9:1 ratio. The *cis* epimer **2.6** was converted to enone (±)-**1.1** in the presence of methyllithium followed by acid hydrolysis and base catalysed aldol cyclisation. This six step synthesis was carried out on the 100 g scale with an overall yield of 29% (*scheme 2.2*).

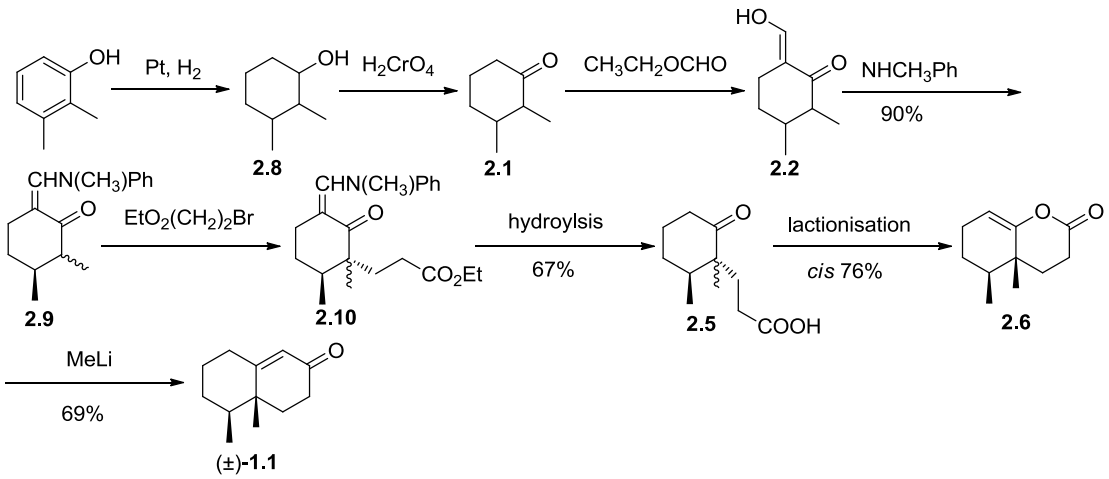
Scheme 2.2: Synthesis of (±)-enone 1.1 by Piers, Britton & De Waal



Torrence & Pinder (1971)

Starting with 2,3-dimethylphenol, Torrence and Pinder[10] initially carried out an annulation reaction of MVK with 2,3-dimethylcyclohexenone **2.1** to synthesise enone **1.1**, however a poor yield and diastereoselectivity was obtained. They then utilised the method of Piers *et al.* although they modified the blocking group to N-methylanilinomethylene **2.9**. (±)-Enone **1.1** was synthesised in eight steps from 2,3-dimethylphenol although an overall yield could not be ascertained as no experimental was included (*scheme 2.3*).

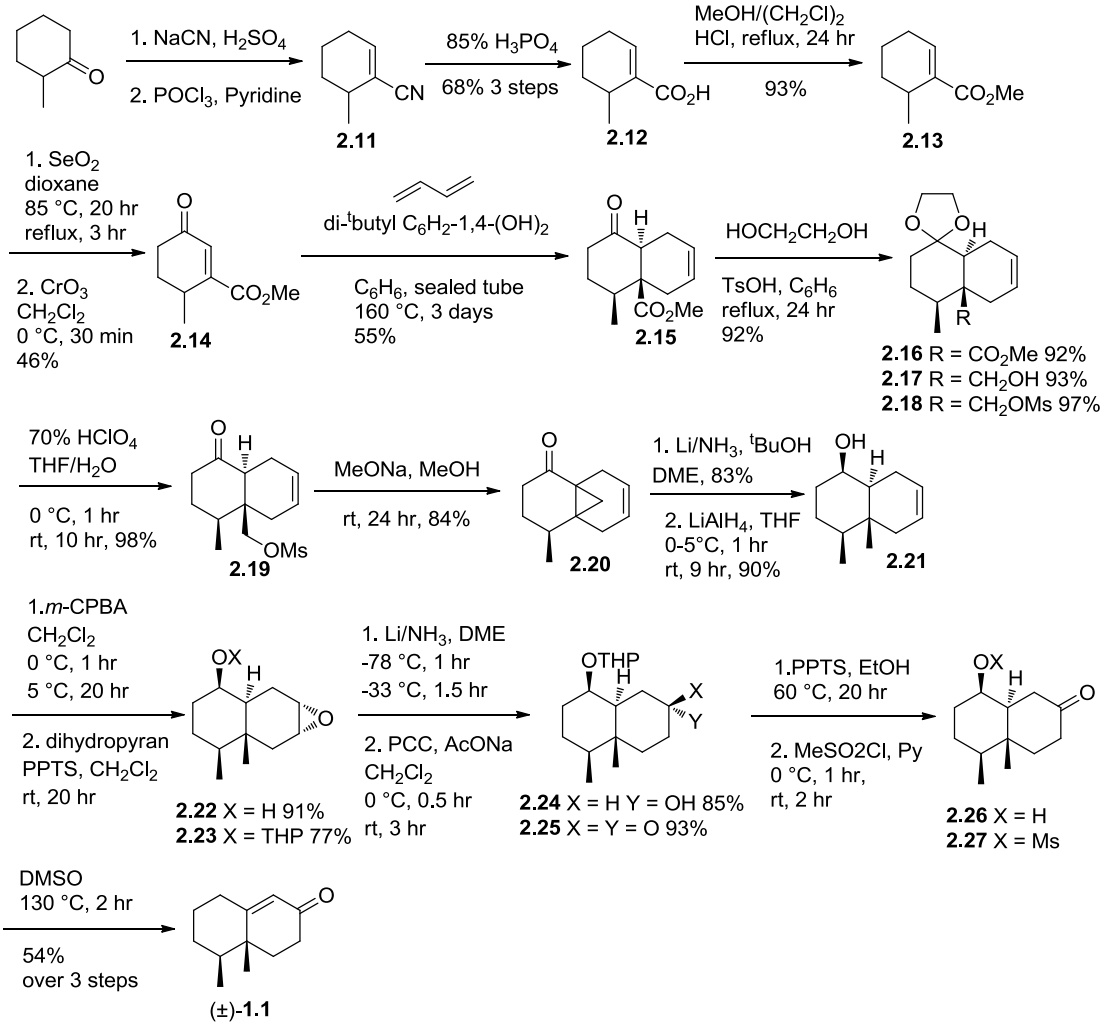
*Scheme 2.3: Torrence and Pinder's synthesis of (±)-enone **1.1***



Torii (1979)

As part of their studies towards development of a stereocontrolled construction of a set of vicinal *cis* methyl groups on an eremophilane skeleton, Torii, Inokuchi and Yamafuji[11] synthesised (±)-enone **1.1**. The significant transformations included a Diels-Alder reaction of **2.14** with butadiene to form the bicyclic core structure **2.15**, installation of the *cis* methyl group at the ring junction via reduction of the cyclopropyl ketone of **2.20**, selective reductive cleavage of **2.23** to give the alcohol **2.24** in the desired position due to the axial ring opening rule (in which axial groups can be more readily replaced than equatorial, as these are more stable) and pyrolysis of the mesylate **2.27** to achieve (±)-enone **1.1** in an overall yield of 3% in 19 steps starting with 2-methylcyclohexanone (*scheme 2.4*).

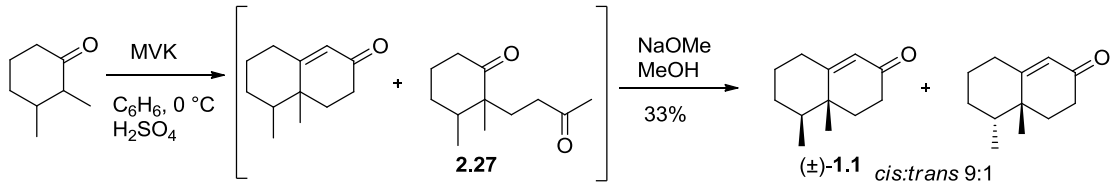
*Scheme 2.4: Torii's synthesis to (±)-enone **1.1***



Zoretic, Golen and Saltzman (1981)

This seemingly simple route to enone (±)-**1.1** is based on the acid-catalysed Robinson annulation reaction (*scheme 2.5*). Michael addition of MVK to 2,3-dimethyl cyclohexanone catalysed by concentrated H_2SO_4 (additional aliquots of MVK and H_2SO_4 added in two hour intervals) yielded a mixture of the octalone and diketone **2.27** as well as 36% of starting material. The crude mixture of octalone and diketone **2.27** underwent aldol condensation in the presence of sodium methoxide in methanol to give a 33% yield of enone (±)-**1.1** in a *cis:trans* ratio of 9:1 as determined by ^{13}C NMR analysis. However, it was later reported by Huffman, Potnis and Satish[12] that this ratio was not reproducible. In their hands, they could only obtain a *cis:trans* ratio of 2.3:1.

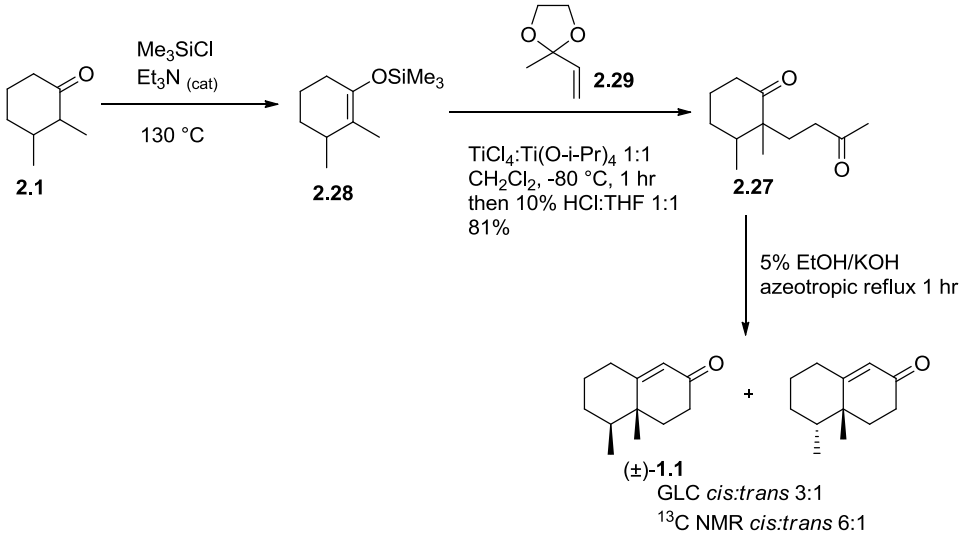
*Scheme 2.5: Zoretic et al.'s route to enone **1.1** based on the acid catalysed Robinson annulation reaction*



Huffman, Potnis and Satish (1985)

A variation to the traditional Robinson annulation procedure was developed by Huffman *et al*.[12] in which the silyl enol ether of 2,3-dimethyl cyclohexanone **2.28** was used to direct the alkylation of the vinyl ketone. Traditionally, MVK is used as the Michael acceptor, however they found that this led to frequent polymerisation problems, therefore the ketal version **2.29**[13] was utilised in the presence of titanium chloride and titanium isopropoxide to form diketone **2.27** after acid hydrolysis. Typical cyclisation conditions yielded the bicyclic enone **1.1** as a *cis:trans* mixture, the ratio of which varied depending on the method used for analysis. As no experimental was given for the formation of **2.28** and no yield reported for the formation of enone (±)-**1.1**, no conclusion can be obtained regarding the efficiency of this route (*scheme 2.6*).

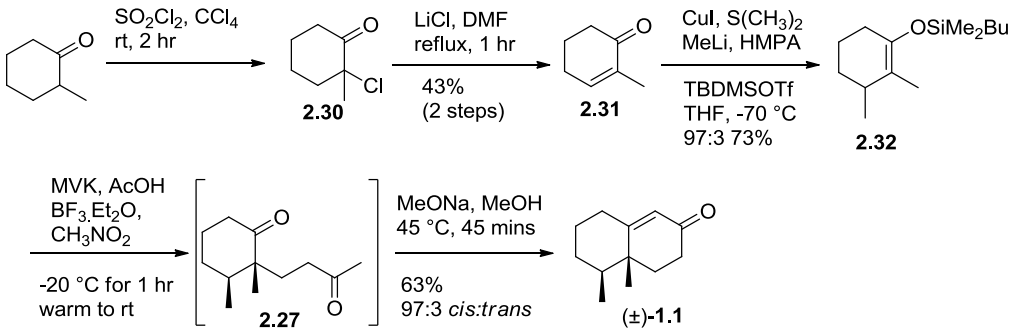
*Scheme 2.6: Huffman et al.'s route to enone **1.1** based on silyl enol ether chemistry*



Duhamel *et al.* (1992)

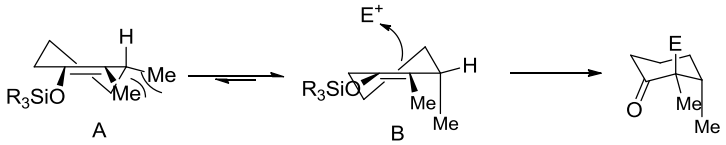
In their investigations towards the synthesis of octalones and hydrindenones, Duhamel *et al.*[14] developed a novel annulation method which included the synthesis of (±)-enone **1.1**, based on their previous studies on Lewis acid catalysed Michael-type additions to silyl enol ethers, similar to Huffman *et al.*'s strategy. Acid catalysed Michael addition of compound **2.32** to MVK in nitromethane in the presence of boron-trifluoride and acetic acid formed intermediate **2.27,** which was not isolated before cyclisation induced by a basic medium (freshly prepared methanolic solution of methoxide) gave the desired product (±)-**1.1** in a mixture of 97:3 *cis:trans* ratio (*scheme 2.7*) in an overall yield of 19% in five steps.

*Scheme 2.7: Duhamel's novel synthesis to enone **1.1** based on an acid-catalysed Michael addition reaction.*



The stereocontrol of the formation of intermediate **2.27** was rationalised due to the starting conformation of enol ether **2.32**.[15] 1,2-allylic strain of the two methyl groups in the cyclohexene ring results in conformation B as the preferred conformer with electrophilic attack on the less hindered face leading to the two methyl groups *cis* to one another preferentially (*scheme 2.8*).

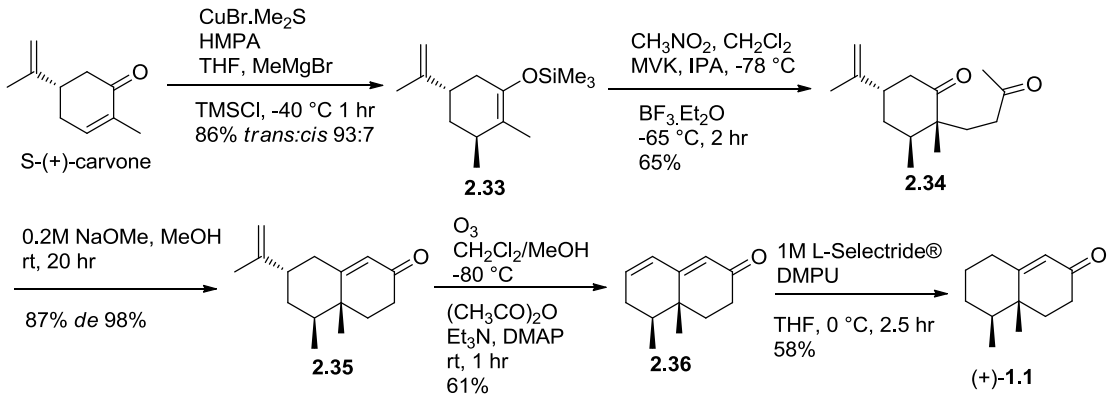
*Scheme 2.8: Structure B as the preferred conformation of **2.32** leading to cis methyl groups*



de Groot *et al.* (1998)

The known stereochemistry of *S*-(+)-carvone (Sigma Aldrich, approximately £50 for 25 mL) was utilised in de Groot *et al.*'s syntheses of various functionalised decalones including enone (+)-**1.1** (*scheme 2.9*).[16] Using chemistry similar to that of Huffman[12] and Duhamel[14], *S*-(+)-carvone underwent conjugate addition of methyl magnesium bromide in the presence of catalytic copper bromide followed by trapping of the enolate with trimethylsilyl chloride to give the silyl enol ether **2.33**. de Groot found that lowering the temperature to -65 °C (instead of -20 °C as reported by Duhamel) improved their yields of the diketone **2.34**. Cyclisation in basic conditions yielded **2.35** which underwent ozonolysis, followed by addition of acetic anhydride, Et_3N, and DMAP. This formed the 5-acetoxy enone in situ which gave the dienone **2.36**, upon treatment with NaOMe. Conjugate reduction of **2.36** with L-Selectride® in the presence of DMPU, followed by treatment with NaOMe resulted in (+)-**1.1** with an overall yield of 17% in five steps.

*Scheme 2.9: de Groot's synthesis of (+)-**1.1** from S-(+)-carvone*

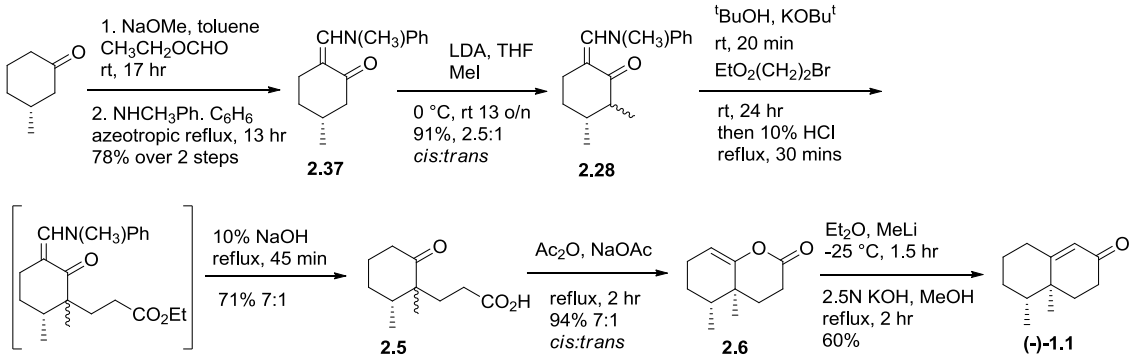


Bonjoch (1999)

Bonjoch *et al.*[17] developed a stereoselective synthesis to enone (-)-**1.1** utilising the known absolute stereochemistry of commercially available (*R*)-(+)-3-methylcyclohexanone (Sigma Aldrich, approximately £100 for 5 g) (*scheme 2.10*). Their route is very similar to that of Piers *et al.* with the exception of the type of blocking group they utilized to ensure alkylation occurred at the desired position. Their chosen blocking group is the same used by Torrence and Pinder previously.[4] The regioselectivity of the installation of the ethyl formate group is attributed to the 1,3-allylic strain in the enolate formation step under thermodynamic

conditions. Subsequent alkylation with MeI furnished the *cis* (2*S*,3*R*) product as the major isomer **2.38** as both methyl groups are in the equatorial position which is more stable. Alkylation with ethyl bromopropionate followed by hydrolysis formed the acid **2.5** which was transformed into the enol lactone **2.6** at which point the *cis:trans* isomers could be separated by crystallization. Methyllithium addition followed by aldol cyclisation gave enone (-)-**1.1** in an overall yield of 25% in seven steps which is a slightly lower yield than Piers *et al*. In 2003, Bonjoch reported a modification to this route in which the lithium salt of dimethyl methylphosphonate was used instead of methyllithium for a more reproducible yield of 60% in the last step. [18]

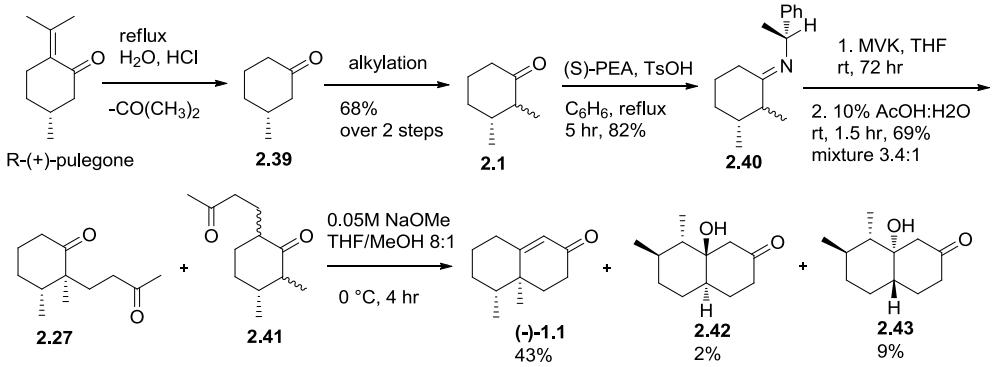
*Scheme 2.10: Bonjoch's stereoselective synthesis to enone (-)-**1.1***



Tenius (2001)

Tenius *et al.*[19] also utilised the known absolute stereochemistry of (*R*)-3-methylcyclohexanone **2.39** in their synthetic route, however they began with the natural product *R*-(+)-pulegone, presumably due to its lower cost (Sigma Aldrich, approximately £60 for 5 g) (*scheme 2.11*). (*R*)-(+)-Pulegone underwent retro-aldolisation to give **2.39** followed by an alkylation step to form (3*R*)-2,3-dimethylcyclohexane **2.1** which was not described in the experimental so the exact conditions are unknown. (*S*)-Phenylethylamine ((*S*)-PEA) was used as a chiral auxiliary to control the stereochemistry of the alkylation step of **2.40** with MVK followed by hydrolysis to give a mixture of **2.27** and **2.41**. Base-catalysed aldol-condensation resulted in 43% of the desired (-)-enone **1.1**. The overall yield achieved was 16% in six steps. Although this route is shorter by one step compared to Bonjoch's route, the overall yield is lower.

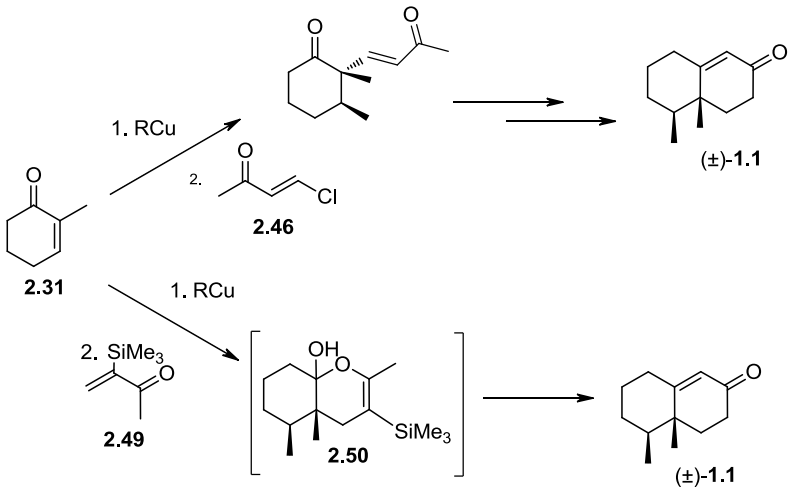
*Scheme 2.11: Tenius's route to enone (-)-**1.1** from R-(+)-pulegone*



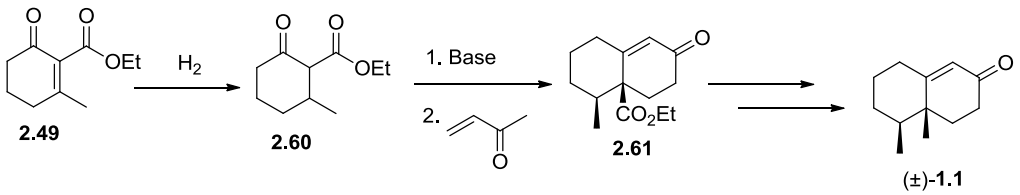
2.2. Formation of bicyclic enone intermediate 1.1

Several routes towards the formation of bicyclic enone **1.1** were investigated concurrently. The strategies were based upon previously published literature. While there are various procedures reported in the literature for the synthesis of this enone, they often start with expensive starting materials or their reported yields or ratio of the relative stereochemistry of the methyl groups were thought to be unsatisfactory. In view of the fact that this was the beginning of the total synthesis, we wanted to develop a procedure with inexpensive and readily available starting materials with reproducible results to allow for large scale synthesis of this important intermediate. Three main routes were investigated.

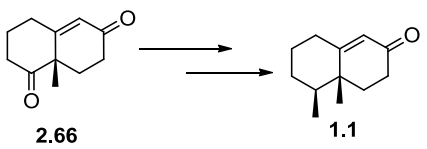
Route 1: 1,4-addition of an organocopper reagent to compound **2.31** followed by trapping of the enolate with a Michael acceptor (**2.46** or **2.49**).



Route 2: Use of ethyl 3-methyl-1-oxo-2-cyclohexene-2-carboxylate (**2.49**).



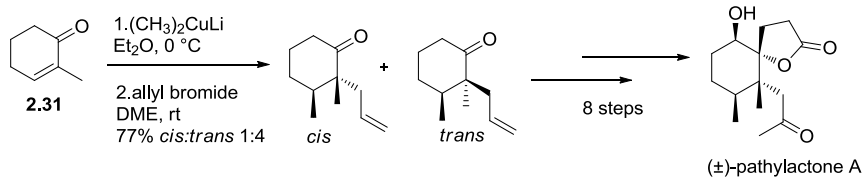
Route 3: Use of Wieland-Miescher Ketone (**2.66**)



2.2.1. Route 1: 1,4-addition & trapping of enolate method

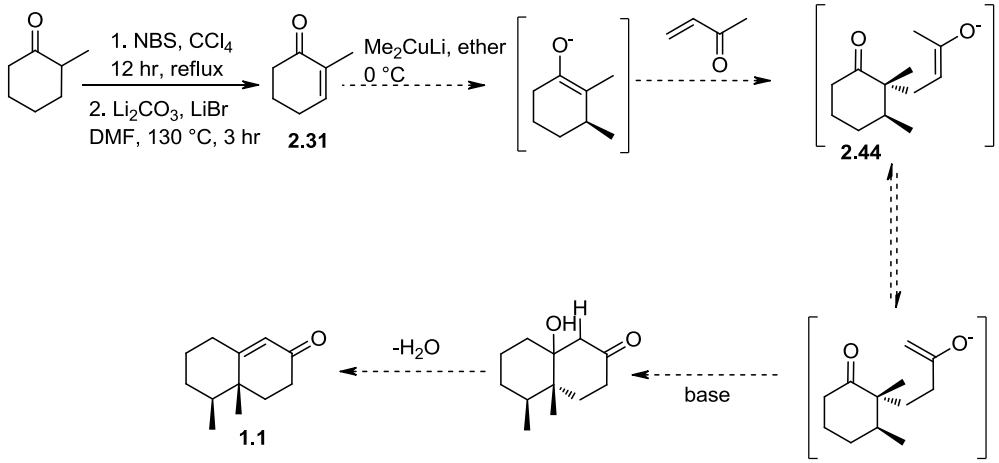
This route was inspired by the work by Coelho and Diaz.[20] In their studies towards the synthesis of (±)-pathylactone A, compound **2.31** undergoes conjugate addition with lithium dimethylcuprate followed by trapping of the enolate intermediate with allyl bromide in a *cis:trans* ratio of 1:4 (*scheme 2.12*).

Scheme 2.12: Initial steps to the synthesis of (±)-pathylactone A by Coelho & Diaz.



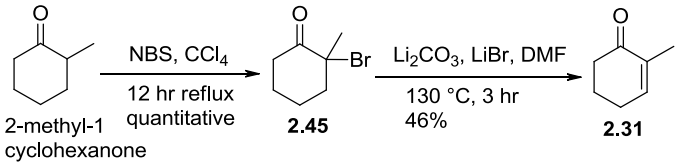
In our route, trapping of the enolate would occur with MVK or similar electrophile providing intermediate **2.44**. This would then undergo a Robinson annulation type reaction forming the desired bicyclic enone **1.1** (*scheme 2.13*). This proposed route is similar to that used by Duhamel and de Groot who also use copper chemistry although they trap the enolate with silyl enol ether and isolate the intermediate before alkylation. Coelho and Diaz's method would be more efficient with two steps occurring in one pot.

*Scheme 2.13: Proposed route 1 to the bicyclic enone **1.1***



The synthesis of 2-methyl-2-cyclohexen-1-one **2.31** was required as it is not commercially available. In a paper by Hua and co-workers,[21] commercially available 2-methyl-1-cyclohexanone was brominated using freshly recrystallised *N*-bromosuccinimide in carbon tetrachloride to form 2-bromo-2-methyl-1-cyclohexanone **2.45** regioselectively in a quantitative yield. Compound **2.45** subsequently underwent dehydrobromination to afford the desired enone **2.31** with an overall yield of 46% (*scheme 2.14*).

*Scheme 2.14: Formation of enone **2.1***



As carbon tetrachloride (bp 77 °C) is a known carcinogen and ozone depletor, alternative solvents were investigated, dichloroethane (bp 84 °C) and toluene (bp 110 °C). However, these experiments failed to yield any brominated product. As a result, the bromination was carried out in carbon tetrachloride.

On the first attempt of the dehydrobomination step, a 22% yield was obtained although this was on a very small scale (scaled down 30 times from literature quantities). In the second attempt in which the reaction was scaled down five times, a 46% yield was obtained. This was still lower then the reported yield of 72%. This low yield may have been due to a smaller scale reaction being carried out.

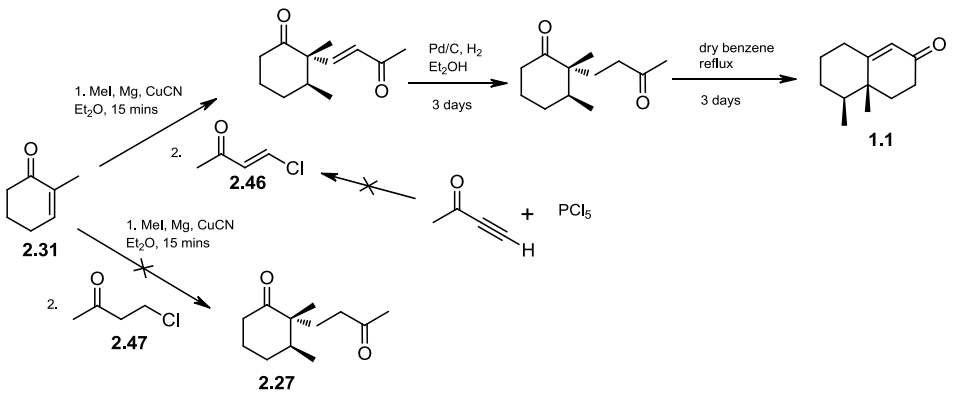
Despite the lower yields, sufficient quantities of enone **2.31** were synthesised to continue with the synthetic route. However, literature precedent for the use of MVK in 1,4-addition reactions described issues of decomposition due to polymerization. Therefore an alternative to MVK was sought.

2.2.2. Route 1A: With 4-chlorobutanone/4-chlorobutenone.

2.2.2.1. Route inspired by Dancer *et al.*

The bicyclic enone **1.1** synthesised by Dancer *et al.*[22] employed a similar route. This methodology paper investigated trapping of ketone enolates with β-sulfonylacrylate thioesters, β-sulfonyl-, β-sulfinyl- and β-chlorovinyl ketones. For enone (±)-**1.1** Dancer *et al.* used (*E*)-4-chlorobut-3-en-2-one **2.46** to trap the enolate generated from conjugate addition of methylcuprate to compound **2.31** and report an overall yield of 66% over three steps (*scheme 2.15*).

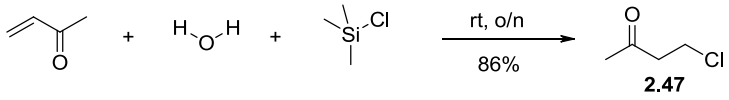
*Scheme 2.15: Route 1B to the bicyclic enone (±)-**1.1***



Although this route appears to be relatively simple with an adequate yield, it was thought to be quite time consuming with the last two steps taking six days. It was proposed that the enolate formed from compound **2.1** could be trapped with 4-chloro-2-butanone **2.47** instead of (*E*)-4-chlorobut-3-en-2-one **2.46** to form compound **2.27**, thereby removing the need for the hydrogenation step.

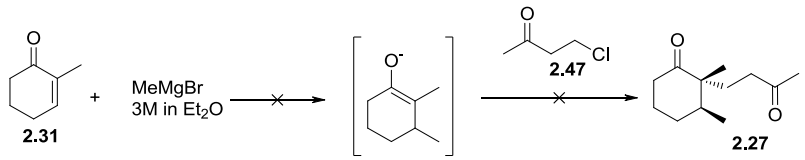
4-Chloro-2-butanone **2.47** was readily synthesised according to the method of Boudjouk, Kim and Han (*scheme 2.16*).[23] This procedure was reproduced with a yield of 86% after optimisation of conditions. A longer reaction time was required; overnight compared to the five hours stated in the literature, and the careful use of the rotary evaporator as the product was found to be quite volatile.

Scheme 2.16: Formation of compound **2.47**



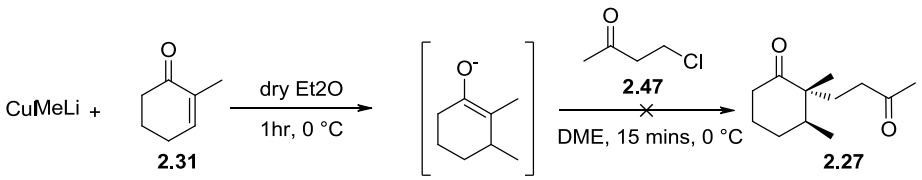
Two methods of forming compound **2.27** were investigated simultaneously. The first was based on methodology by Dancer and coworkers,[24] although initially methylmagnesium bromide was used from a commercial source instead of being made *in situ* (*scheme 2.17*). The reaction was repeated several times but no product was observed. The original method of forming the Grignard reagent using magnesium, methyl iodide and copper cyanide, followed by the addition of chlorobutanone was also investigated, however this too failed to give any compound **2.27.** The main product isolated after work up was found to be the starting enone **2.31**.

Scheme 2.17: Attempt at the formation of compound ***2.27*** *using MeMgBr*



The second method of forming compound **2.27** was based on work by Coelho and Diaz[20] in which the enone **2.31** is added to lithium dimethylcuprate which was formed in situ, then the enolate is trapped with compound **2.27** (*scheme 2.18*).

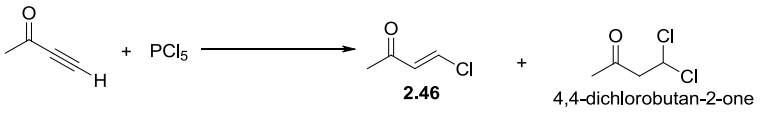
Scheme 2.18: Attempt at the formation of compound ***2.27*** *using* Me_2CuLi



No product was identifiable by ^{1}H NMR spectroscopy. It was thought that the chlorobutanone moiety was too unreactive under the reaction conditions as some of the dimethyl cyclohexanone intermediate was identified indicating the 1,4-addition of the lithium dimethylcuprate was successful but quenching of the enolate was not. The original method employed the use of (*E*)-4-chlorobut-3-en-2-one, however literature precedence relating to the formation of this enone detailed procedures requiring gaseous compounds which were thought to be problematic to work with. As experiments with chlorobutanone **2.47** were found to be unsuccessful, attempts at synthesising chlorobutenone **2.46** was then investigated.

Dancer *et al.* utilised the procedure reported by Benson and Pohland[25] to synthesise **2.46**, in which acetyl chloride was added to acetylene in carbon tetrachloride followed by the addition of aluminium chloride. In an attempt to avoid hazardous solvents and gaseous starting materials, further literature searches were carried out to find an alternative. Only one procedure was found which did not involve the use of gaseous starting materials. In a brief communication by Naser-Ud-din and Skattebøl,[26] 3-butyn-2-one was added to a suspension of PCl_5 in Et_2O and stirred overnight forming two products (*scheme 2.19*) with (*E*)-4-chlorobut-3-en-2-one as the major product **2.46**.

*Scheme 2.19: Formation of (E)-4-chlorobut-3-en-2-one **2.46** by Naser-Ud-din and Skattebøl*

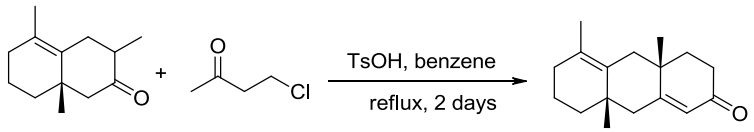


The ^{1}H NMR spectra of the crude mixture indicated both products present, although the 4,4-dichlorobutan-2-one was found to be the major product. However, only 4,4-dichlorobutan-2-one was isolated by column chromatography. It was speculated that compound **2.46** is not stable under chromatographic conditions. Further attempts at synthesising compound **2.46** were suspended as more viable reaction routes emerged.

2.2.2.2. Alternative use of chlorobutanone

Further investigations on the transformation of enone **2.31** to form the bicyclic enone **1.1** revealed a synthetic procedure by Paquette, Belmont and Hsu[27] which had a similar transformation utilising chlorobutanone (*scheme 2.20*).

Scheme 2.20: Annulation reaction carried out by Paquette, Belmont and Hsu

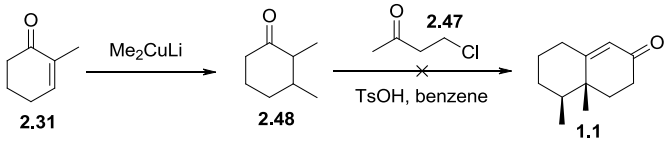


80%

This procedure was adapted using readily available materials (*scheme 2.21*). Enone **2.31** was methylated with dimethyllithium cuprate to form intermediate **2.48** which resembles the starting material used by Paquette *et al*. Compound **2.48** was isolated as a mixture of *cis* and *trans* isomers with spectroscopic data in accordance with literature values.[28] Due to the overlap of signals, the ratio of diastereoisomers was not ascertained.

Compound **2.48** was reacted with chlorobutanone but failed to yield the bicyclic enone after three days heating to reflux. No product signals could be identified by ^{1}H NMR spectroscopy although dimethylcyclohexanone signals were thought to be present.

Scheme 2.21: Formation of bicyclic enone based on Paquette, Belmont and Hsu method

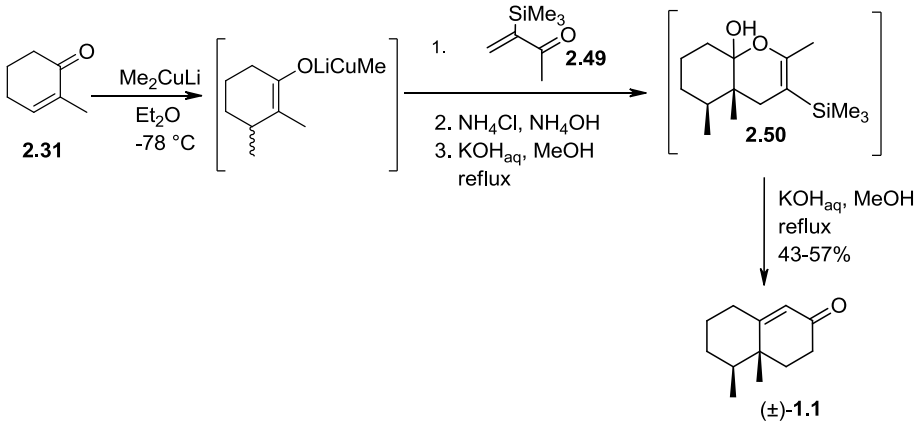


It was thought that compound **2.47** was not a reactive enough system for these reaction conditions so this route was halted.

2.2.3. Route 1B: With trimethylsilyl-3-buten-2-one.

Further investigations yielded another synthetic route (*scheme 2.22*) to the bicyclic enone (±)-**1.1** by Boeckman, Blum and Ganem.[29] The enolate generated by the 1,4-addition of dimethyllithium cuprate to enone **2.31** is trapped by the Michael acceptor, 3-trimethylsilyl-3-buten-2-one **2.49**, in an annulation reaction to form intermediate **2.50**. Treatment of this intermediate with potassium hydroxide and methanol generates the desired bicyclic enone (±)-**1.1** in yields of 43-57%.

*Scheme 2.22: Formation of bicyclic enone **1.1** by Boeckman, Blum and Ganem*



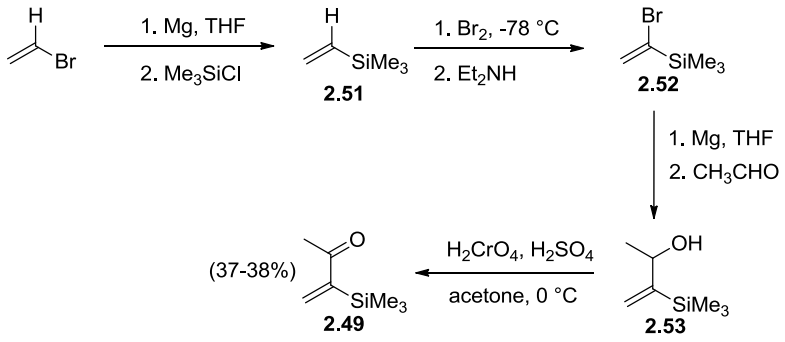
The overall procedure for this synthetic route appeared to be quite simple, although the challenge was found to be in the formation of the Michael acceptor **2.49**. It was soon realised that synthesising trimethylsilyl enones is a very challenging task with various published procedures reporting low yields, multiple steps or specialist starting materials required.

Several methods for the synthesis of trimethylsilyl butenone **2.49** were investigated simultaneously.

2.2.3.1. Trimethylsilylbutenone synthesis – method A.

The procedure used by Boeckman, Blum and Ganem (*scheme 2.23)* to synthesise trimethylsilyl butenone **2.49** contained four steps with a reported overall yield of 37-38%.[30] Attempts to repeat this procedure resulted in limited success. Reaction of vinylbromide with magnesium in THF and chlorotrimethylsilane yielded the desired product, vinyltrimethylsilane **2.51** in a maximum yield of 38%, although reported yields for this first step was 67-78%. There was much difficulty in the distillation of the product from the solvent THF, as there is only a 2 °C difference in boiling point. Despite repeating the experiment multiple times, compound **2.51** could only be obtained dissolved in THF (approximately 90% THF).

*Scheme 2.23: Formation of trimethylsilyl butenone (**2.49**) used by Boeckman, Blum and Ganem*



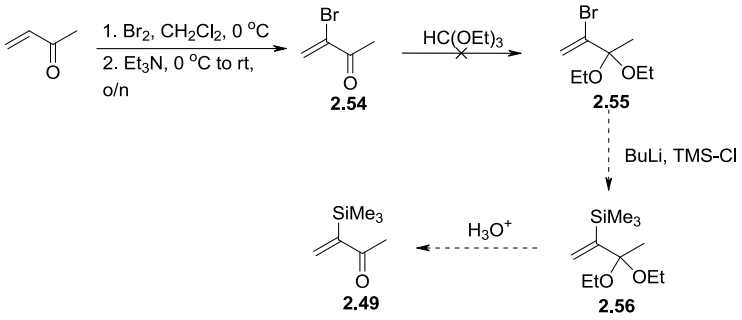
Compound **2.51** was used in the next step despite containing large amounts of THF. The addition of bromine and diethylamine yielded compound **2.52** in an approximate yield of 29%. By ^{1}H NMR spectroscopy, no starting material was found to be present but other unexpected impurity peaks were observed. As the initial steps of this synthetic route were found to be already low yielding and time consuming, this synthetic route for the formation of trimethylsilyl butenone was suspended.

2.2.3.2. Trimethylsilylbutenone synthesis – method B.

This synthetic route (*scheme 2.24*) was devised using a combination of published methods. Bromination of MVK would form 3-bromo-but-3-en-2-one **2.54**.[31] The ketone would then be protected with trimethyl orthoformate to form compound **2.55**.[32] This product would then undergo lithium-halogen exchange with the resulting anion being quenched with TMSCl. Subsequent deprotection[33] of the carbonyl moiety would form the desired compound **2.49**.

Compound **2.54** was successfully synthesised in a yield of 90%. As it was found to decompose under chromatographic conditions, it was used without further purification. Impurities in the crude reaction material were estimated to be negligible by ^{1}H NMR spectroscopy. Enone **2.54** was also found to decompose readily at room temperature and even when stored at low temperatures wrapped in foil, which resulted in the need for multiple batches being synthesised.

Scheme 2.24: Method B to trimethylsilylbutenone.



Several procedures (*table 2.1*) were carried out in an attempt to synthesise compound **2.55** from compound **2.54**, however none were successful in forming the desired product in satisfactory yields. Although in some cases the ketone did appear to have been protected with the orthoformate, ^{1}H NMR spectroscopy indicated the loss of the alkene protons.

*Table 2.1: Conditions used to form compound **2.55***

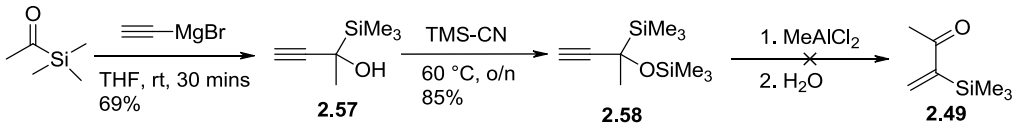
Ref.	Reagents	Conditions	Results
34	1.25 equiv. $HC(OEt)_3$ + NH_4NO_3 in EtOH	Reflux	Possible trace amounts of product + SM
35	2.4 equiv. $HC(OEt)_3$ + H_2SO_4	rt	Decomposition
36	20 equiv. K_2CO_3 in EtOH	reflux	No SM or product
37	1.1 equiv. $HC(OEt)_3$ + 2 equiv. EtOH + 0.1 equiv. TsOH	rt	No SM or product
38	1.3 equiv. $HC(OEt)_3$ + NH_4NO_3 in EtOH	Heated to reflux with heat gun, left for 15 mins, repeat and left stirring at rt for 2 days	Possible trace of product but many compounds present

This synthetic route was put on hold as a new route was investigated.

2.2.3.3. Trimethylsilybutenone synthesis – method C (Acetyltrimethylsilane method)

A third synthetic route was devised for the formation of compound **2.49** (*scheme 2.25*).

Scheme 2.25: Method C to trimethylsilyl butenone



Acetyltrimethylsilane was shown to react with ethynylmagnesium bromide to form compound **2.57**, which further reacts with trimethylsilyl cyanide to form compound **2.58** in a synthetic procedure described by R.Cunico.[39] Compounds **2.57** and **2.58** were synthesised successfully using this procedure with good yields.

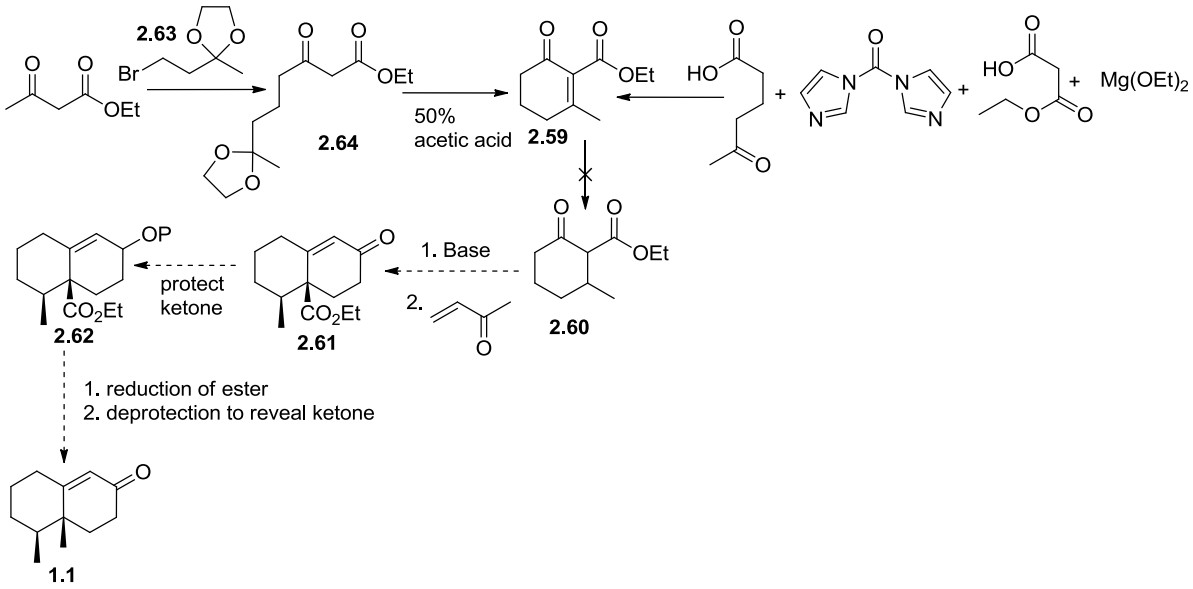
The full procedure had not been published for the transformation of **2.58** to **2.49**, although Enda and Kuwajima claim an 85% yield.[40] They claim that "on exposure to an equimolar amount of methylaluminium dichloride, the ethers [ie. compounds of the type **2.58**] undergo rapid isomerisation and afford the corresponding structures [i.e. compound **2.49**] after quenching with water".

The reaction was carried out in Et_2O, CH_2Cl_2 or THF. $MeAlCl_2$ was added at 0 °C in all reactions. No reaction occurred in Et_2O with only starting material being recovered after two days stirring at room temperature. In both CH_2Cl_2 and THF reactions, no starting material was found to be present after overnight reaction at room temperature; no product was detected by ^1H NMR spectroscopy. Heating to reflux for varying time periods (30 mins to 4 hours) yielded no product. No further publications utilising this transformation have been found therefore this particular synthetic route was discontinued.

2.2.4. Route 2 – Use of ethyl 3-Methyl-1-oxo-2-cyclohexene-2-carboxylate (2.59)

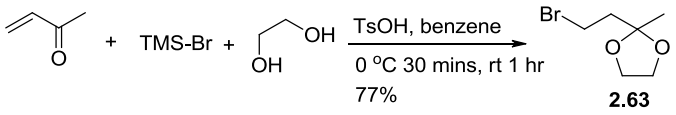
As previous attempts to form nominine using enone **2.31** had proved to be problematic, a new synthetic route was developed based on compound **2.59**, which would require hydrogenation of the double bond to form compound **2.60** (*scheme 2.26*)**.** This would then undergo an annulation reaction with MVK in the presence of a base such as NaH to form compound **2.61**. It was believed that compound **2.60** would be a more reactive alternative to dimethylcyclohexanone **2.48** due to the increased acidity of the hydrogen between the carbonyl groups. Protection of ketone **2.61** would be required to facilitate the complete reduction of the ester moiety of **2.62**. Subsequent deprotection would furnish the desired enone **1.1**.

*Scheme 2.26: Proposed synthetic route to enone **1.1** using ethyl 3-Methyl-1-oxo-2-cyclohexene-2-carboxylate **2.59.***



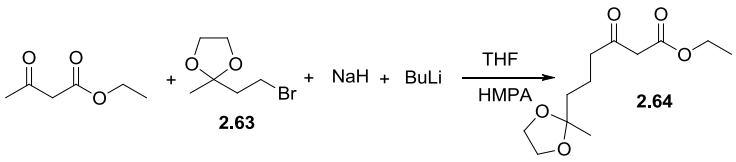
The formation of compound **2.59** was initially based on a procedure by Kato, Kamat and Yoshikoshi in their investigations towards useful synthetic intermediates.[41] Ethyl acetoacetate is a readily available starting material, however compound **2.63** required synthesis. 2-(2-Bromoethyl)-2-methyl-1,3-dioxolane **2.63** was synthesised from MVK, trimethylsilyl bromide and ethylene glycol in a method described by Hsung,[42] obtaining a yield of 77% (*scheme 2.27*). The product was used without further purification.

*Scheme 2.27: Formation of 2-(2-bromoethyl)-2-methyl-1,3-dioxolane **2.63***



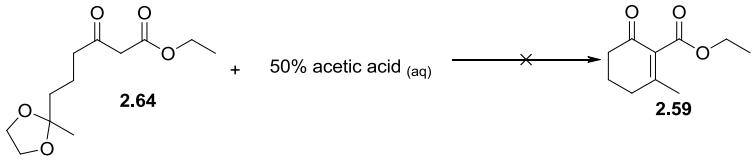
Deprotonation of ethyl acetoacetate with sodium hydride and butyllithium, followed by addition of compound **2.63** as described in the original method by Kato *et al.* (*scheme 2.28*) yielded only starting materials in all attempts. Despite drying the ethyl acetoacetate over magnesium sulphate, increasing the number of equivalents of compound **2.63**, using a new batch of sodium hydride, purifying the sodium hydride from mineral oil with hexane and adding sodium sulphate to the reaction mixture to remove any water present, no product was isolated in any of these experiments. However, the reaction was found to be successful on addition of 0.5 equivalents of anhydrous HMPA and compound **2.64** was synthesised in a 65% yield. HMPA is known as a useful additive in reactions with BuLi as it complexes to lithium cations further polarising the Li-C bond accelerating metalation.

*Scheme 2.28: Formation of compound **2.64** using Kato et al. method*



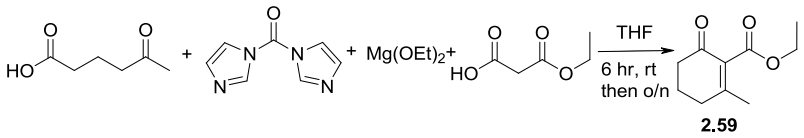
To facilitate the deprotection of the ketal followed by subsequent ring closure to form **2.59**, Kato's procedure reported the use of 50% aqueous acetic acid for 30 hours under nitrogen at room temperature (*scheme 2.29*). However, after this period of time, TLC indicated multiple products with starting material still present. After 105 hours, reaction was worked up to give only 34 mg of a crude yellow oil (after starting with 100 mg of compound **2.64**). ^{1}H NMR spectroscopy indicated no product peaks. The conditions used appeared to be causing decomposition of the starting material after prolonged periods of time.

*Scheme 2.29: Formation of compound **2.59** using Kato et al. method*



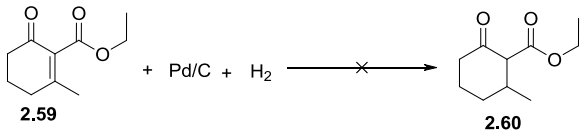
An alternative procedure by Ikeda *et al.*[43] for the synthesis of compound **2.59** was also investigated, which proved to be more successful. Compound **2.59** was synthesised (*scheme 2.30*) in a 74% yield (literature yield 80%). This one step procedure was found to be a simpler (all reagents commercially available) and a faster method compared to Kato *et al.*'s procedure. Carbonyldiimidazole is used to couple acetobutyric acid with the magnesium salt of monoethyl malonate.

*Scheme 2.30: Formation of compound **2.59** using Ikeda's method*



Reduction of the double bond of **2.59** was facilitated by hydrogenation with Pd/C (20 wt%) in EtOAc (*scheme 2.31*). After 2.5 hours at room temperature, TLC indicated no starting compound **2.59** present but three products was observed. The ^{1}H NMR spectra was too complex to determine whether or not the desired product was present. Unfortunately, after multiple attempts at column chromatography, the compounds could not be separated despite varying solvent systems.

*Scheme 2.31: Hydrogenation of compound **2.59** to form compound **2.60***



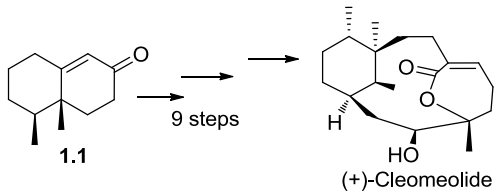
The experiment was repeated a second time for only 40 minutes. The crude ^{1}H NMR spectra was again too complicated to determine whether or not product was present but this time starting compound **2.59** could be seen by TLC, as well as only two other compounds.

It was realised at this time that another route which was being investigated concurrently would be more successful, therefore this route was discontinued and efforts were concentrated on route 3.

2.2.5. Route 3 – Use of Wieland-Miescher Ketone

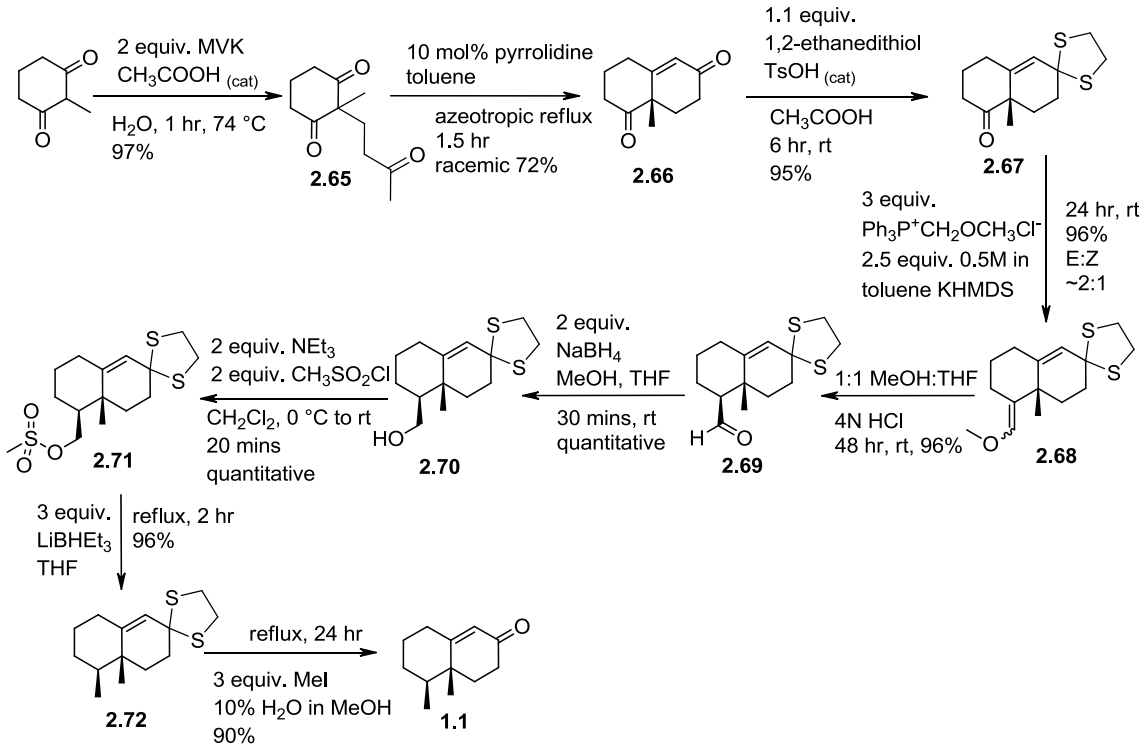
A different strategy to bicyclic enone **1.1** was developed by Paquette *et al.*[44] which they used in their total synthesis of the macrocyclic (+)-cleomeolide (*scheme 2.32*).

*Scheme 2.32: Paquette's use of enone **1.1** to synthesise(+)-cleomeolide*



Despite containing several steps, this synthetic route was found to be reproducible and after some development of the steps, it was found to be suitable for large scale synthesis of enone **1.1** (*scheme 2.33*). Large scale synthesis of enone **1.1** was carried out using available facilities at Pfizer such as the 5 L automated reactor vessel. This allowed up to 0.4 moles (50 g) of starting material to be used per batch increasing the efficiency of this route.

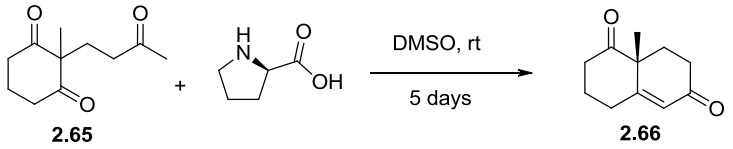
*Scheme 2.33: Modified Paquette's method to enone (±)-**1.1***



Compound **2.65** was successfully synthesised using a procedure described by Buchschacher *et al.*[45] Michael addition of 2-methyl-1,3-cyclohexanedione and MVK, in the presence of catalytic amounts of acetic acid and hydroquinone in water at 74 °C for one hour afforded compound **2.65** in 97% yields after removal of a white solid impurity by filtration which was thought to be polymerisation of the MVK.

Buchschacher *et al.* also described an asymmetric procedure for the aldol addition and subsequent elimination to furnish compound **2.66** (also known as the *S*-(+)-Wieland-Miescher ketone*)* with the use of L-proline (*scheme 2.34*). Compound **2.65** was stirred with 5 mol % of L-proline in DMSO for five days at room temperature. The crude was purified by column chromatography to give *S*/*R*-enedione **2.66** (0.56 g, 43%).

*Scheme 2.34: Formation of compound **2.66** – chiral product*



2.65 **2.66**

Buchschacher's enantiomeric purification utilised pure *S*-enedione crystals to seed the *S*/*R* enedione, dissolving the product in Et_2O and the mixture left undisturbed at -20 °C for 18 hours. The crystals were collected by filtration and the re-crystallisation procedure repeated with the filtrate. However, when this was carried out, no crystals formed, despite leaving mixture at -20 °C for extended periods of time. As the experimental scale (1.5 g) carried out was considerably less then the published procedure (154.2 g), this could be a possible reason for the failure in recrystallisation.

This method was later repeated on a larger scale at the Pfizer laboratories. The residue was distilled and crystallised using pure seed crystals (obtained from Sigma Aldrich). Although 3.10 g (42% (65% ee)) of crystals were obtained from repeated recrystallisations, it was discovered that the crystals contained 17% of the *R* enantiomer, as shown by chiral HPLC.

Another method of recrystallisation by Harada *et al.*[46] was also attempted. This involved the *S*/*R* enedione to be dissolved in a 10:1 mixture of diethyl ether and ethylacetate and left at -70 °C (cardice box) for five hours, however this failed to yield any crystals despite extending the time left in the box. The mixture gave $[\alpha]_D^{25}$ +8.36 (toluene, *c* 1.0), whereas the published value of the pure crystals was $[\alpha]_D^{25}$ +97.3 (toluene, *c* 1.0) indicating a large amount of the *R* enantiomer present. However, the procedure stated a 56.8% yield of the (*S*)-enedione. It is unclear if the yield is a result of just the asymmetric process or how efficient the recrystallisation process is.

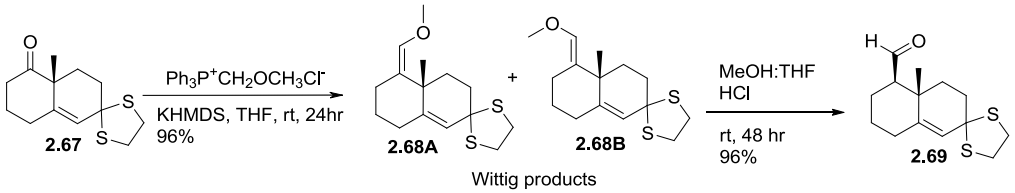
As the formation of the asymmetric enedione was quite time consuming, the racemic version was synthesised to be used in the continuation of *scheme 2.33*. In a procedure described by Ramachandran and Newman,[47] compound **2.65** was azeotroped under Dean-Stark conditions in benzene with 10 mol% pyrrolidine for 1.5 hours. It was found that replacing benzene with the more environmentally preferred toluene did not affect the yield. The crude reaction material was purified by column chromatography to isolate a yield of 74% of compound (±)-**2.66**.

The racemic Wieland-Miescher ketone was selectively protected with 1,2-ethanedithiol to obtain compound **2.67** in 95% yield. The published procedure[44] did not purify this compound before the next step; however it was found that column chromatography was required to remove small amounts of the diprotected bicyclic impurity.

With the carbonyl of the enone masked as a dithiolane, this resulted in the selective transformation of the remaining carbonyl into the desired methyl group. Literature procedure then described a Wittig reaction of compound **2.67** with potassium hexamethyldisilazane and (methoxymethyl) triphenylphosphonium chloride for 24 hours to form the methoxymethylene intermediate, which was hydrolysed without isolation with 4N HCl and MeOH:THF (1:1) mixture (36 hours stirring at room temperature). Initial experiments obtained a low yield of 14% of the aldehyde **2.69** (literature yields 93%). With further repetitions of the reaction, it was discovered the yield increased if the methoxymethylene intermediates (**2.68A** and **2.68B**) were isolated and purified before the hydrolysis step.

It was believed that the excess (methoxymethyl) triphenylphosphonium chloride interfered with the hydrolysis step therefore reducing overall yields particularly in larger scale reactions. Two Wittig products **2.68A** and **2.68B** were isolated in a total yield of 96% (*scheme 2.35*).

*Scheme 2.35: Formation of compound **2.69***



Of the two alkene isomers, the major product **2.68B** (*E alkene*) is the more stable as there are less steric constraints due to the methoxy group pointing away from the methyl group. It was found that samples of pure **2.68A** decomposed over time to the aldehyde product as well as some isomerisation to **2.68B**.

As KHMDS was required in excess, various bases were investigated to find a more inexpensive alternative for large scale synthesis. However, it was found that the reaction did not form any product with NaHMDS, n-BuLi or NaH. (Methoxymethyl) triphenylphosphonium chloride in THF was cooled to 0 °C before the addition of the base and stirred. A colour change from a white suspension to an orange/red colour indicated the formation of the ylide. No ylide was formed with NaHMDS or NaH even when the reaction with NaH was refluxed for two hours. Although an orange solution formed immediately with the addition of n-BuLi, after addition of compound **2.67**, no Wittig product or starting material was isolated. It was concluded that KHMDS must be used in this Wittig reaction.

The Wittig products were hydrolysed affording the aldehyde **2.69** in 96% yield. From the ^{1}H NMR spectra, it was concluded that only one diastereoisomer was formed as only one aldehyde proton was observed forming selectively the desired *cis* stereochemistry as confirmed by comparison with literature data.

Reduction of compound **2.69** with sodium borohydride resulted in a quantitative yield of compound **2.70.** The alcohol was mesylated with methanesulfonyl chloride to afford compound **2.71** in a quantitative yield which was taken on crude in the next step.

To cleave the sulfonyl group to form compound **2.72**, literature procedure stated the addition of two equivalents of Superhydride® (lithium triethylborohydride) and stirred for 20 hours at room temperature. However, when this was carried out, no product was formed and only starting material was recovered. Additional equivalents of Superhydride® and prolonged reaction times at room temperature did not affect the outcome. Only starting material was recovered. As the reaction did not appear to work at room temperature, the reaction was heated to reflux. After six hours, starting material was still present although a less polar spot was prominent by TLC, so the reaction was left under reflux conditions for a total of 24 hours to ensure completion. The product was obtained in 11% after column chromatography. In further repetitions of this reaction, 60% of product was isolated after five hours of heating to reflux and 66% isolated after two hours, indicating that the reaction does not fully consume all starting material and prolonged refluxing caused decomposition of product or starting materials. After screening of conditions, optimal conditions were found to be three equivalents of Superhydride® heating to reflux for two hours achieving an optimum yield of 96% of compound **2.72**.

Deprotection of the dithiolane group was initially carried out with thallium trinitrate trihydrate ($Tl(NO_3)_3.3H_2O$) as reported by Paquette. Literature procedure reported a 90% yield after stirring compound **2.72** in THF and H_2O with $Tl(NO_3)_3.3H_2O$ in MeOH for only ten minutes at room temperature. However, when this reaction was carried out (experiment 1 of *table 2.2*), after two hours starting material was still present by TLC so another equivalent of $Tl(NO_3)_3.3H_2O$ in MeOH was added. After an additional hour of stirring, TLC indicated more products as well as the starting material indicating additional equivalents of $Tl(NO_3)_3.3H_2O$ has a negative effect on the reaction. Approximately 39% of product was isolated from this attempt.

*Table 2.2: Investigating deprotection methods of compound **2.72***

Ref.	Experiment #	Conditions	Yield	Notes
44	*Literature reported*	*1.2 equiv. $Tl(NO_3)_{3}.{}_3H_2O$ in MeOH THF/H_2O, rt, 10 min*	*90%*	
44	1 (i)	2 equiv. $Tl(NO_3)_{3}.{}_3H_2O$ in MeOH THF/H_2O, rt, 2 hr Then additional 1 equiv. $Tl(NO_3)_{3}.{}_3H_2O$, rt, 1 hr	39%	Varying yields obtained - not reproducible. Reagent is highly toxic and harmful to the environment
	1 (ii)	1.3 equiv. $Tl(NO_3)_{3}.{}_3H_2O$ in MeOH THF/H_2O, rt, 1 hr	71%	
	1 (iii)	1.3 equiv. $Tl(NO_3)_{3}.{}_3H_2O$ in MeOH THF/H_2O, rt, 1 hr	58%	
	1 (iv)	1.3 equiv. $Tl(NO_3)_{3}.{}_3H_2O$ in MeOH THF/H_2O, rt, 3 hr	60%	
	1 (v)	1.3 equiv. $Tl(NO_3)_{3}.{}_3H_2O$ in MeOH THF/H_2O, rt, 1 hr	23%	
48	2 (i)	1 equiv. $FeCl_3$, 1 equiv. KI Anhydrous MeOH, reflux, 6.5 hr	46%	Other unidentified impurity formed – bicyclic like product but could not be identified. Alcohol product sometimes isolated instead of enone.
	2 (ii)	1 equiv. $FeCl_3$, 1 equiv. KI Anhydrous MeOH, reflux, 6 hr Then additional 1 equiv. $FeCl_3$, rt, o/w	45%	
	2 (iii)	1 equiv. $FeCl_3$, 1 equiv. KI Anhydrous MeOH, reflux, 4.5 hr Then additional 1 equiv. $FeCl_3$, reflux 2 hr Then additional 1 equiv. KI, rt, o/n	50%	
49	3	4 equiv. NCS, 4.5 equiv. $AgNO_3$ 70 % aqueous CH_3CN, 0 °C, 25 mins	28%	Solubility issues.
50	4 (i)	2.5 equiv. diacetoxyiodobenzene $(CH_3)_2CO$:H_2O, rt, o/n	29%	Solubility issues. Another compound isolated where alkene proton is missing.
	4 (ii)	2.5 equiv. diacetoxyiodobenzene $(CH_3)_2CO$:H_2O, rt, 1 hr	33%	
51	5 (i)	2 equiv. mCPBA, CH_2Cl_2, -20 °C 15 mins then rt, 15 mins. Quench with $NaHCO_3$ and crude isolated. $(CH_3CO)_2O$: Et_3N: $THF_{(aq)}$ 3:4:10, 40 °C o/n	Failed	Mostly starting material isolated. Crude ^1H NMR spectra very messy.
52	5 (ii)	1.5 equiv. mCPBA, 2 equiv. TFA CH_2Cl_2, 0 °C to rt o/n	Failed	Only starting material isolated
53	6	1.5 equiv. DDQ $(CH_3)_2CO/H_2O$, rt, o/n Reflux 7 hr, rt o/n	21%	More starting material isolated than product
54 55	7	After optimisation; 3 equiv. MeI MeOH and 10 % H_2O, reflux, 24 hr	90%	Successful simple procedure.

While there are many reported methods for the deprotection of dithioacetals, we wanted to avoid the use of any toxic transition metals in stoichiometric amounts at elevated temperatures which is common for this type of deprotection. Several methods of deprotection were subsequently investigated to achieve a higher yielding and less toxic method (*table 2.2*).

Success was found by heating to reflux compound **2.72** in a solution of 10% H_2O in MeOH and three equivalents MeI for 24 hours. Yields were improved from 45% to 90% of (±)-**1.1** after optimisation of parameters. MeI is a cheaper alternative to the thallium reagent especially when working on a large scale.

2.2.6. Large scale synthesis of enone 1.1

The three month placement at the Pfizer laboratories (Sandwich, Kent) gave us the opportunity to carry out the synthesis of enone (±)-**1.1** on a large scale making use of their superior resources such as large scale equipment, automated reactor vessels and funding for chemicals and reagents.

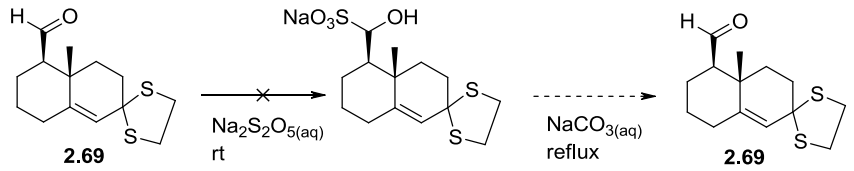
During the placement it was discovered that large scale chemistry is physically demanding and very time consuming. For example, after the Wittig reaction on compound **2.67**, a large silica plug was required to remove excess reagent which took many litres of solvent per batch which also required evaporation under reduced pressure.

Although equipment available at Pfizer allowed work on a much larger scale, there were limitations due to sharing of equipment and maximum volume in reactor including work up solutions, which restricted progress. The largest reaction carried out at Pfizer was 0.4 mol (50 g) of the starting 2-methyl-1,3-cyclohexanedione compared to 0.1 mol (14 g) carried out at university. A total of 1.57 mol (198 g) of starting cyclohexanedione was taken through during the placement.

Alternative purification methods had to be investigated as column chromatography would be too time consuming for each step and waste a lot of solvent on this scale. The use of toluene instead of benzene, which is prohibited at Pfizer, did not seem to affect yields for the formation of compound **2.66**. The large scale batches allowed for an efficient short path distillation of compound **2.66** which reduced purification times. Recrystallisation of the distilled residue was successful and white crystals were formed, although the remaining residue was also used to increase yields.

An alternative purification method used at Pfizer to isolate aldehyde compounds was investigated in which the bisulfite adduct of the aldehyde is formed using sodium metabisulfite ($Na_2S_2O_5$) so it could be extracted from the organic solution into the aqueous phase (*scheme 3.36*). The aldehyde would then be reformed by refluxing with aqueous sodium carbonate.

Scheme 2.36: Alternative aldehyde purification method



However, the aldehyde failed to form the bisulfite adduct despite varying conditions including stirring for extended periods of time and even refluxing overnight in different solvents. It was concluded that compound **2.69** was too sterically hindered for this method to be successful.

Recrystallisation of aldehyde **2.69** was partially successful. On leaving the crude liquid at room temperature overnight, some of the pure product precipitated out as a white powdery solid. The remaining residue was recrystallised from diethyl ether to remove the triphenylphosphonium oxide impurity. Some batches which contained a small amount of impurity were further purified by column chromatography.

A large amount of time was spent synthesising enone (±)-**1.1** on a large scale as it is a vital intermediate. It was discovered that after prolonged storage in the fridge, enone **1.1** started to decompose whereas its precursor could be kept at room temperature as a pure white solid without noticeable signs of decomposition. Overall, 32 g of pure enone (±)-**1.1** and 14 g of the protected compound **2.72** was synthesised.

2.3. Conclusion to chapter 2

Different routes to enone **1.1** were investigated with varying success depending on availability of starting materials and complexity of reactions. Initially, we wanted to develop a novel method to this intermediate based on readily available starting materials but as time progressed and the lack of success with proposed routes were revealed, it was decided we would focus on Paquette's method (route 3).

We had by no means exhausted the possibilities of each route, for example in route 1, we could have used Michael acceptors such as Huffman's methyl vinyl ketal **2.29** or the protected bromo butanone **2.63**. However, Paquette's method gave us the option for synthesising enone **1.1** in its optically pure form (either enantiomer depending on which proline catalyst was used), especially at a later date when the route to nominine had been established. Although this route was already published and was composed of several steps, it was found to be reproducible with excellent yields and in the interest of progress it was taken on for large scale synthesis.

We have adapted Paquette's synthesis of enone **1.1** with modification of solvents and purification procedures. For example, the use of benzene was replaced by the less toxic toluene and recrystallisation or distillation was favoured over column chromatography. In some cases, reaction times were extended or reaction temperatures increased in order to increase yields.

The most significant difference was the deprotection of the dithioacetal group in which Paquette *et al*. used 1.3 equivalents of thallium trinitrate trihydrate. On a large scale, this would be too expensive and toxic therefore several different methods were investigated. It was found that refluxing compound **2.72** with the inexpensive MeI in MeOH with 10% H_2O gave excellent yields. Large scale synthesis of intermediate (±)-**1.1** was successful with an overall yield of 53% over nine steps. Although the number of steps may be considered quite high, the overall yield is superior in comparison to previously published procedures.

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Chapter 3. Total synthesis of dehydrofukinone and fukinone

3.1. Introduction

Dehydrofukinone and fukinone are fragrant compounds which belong to a family of sesquiterpenes derived from eremophilane type compounds. These natural products comprise of a decalin core with an isopropylidene unit and differ by an additional alkene in dehydrofukinone.

Fukinone was first isolated and its structure determined in 1968 by Naya *et al*.[1] It was obtained as a colourless oil from the methanolic extract of *Petasites japonicus* Maxim (sweet coltsfoot/butterbur) which grows wild in Japan and is often cultivated as a leafy vegetable. Fukinone was shown to exhibit inhibitory activity on mast cell degranulation (IC_{50} 19.1 μM),[2] one of the symptoms of pollenosis, in a study on the effects of Japanese butterbur extract on type I allergic symptoms. Fukinone has also been isolated from *Arctium lappa* (Japan),[3] *Ligularia persica* (Iran)[4] and *Calcalia hastate* L.(Japan).[5]

Dehydrofukinone was first isolated from the leaves of *Arctium lappa* L. in 1972 also by Naya *et al*.[1] It has since been isolated in numerous instances from a variety of species around the world such as *Cacalia hastate* L. (Japan),[6] *Senecio aureus* L (USA),[7] *Senecio glaucus* (Egypt),[8] in which it was reported to smell apricot-like, *Ligularia dictyoneura* (China)[9] and *Senecio adenotrichius* (Chile)[10] in which a surprisingly high amount of 70.9% was isolated. It is also known as dihydrokaranone.

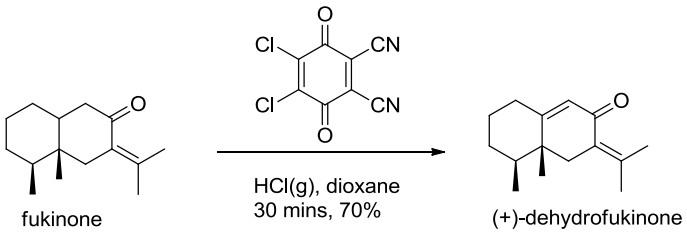
Although no biological activity has so far been reported, the enzymatic synthesis of furanoterpenes from dehydrofukinone using cytochrome P450 has been investigated.[11] Furanoterpenes have been found to be toxic and used as defence compounds by plants.[12] In the previous chapter, we achieved a multigram synthesis of enone **1.1**. In tandem with studies towards nominine, we were interested in investigating other applications of **1.1** and chose to carry out total syntheses of fukinone and dehydrofukinone.

3.2. Review of published syntheses of dehydrofukinone and fukinone

3.2.1. Previous syntheses of dehydrofukinone

There are eight previous syntheses reported with the first synthesis occurring four years prior to the original natural isolation of dehydrofukinone. It was first synthesised during the isolation and characterisation experiments of fukinone in 1968 by Naya *et al*.[1] In a one step dehydrogenation reaction, fukinone was transformed into (+)-dehydrofukinone using $HCl_{(g)}$ and DDQ in dioxane in a 70.6% yield (*scheme 3.1*).

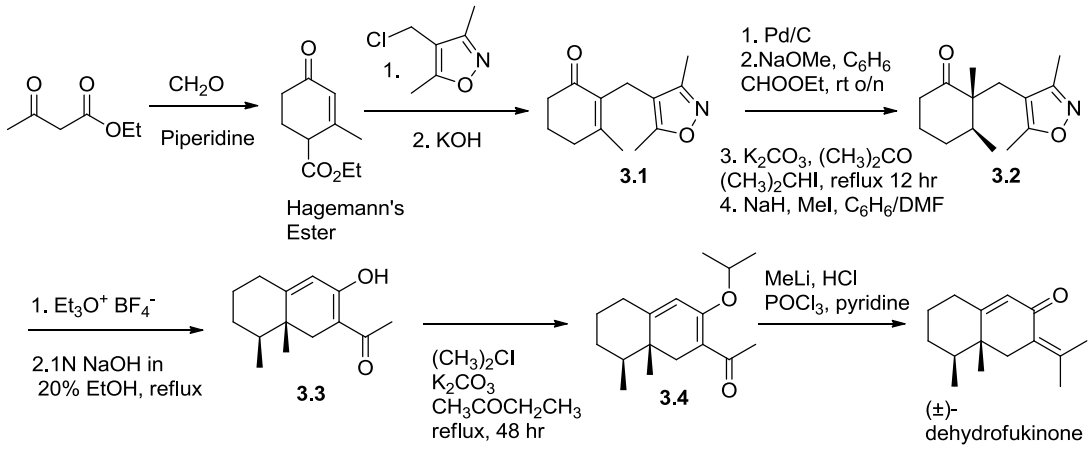
Scheme 3.1: First synthesis of dehydrofukinone from fukinone by Naya et al. in 1968.



Ohashi (1969)

The first fully synthetic route to dehydrofukinone was completed by Ohashi in 1969.[13] In his investigations into the synthesis of sesquiterpenes related to eremophilone, a new general synthetic method to these structures was developed via isoxazole annelation. The starting isoxazole **3.1** was prepared by the alkylation of Hagemann's ester,[14] (a versatile intermediate which has been used in several natural product syntheses),[15] with 4-chloromethyl-3,5-dimethylisoxazole followed by the removal of the ethoxycarbonyl group with KOH. The double bond was hydrogenated and the methylene group was protected using an isopropyl oxymethylene method in a two step process.[16] This intermediate allowed for the methylation at the desired position and after deprotection gave compound **3.2** which was cyclised to compound **3.3** using triethyloxonium fluorborate and NaOH in ethanol. The enol ether **3.4** was formed and successive treatment with MeLi, dilute HCl and $POCl_3$ in pyridine gave the natural product (±)-dehydrofukinone. This brief publication did not include an experimental so an overall yield could not be ascertained but its estimated total number of steps was 12 or more (*scheme 3.2*).

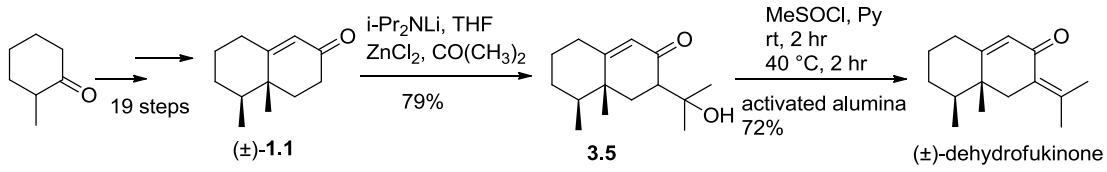
Scheme3.2: First total synthesis of dehydrofukinone by Ohashi – minimum 12 steps



Torii (1979)

Using the novel procedure they developed towards the synthesis of (±)-enone **1.1**, Torii, Inokuchi and Yamafuji[17] then carried out an aldol reaction to install the isopropenyl moiety. Subsequent dehydration of the mesylate of **3.5** gave (±)-dehydrofukinone in an overall yield of 2% in 22 steps starting with 2-methylcyclohexanone (*scheme 3.3)*.

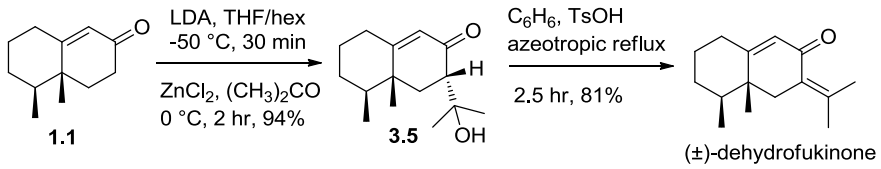
Scheme 3.3: Synthesis of dehydrofukinone by Torii et al.



Hagiwara (1980)

Hagiwara, Uda and Kodama[18] developed syntheses to five eremophilane sesquiterpenes which involved the aldol condensation of the kinetic enolate of intermediate **1.1** (using Piers, Britton & De Waal's synthesis of the enone) using the same strategy as Torii. The aldol product **3.5** was formed from the treatment of enone **1.1** with LDA and acetone in the presence of $ZnCl_2$ (which was found to be essential in obtaining high yields). Dehydration of **3.5** generated (±)-dehydrofukinone in an overall yield of 22% in eight steps (*scheme 3.4*).

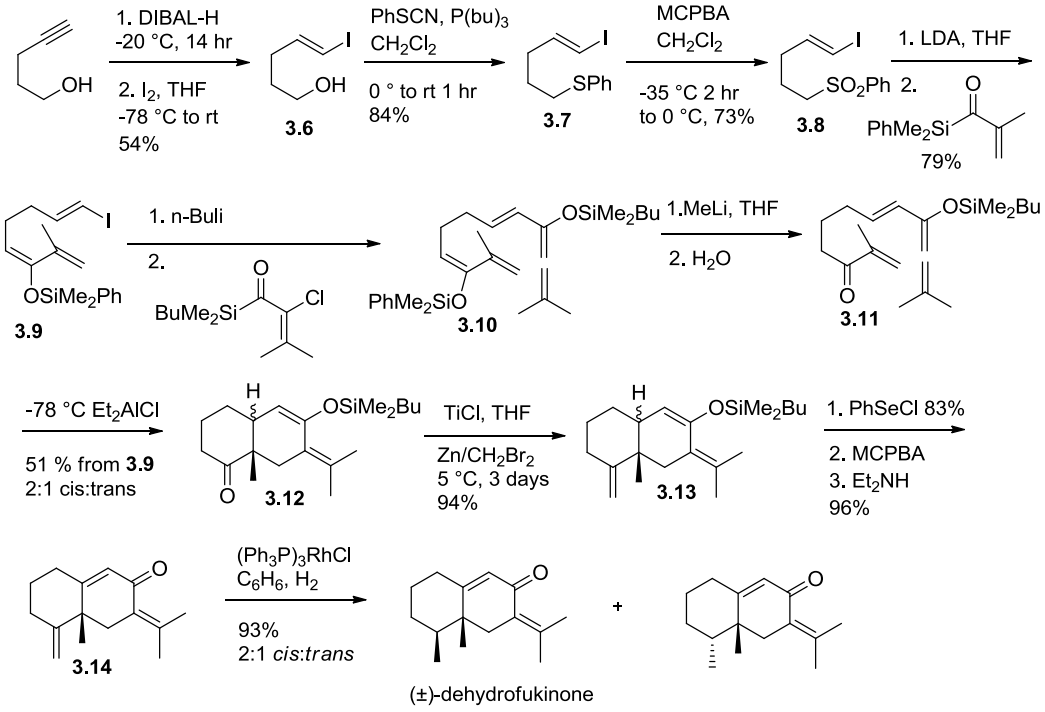
*Scheme 3.4: Hagiwara's procedure to (±)-dehydrofukinone from enone **1.1**.*



Reich (1986)

This synthesis by Reich *et al.*[19] was based on the intramolecular Diels-Alder reactions of siloxy vinylallenes. The key intermediate **3.11** was set up for a Diels-Alder cyclisation under Lewis acid catalysis with diethylaluminium chloride to form intermediate **3.12**. Methylenation followed by selenylation-selenoxide elimination gave intermediate **3.14** which was hydrogenated to give the desired product in a 2:1 *cis:trans* ratio. This 15 step synthesis afforded (±)-dehydrofukinone in an overall yield of 7% (*scheme 3.5*).

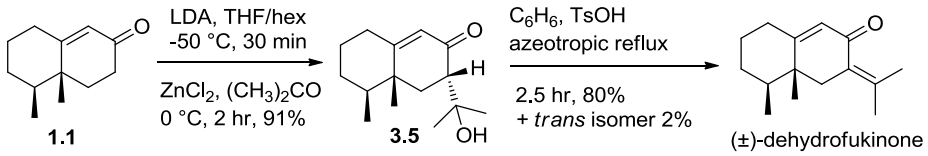
Scheme 3.5: Reich's synthesis of (±)-dehydrofukinone based on Diels-Alder reactions of siloxy vinyallenes.



Duhamel (1992)

Using their novel synthesis of enone **1.1**, Duhamel[20] then utilized Hagiwara's procedures to synthesise (±)-dehydrofukinone in 14% overall yield over seven steps with 2% of *trans* product as identified by ^{1}H NMR spectroscopy (*scheme 3.6*).

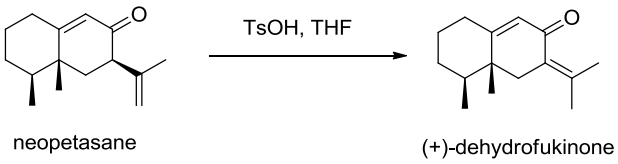
*Scheme 3.6: Duhamel's use of Hagiwara's procedures to form (±)-dehydrofukinone from their novel synthesis of enone **1.1**.*



Ishihara (1993)

(+)-Dehydrofukinone was synthesised in a one step acid catalysed isomerisation of neopetasane in order to establish the structure of this natural product (no yield was given; *scheme 3.7*).

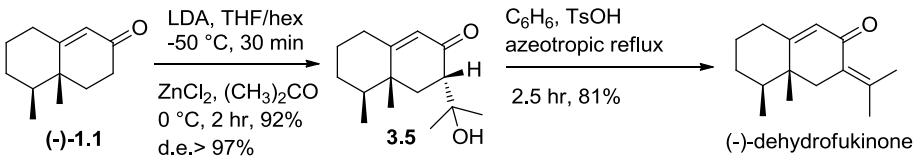
Scheme 3.7: Synthesis of (+)-dehydrofukinone from neopetasane



Tenius (2001)

Tenius *et al.*[21] used their novel route to enone *R*-(-)-**1.1** and Hagiwara's procedure to prepare (-)-dehydrofukinone in an overall yield of 12% in eight steps (*scheme 3.8*).

Scheme 3.8: Tenius's synthesis of (-)-dehydrofukinone



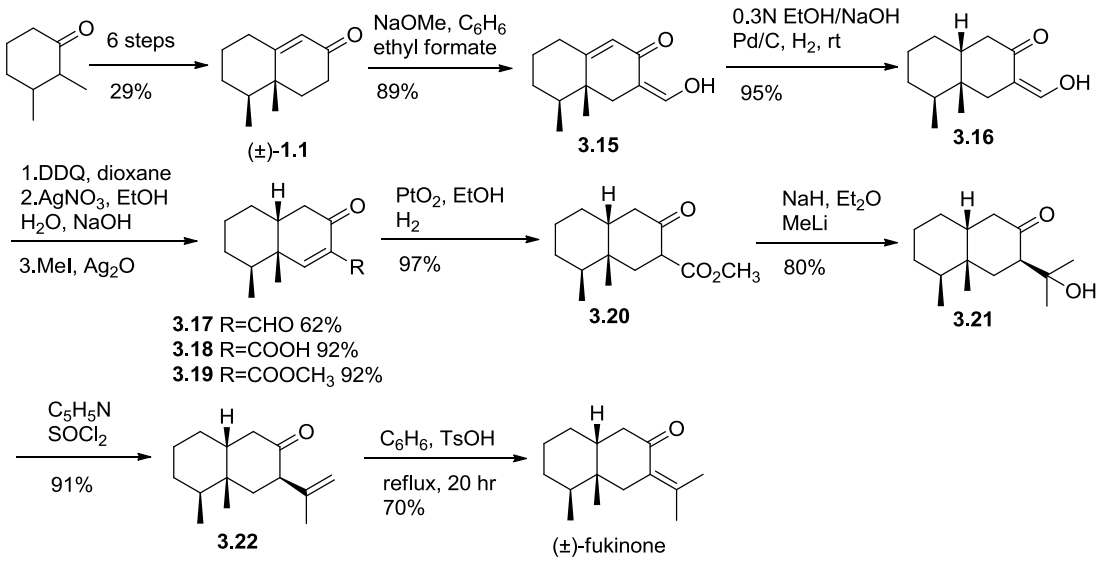
3.2.2. Previous syntheses of fukinone

There are six previous total syntheses reported for fukinone.

Piers & Smillie (1970)

The first approach to the total synthesis of fukinone was carried out by Piers and Smillie[22] who utilised their synthesis of enone **1.1** previously reported in 1969. The hydroxy methylene derivative **3.15** was hydrogenated to give the *cis*-decalin **3.16** which was oxidised with DDQ to afford the aldehyde **3.17** (*scheme 3.9*). Further oxidation with silver nitrate gave the acid **3.18** which underwent esterification **3.19** before hydrogenation to afford the keto ester **3.20**. The keto alcohol **3.21** was obtained after treatment with sodium hydride and trapping of this enolate with methyllithium. Although the stereochemistry of the alcohol was indicated as *cis* in their reaction scheme, Piers and Smillie did not provide an explanation for their reasoning nor did they provide any spectroscopic data. Alcohol **3.21** was used crude; it was treated with thionyl chloride which gave isofukinone which was converted to fukinone in refluxing benzene in the presence of *p*-toluenesulfonic acid. This 15 step synthesis afforded (±)-fukinone in an overall yield of 6%.

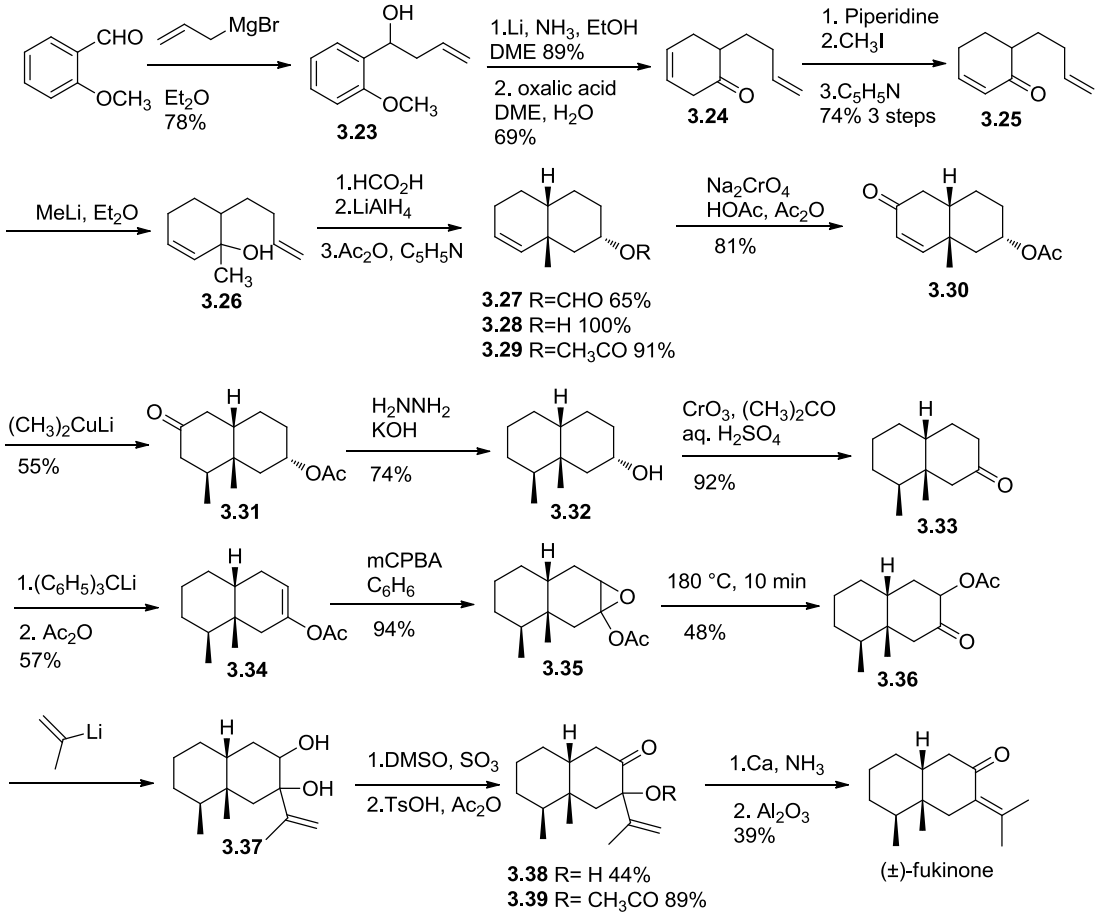
Scheme 3.9: Piers & Smillie's synthesis to (±)-fukinone.



Marshall & Cohen (1970-1971)

This novel strategy began with 2-methoxybenzaldehyde (*scheme 3.10*).[23] The key steps of this lengthy preparation included a Birch reduction of the benzylic alcohol **3.23**, an allyl-cation initiated alkene cyclisation to form **3.27** in which *cis* fusion of the rings was established from previous studies.[24] Conjugate methylation of compound **3.30** with lithium dimethylcuprate to give the *cis* product as a single stereoisomer, a Wolff-Kishner reduction followed by oxidation with Jones reagent afforded the intermediate **3.33**. Installation of the α-isopropylidene functionality began with the use of a bulky base to direct the desired enolate formation followed by acid catalysed enol acetylation to form **3.34**, thermal rearrangement of epoxide **3.35** afforded the acetoxy ketone **3.36**. Addition of isopropenyllithium, oxidation, acetylation and reduction to remove the acetoxy group followed by isomerisation afforded (±)-fukinone in 23 steps with a 0.2% overall yield.

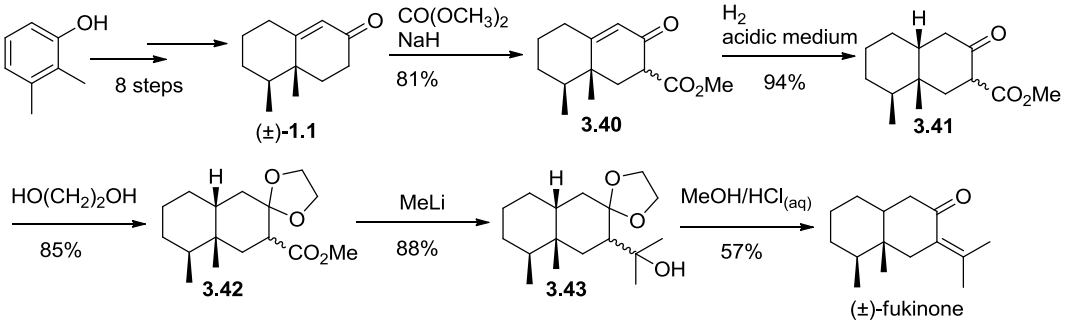
Scheme 3.10: Marshall & Cohen's synthesis to (±)-fukinone.



Torrence & Pinder (1971)

Utilising their novel synthesis to enone **1.1**, Torrence and Pinder[25] further elaborated this compound to install the required isopropylidene functionality for the synthesis of fukinone (*scheme 3.11*). Installation of the ester functionality afforded **3.40** which was hydrogenated in acidic medium (not specified which) to give the desired *cis* decalone **3.41** with apparently little evidence of the *trans* isomer. The ketone was protected prior to the addition of methylithium to form the carbinol **3.43**, which after hydrolysis and dehydration afforded (±)-fukinone in 13 steps. An overall yield could not be ascertained as an experimental was not published.

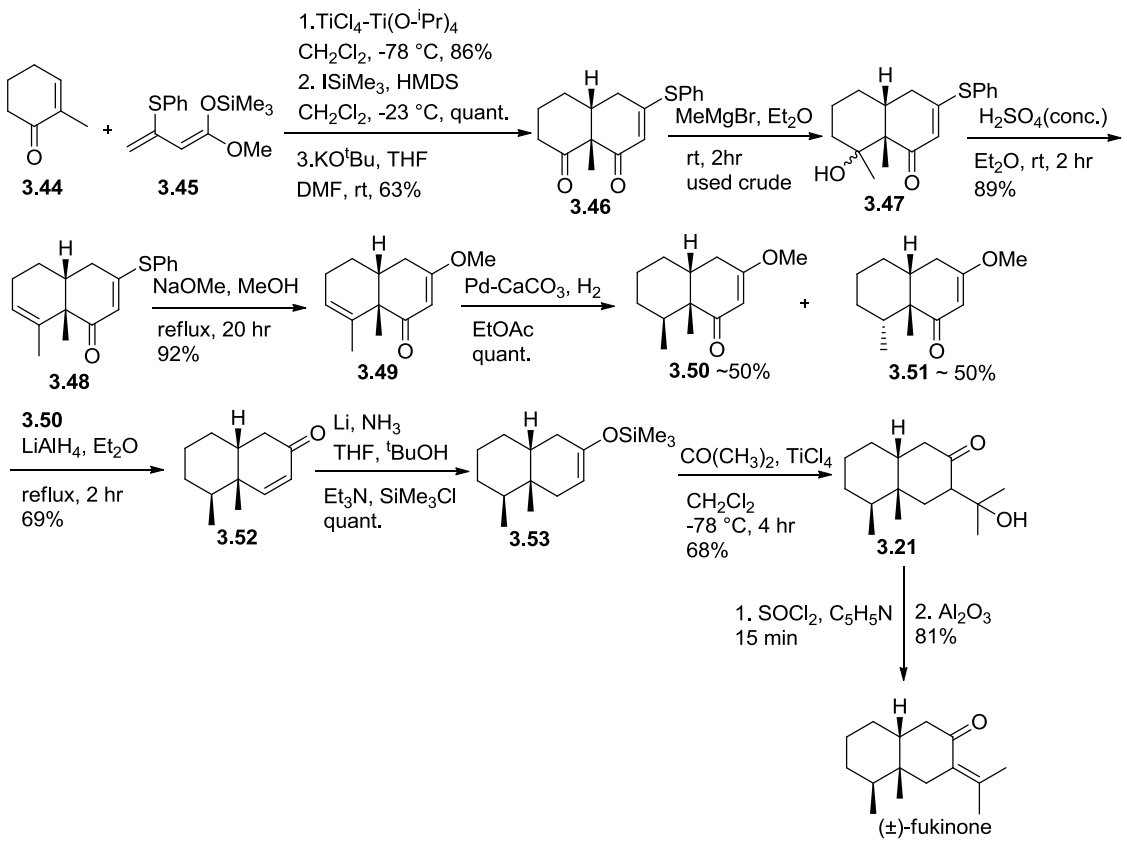
Scheme 3.11: Torrence & Pinder's synthesis to fukinone.



Chan & Prasad (1987)

Chan and Prasad's route to fukinone[26] was based on intermediate **3.46** which they had developed using a novel annulation reaction based on the Michael reaction of butadiene **3.45** with α,β-unsaturated ketone **3.44** under Lewis acid conditions. The *cis*-stereochemistry of **3.46** was selectively synthesised under these annulation conditions. Installation of the second methyl group was accomplished using methylmagnesium bromide **3.47** which was followed by dehydration to form compound **3.48**. A methoxy moiety replaced the sulphur group and the ensuing hydrogenation afforded the enones **3.50** and **3.51** in quantitative yield in a 1:1 ratio. After column chromatography, the desired *cis* epimer **3.50** was taken on and reduced followed by acid hydrolysis to form compound **3.52**. Treatment with Li-NH_3 generated the required enolate which was quenched with chlorotrimethylsilane to form **3.53**. This enol silyl ether underwent Mukaiyama Aldol addition with acetone in the presence of titanium chloride which gave the aldol **3.21**. As with Piers and Smillie's route, this was dehydrated and isomerised, using alumina oxide, to afford (±)-fukinone in 12 steps from 2-methyl-2-cyclohexenone with an overall yield of 8% (*scheme 3.12*).

Scheme 3.12: Chan & Prasad's route to (±)-fukinone.

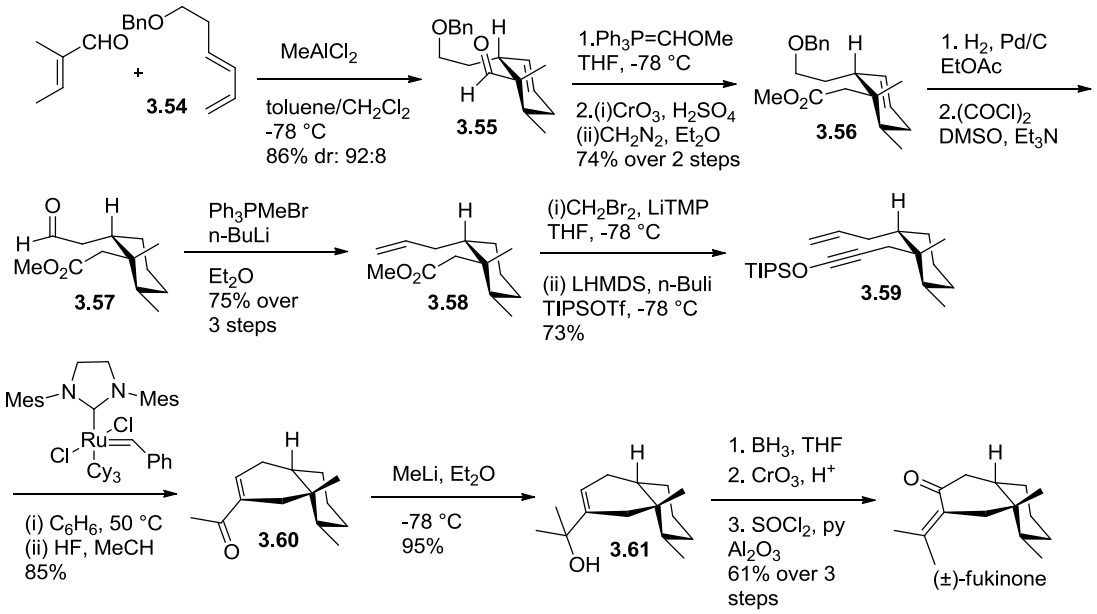


Kozmin (2004)

This approach to fukinone was based on siloxyalkyne-alkene metathesis chemistry which Kozmin and Reddy[27] had developed towards the synthesis of eremophilane type natural products (*scheme 3.13*). The key siloxy-alkyne intermediate **3.59** was synthesised from a route beginning with the diastereoselective endo-selective Diels-Alder reaction of commercially available *trans*-2-methly-2-butenal and diene **3.54** to furnish the aldehyde **3.55**. Subsequent conversion of the aldehyde to the ester **3.56** allowed for the hydrogenation of the alkene as well as the benzyl protecting group, followed by oxidation of the alcohol gave compound **3.57**. A Wittig reaction was used to convert the aldehyde using triphenylphosphonium methyl bromide to the require alkene **3.58**. Installation of the siloxyalkyne moiety was achieved via the dibromomethyl ketone which was subjected to LHMDS and n-BuLi to install the alkyne which was silylated to afford the intermediate **3.59**. Ring closing metathesis was affected by the use of Grubbs ruthenium catalyst followed by removal of the protecting group using HF to give the enone **3.60**. This intermediate was used to synthesise several eremophilane natural

products including fukinone. 1,2-Addition of methyllithium to compound **3.60** gave the alcohol **3.61** which underwent hydroboration, Jones oxidation and dehydration to afford (±)-fukinone. The overall yield and total number of steps could not be calculated as no information was published relating to the synthesis of the starting diene **3.54**.

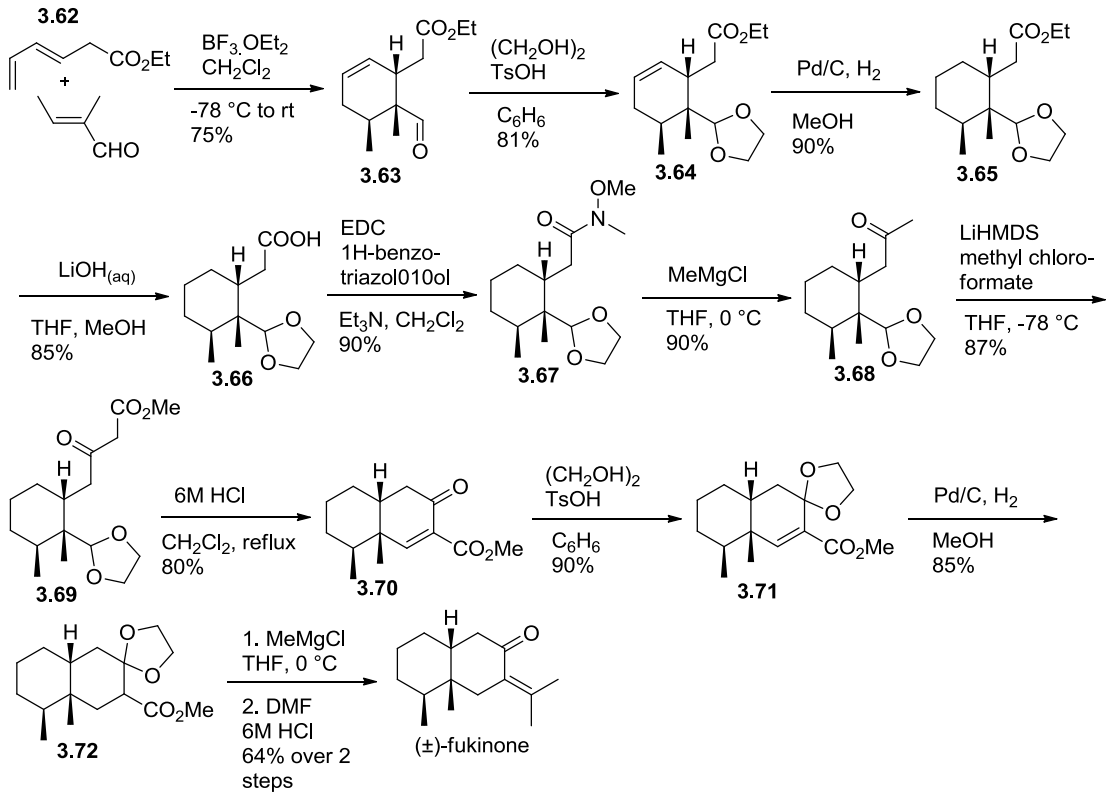
Scheme 3.13: Kozmin & Reddy's route to fukinone.



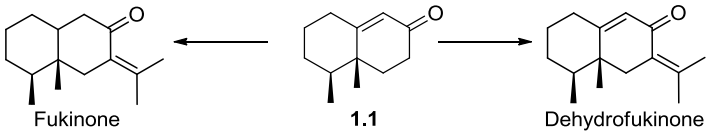
Das (2009)

Reddy also worked on this most recent synthesis of fukinone in Das's group.[28] This synthesis started with a stereoselective Diels-Alder reaction similar to the previous synthesis with the exception that carboxylic ester diene **3.62** was used as an alternative to the benzyl diene **3.54** (*scheme 3.14*). Elongation of the carbon chain was achieved via hydrolysis of the ester to form the acid **3.66** which was coupled with *N,O*-dimethylhydroxylamine hydrochloride to afford the Weinreb amide **3.67** and addition of a Grignard gave the methyl ketone **3.68**. Deprotonation with LiHMDS and subsequent addition of methylchloroformate afforded the desired chain length in **3.69** which underwent an acid mediated aldol condensation to form the bicylic intermediate **3.70**. Protection of the carbonyl followed by hydrogenation to remove the double bond formed compound **3.72** which was reacted with four equivalents of methylmagnesium bromide, followed by treatment with 6M hydrochloric acid afforded (±)-fukinone. Once again, the overall yield and total number of steps could not be calculated as no information was published relating to the synthesis of the starting diene **3.62**.

Scheme 3.14: Das et al.'s route to fukinone.



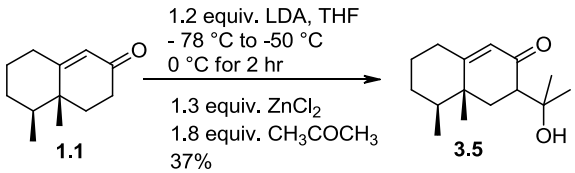
3.3. Synthesis of dehydrofukinone



Fukinone and dehydrofukinone can easily be accessed from intermediate **1.1** as previous syntheses have shown, although their route to compound **1.1** differed to ours.[17,18,20,21,25] The vital intermediate to these natural products was identified as the aldol compound **3.5** which after dehydration would afford dehydrofukinone. The aldol condensation of compound **1.1** to form intermediate **3.5** was investigated.

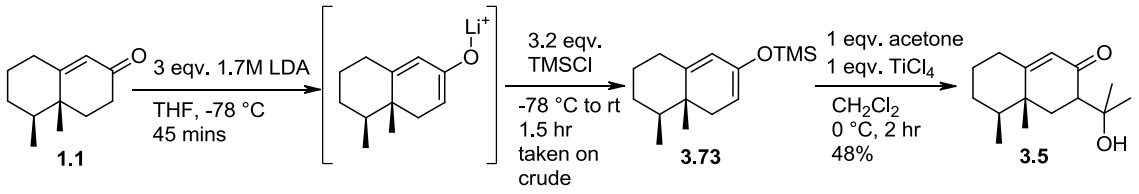
Utilising Hagiwara's[18] conditions of LDA in THF at -50 °C, followed by the addition of the Lewis acid $ZnCl_2$ and freshly distilled acetone, intermediate **3.5** was formed in a 37% yield (*scheme 3.15*). It was observed that yields decreased with time which could be due to the ageing bottle of $ZnCl_2$ in THF. The yield did not improve when freshly prepared LDA was used although it was later noted that an improved method of forming LDA would be to stir the n-BuLi and DIPEA at 0 °C for half an hour instead of at -78 °C. This could have attributed to the lower yields of compound **3.5**. Only one diastereoisomer of compound **3.5** was observed by ^{1}H NMR spectroscopy. It was proposed that the isopropyl group would be *trans* relative to the methyl groups due to steric considerations although this was not formally determined as the following step would be dehydration which would remove that particular stereocentre. Data obtained for this intermediate corresponded to previously reported values.[17]

*Scheme 3.15: Formation of intermediate **3.5** from compound **1.1** via an aldol condensation reaction using Hagiwara's conditions.*



An alternative method was developed which involved trapping the lithium enolate with TMSCl for a more stable intermediate before reacting with an alternative Lewis acid titanium tetrachloride and acetone (*scheme 3.16*).[29]

*Scheme 3.16: Alternative method to the formation of compound **3.5**.*

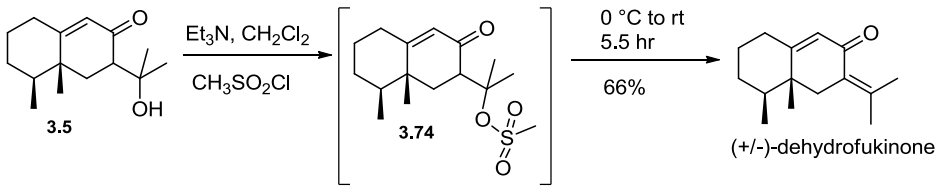


Formation of compound **3.73** was based on a procedure used to form the silyl enol ether of the Wieland-Miescher ketone,[30] and this was taken onto the next step without purification. An additional olefinic proton as well as a singlet corresponding to 9H of the TMS group was observed in the crude ^{1}H NMR spectra. The following aldol reaction using the silyl enol ether compound **3.73** and acetone which was activated by titanium tetrachloride. Yields of up to 48% were obtained which was an improvement to the previous aldol procedure.

Dehydration of the aldol product **3.5** to afford dehydrofukinone was initially carried out using microwave dried molecular sieves and camphorsulfonic acid as a miniature Dean-stark apparatus suitable for test reactions on a small scale was not available. This method did form dehydrofukinone but the yield obtained was found to be moderate at 30%.

An improved method was found through mesylation of the alcohol to form a better leaving group, although the mesylate **3.74** was not isolated, before eliminating in the presence of excess base. This afforded (±)-dehydrofukinone in increased yields of 66% (*scheme 3.17*).

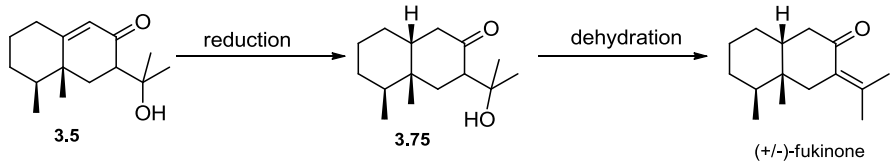
Scheme 3.17: Formation of(±)*-dehydrofukinone from aldol product **3.5***



3.4. Synthesis of fukinone

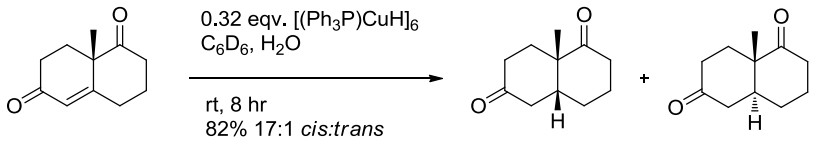
The synthesis of fukinone could also be readily accomplished from intermediate **3.5**, with the addition of a reduction step prior to dehydration (*scheme 3.18*). The challenge was in the selective reduction of the α,β-unsaturated ketone to give only the desired *cis* isomer therefore a variety of conditions were investigated.

Scheme 3.18: Route to (±)-fukinone



There have been several examples of bicyclic enone systems which have been selectively reduced to give the desired *cis* isomer as the major product. For example, the Wieland-Miescher ketone was reduced using Stryker's reagent to give 17:1 *cis*:*trans* ratio in 82% yield[31] (*scheme 3.19*).

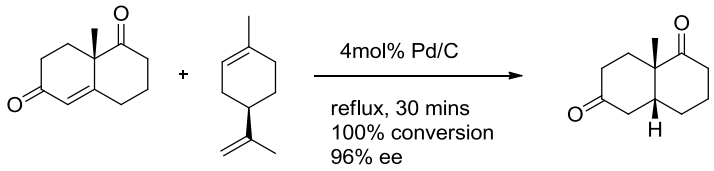
Scheme 3.19: Reduction of Wieland-Miescher ketone with Stryker's reagent



Stryker's reagent $[(Ph_3P)CuH]_6$ is a mild hydride source shown to be effective in the chemoselective reduction of conjugate systems such as α,β-unsaturated ketones. However, no reaction was observed when these conditions were carried out on compound **3.5** (*table 3.1*). Modifications of these conditions later report the use of silanes to facilitate the 1,4-hydride addition,[32] however this also gave no reaction with only starting material obtained after prolonged periods.

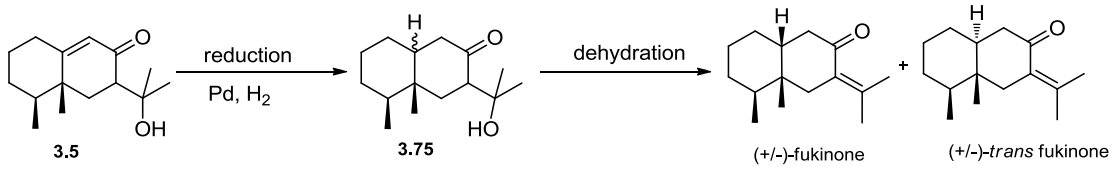
The use of palladium catalysts were then investigated. (*R*)-(+)-Limonene has been used as a source of hydrogen in the presence of Pd/C to afford excellent selectivity for the *cis* isomer in the reduction of Wieland-Miescher ketone (*scheme 3.20*).[33] However, once again, these conditions resulted only in starting material despite prolonged heating.

Scheme 3.20: Reduction of Wieland-Miescher ketone with limonene



It was the simple hydrogenation conditions of Pd/C or Pd/$CaCO_3$ under H_2 atmosphere that resulted in the desired reduced product **3.75**. Literature conditions using palladium in various solvents on bicyclic enones giving a majority of the *cis* isomer were tested (entry 4-10 of table 3.1). A clear ratio of *cis*/*trans* products obtained after the reduction could not be ascertained due to their inseparable nature and the complex ^{1}H NMR spectra obtained, but the presence of the desired product was confirmed by the loss of the alkene proton and the correct mass observed in LCMS. This crude material was taken on for dehydration to give the natural product fukinone as the minor product in a mixture of two compounds (*scheme 3.21*).

*Scheme 3.21: Synthesis of (±)-fukinone from intermediate **3.5***



Changing the reduction conditions resulted in varying ratios of isomers but fukinone was found to be the minor product in each case. The other isomer obtained along with fukinone was proposed to be the *trans* diastereoisomer obtained as a result of the reduction. Despite traditional column chromatography as well as reverse phase HPLC (CH_3CN/H_2O) the two isomers could not be separated (seen as a single peak). Only the correct mass for the desired product was observed by LCMS. It should be noted that fukinone, and its isomer, is prone to autoxidation[34] so prolonged purification attempts lead to decomposition of material. Decomposition of material was also observed after storage of material at 4 °C over time.

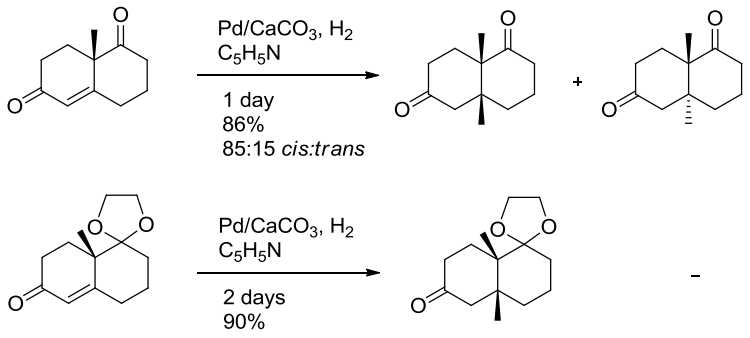
The dehydration conditions did not greatly affect the ratio of product or yield obtained. The optimum conditions were found to be reduction with Pd/C in ethanol followed by dehydration via the mesylate to give 53% of products in a 1:3 ratio (entry 10 of *table 3.1*).

*Table 3.1: Synthesis of fukinone from intermediate **3.5**.*

Entry	**Reduction conditions**	**Dehydration conditions**	**Result** % over 2 steps (fukinone:other)
1	32 mol% Stryker's reagent, benzene, H_2O, rt, 72 hr[31]	-	No reaction
2	5 mol% Stryker's reagent, $PhSiH_3$, toluene, 72 hr[32]	-	No reaction
3	Pd/C, (R)+limonene, reflux, 18 hr[33]	-	No reaction
4	Pd/C, H_2, 95 % ethanolic NaOH, rt, 22 hr[22]	-	Decomposition
5	Pd/C, H_2, EtOAc, rt, 48 hr	CsOH, benzene, mol. sieves, reflux 6hr	39% (1:5)
6	Pd/C, H_2, MeOH, rt, 20 hr[35]	Et_3N, CH_3SO_2Cl, CH_2Cl_2, 0°C to rt o/n	40% (1:4)
7	Pd/$CaCO_3$, H_2, py, rt, 72 hr[36]	Et_3N, CH_3SO_2Cl, CH_2Cl_2, 0°C to rt 6hr	47% (1:3)
8	Pd/$CaCO_3$, H_2, py, rt, 72 hr	$SOCl_2$, pyridine then alumina	50% (1:3)
9	Pd/C, H_2, EtOH, rt, 16 hr[30]	$SOCl_2$, pyridine then alumina	45% (1:3)
10	Pd/C, H_2, EtOH, rt, 16 hr	Et_3N, CH_3SO_2Cl, CH_2Cl_2, 0°C to rt 6hr	53% (1:3)

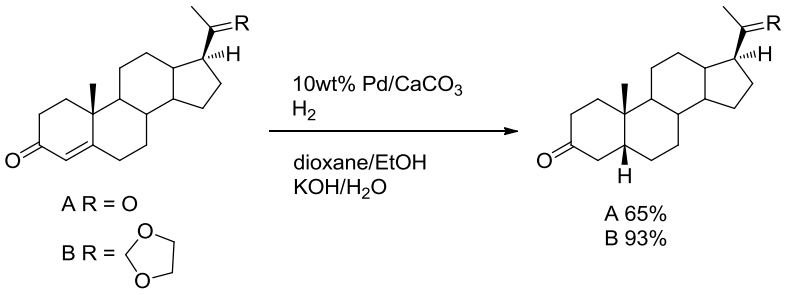
There have been reports that illustrate the sensitivity of reactions to changes in functional groups on the molecule of the decalin structure. For example, in the hydrogenation of the Wieland-Miescher ketone, a 85:15 *cis:trans* isomer ratio was observed;[36] however, when the C-9 ketone was protected with the dioxolane group, the *cis* isomer was formed exclusively (*scheme 3.22*).

Scheme 3.22: Hydrogenation of Wieland-Miescher ketone & analogue



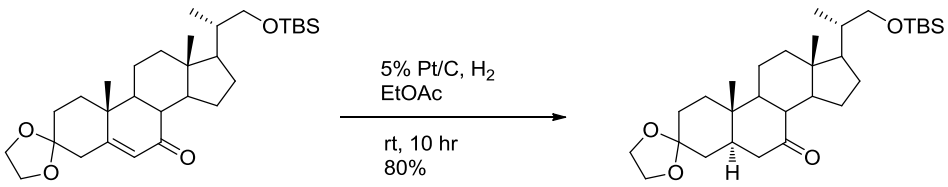
It is interesting to observe that the reduction of progesterone by Capitaine & Engel[37] with $Pd/CaCO_3$ gave a higher stereoselectivity when the non participating carbonyl was protected with a diol even though it is not close to the enone undergoing reduction (*scheme 3.23*).

Scheme 3.23: Reduction of progesterone by Capitaine & Engel.



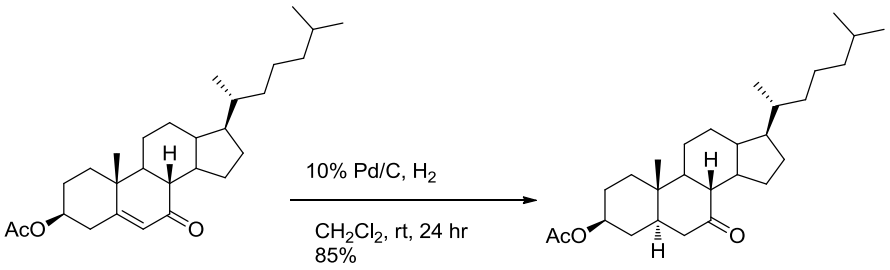
Yet, with a compound towards the synthesis of an analogue of squalamine, where there is a ketal present much closer to the reacting enone, the *trans* isomer is preferred (*scheme 3.24*).[38]

Scheme 3.24: Reduction of a compound synthesised enroute to the synthesis of a squalamine analogue.



Despite there being less steric hindrance with the reduction of a ketocholesteryl acetate,[39] the *trans* isomer was still predominantly formed in the presence of Pd/C in CH_2Cl_2 (*scheme 3.25*).

Scheme 3.25: Reduction of a ketocholesteryl acetate.

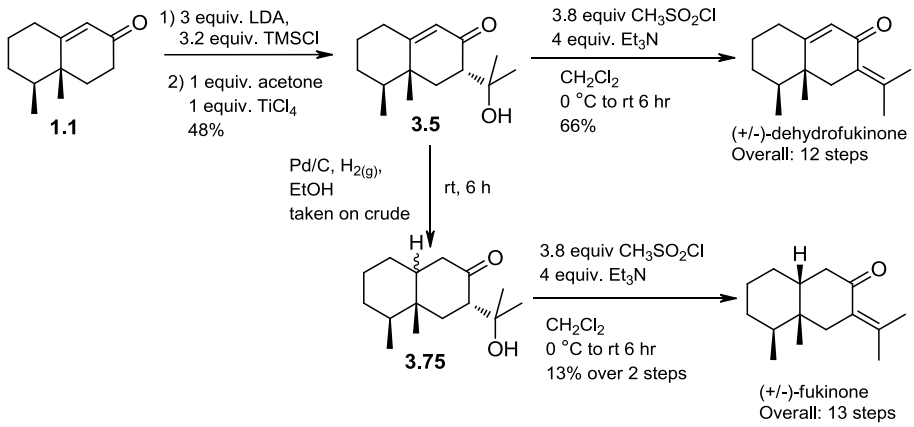


These literature results have shown that different bicyclic systems will give different ratios of *cis:trans* isomers when reduced and that no single condition will give the same result for all systems. The electronics, conformation and sterics of a system greatly affects the ratio outcome as well as the type of catalyst and solvent used, so a more thorough screening is required to obtain selective *cis* formation of our particular system to give *cis* **3.75**.

3.5. Conclusion to chapter 3

Although dehydrofukinone and fukinone have been previously synthesised, ours is a different fully synthetic route with a comparable number of steps and yield (*scheme 3.26*). This divergent pathway allowed us to synthesise two natural products from intermediate **1.1** in a quick and simple manner.

*Scheme 3.26: Synthesis of dehydrofukinone and fukinone from intermediate **1.1**.*

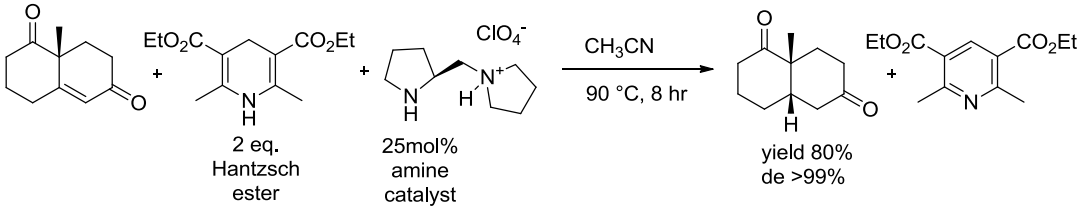


Dehydrofukinone was synthesised with an overall yield of 17% in 12 steps and fukinone was synthesised with an overall yield of 4% in 13 steps. Duhamel reported the shortest route to (±)-dehydrofukinone 14% overall in 7 steps. Tenius achieved the shortest stereospecific synthesis of the enantiomer of the natural product dehydrofukinone in 12 % yield over 8 steps. Chan & Prasad synthesised (±)-fukinone in the shortest route 12 steps from 2-methyl-2-cyclohexenone with the highest overall yield of 8%. There has not been a stereoselective synthesis of fukinone published so its absolute stereochemistry has yet to be determined.

The synthetic route was not optimised due to time restraints. There are several opportunities for improvements to the reaction conditions but as this was not the main goal of this project, we decided to refocus our attention onto the total synthesis of nominine.

As the use of palladium catalysts appears to form the *trans* isomer preferentially in the reduction of compound **3.5**, an example of further work would be to screen stereoselective reduction conditions for the synthesis of compound **3.75** to ensure the *cis* stereocentre at the ring junction is formed for the natural product fukinone. Organocatalysis using chiral amines and Hantzsch esters as the hydride source has been shown to regioselectively and stereoselectively reduce Wieland-Miescher ketone analogues in good yield (*scheme 3.27*).[40]

Scheme 3.27: Reduction of Wieland-Miescher ketone using organocatalysis.



The use of enantioselective chromatography using chiral columns could also give better separation of the isomers formed.

3.6. References for Chapter 3.

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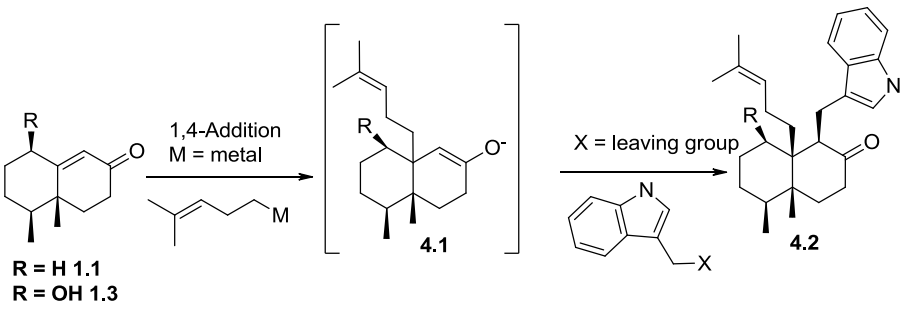
Chapter 4. Studies towards total synthesis of nominine

4.1. 1,4-Addition reactions.

The key step in the proposed synthetic route to nominine involves the regioselective 1,4-addition of the alkene moiety to the bicyclic intermediate enone **1.3** (or enone **1.1**), followed by trapping of the enolate with the halogenated indole moiety while ensuring that *cis* stereochemistry is achieved.

Scheme 4.1: Proposed 1,4-addition: key step to synthesis of nominine

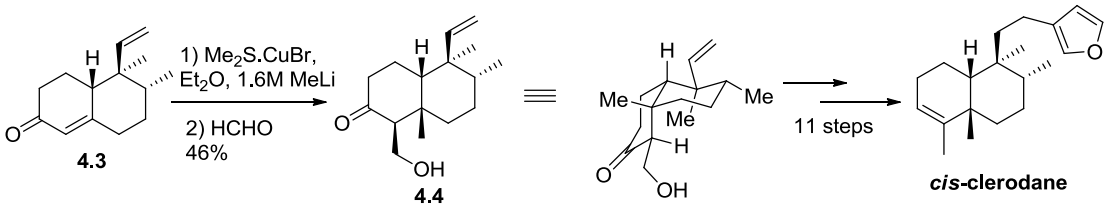


This vicinal difunctionalisation would involve the initial Michael addition of the alkyl metal (most commonly cuprate) nucleophile to a Michael acceptor (enone **1.3** or enone **1.1**) which would cause the β-carbon to be substituted with the alkyl group. The resulting nucleophilic α-carbon is now enolate **4.1** which could then be trapped with the indole halide electrophile to give compound **4.2** (*scheme 4.1*).

It was proposed that the 1,4-addition would occur in a *cis* fashion due to the conformation of bicyclic enone **1.1** in which addition on the convex face would be preferred due to less steric hindrance. The hydroxyl group in enone **1.3** could aid in the *cis* addition of the alkyl nucleophile by acting as a directing group and coordinating with it. Literature precedence

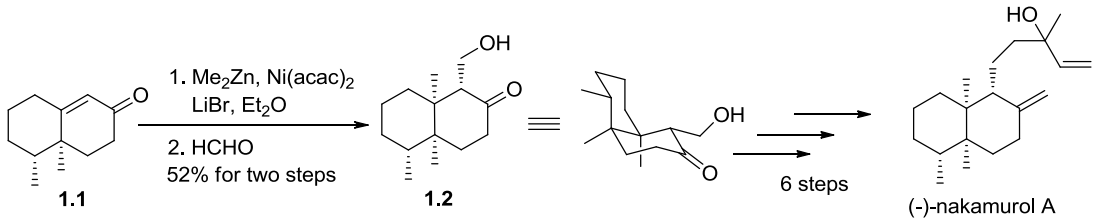
supports this proposal in which Tokoroyama *et al.*[1] utilised vicinal difunctionalisation of decalins to give the desired *cis* stereochemistry enroute to their synthesis of natural *cis*-clerodane diterpenoids (*scheme 4.2*). Conjugate addition of dimethyl lithium in ether to intermediate **4.3** followed by trapping of the enolate with formaldehyde gave the difunctionalised decalin **4.4** as a single diastereoisomer. The stereochemistry was confirmed by conformational analysis and comparison with similar compounds.

Scheme 4.2: Tokoroyama's synthesis of cis-clerodane utilising vicinal difunctionalisation



Bonjoch *et al.*[2] also utilised this method in their total synthesis of (-)-nakamurol A (*scheme 4.3*) although they modified the conjugate addition procedure in which Me_2Zn and a $Ni(acac)_2$ complex were used instead of $Me_2CuLi.MeS$.

Scheme 4.3: Initial steps in the synthesis of (-)-nakamurol A by Bonjoch et al.

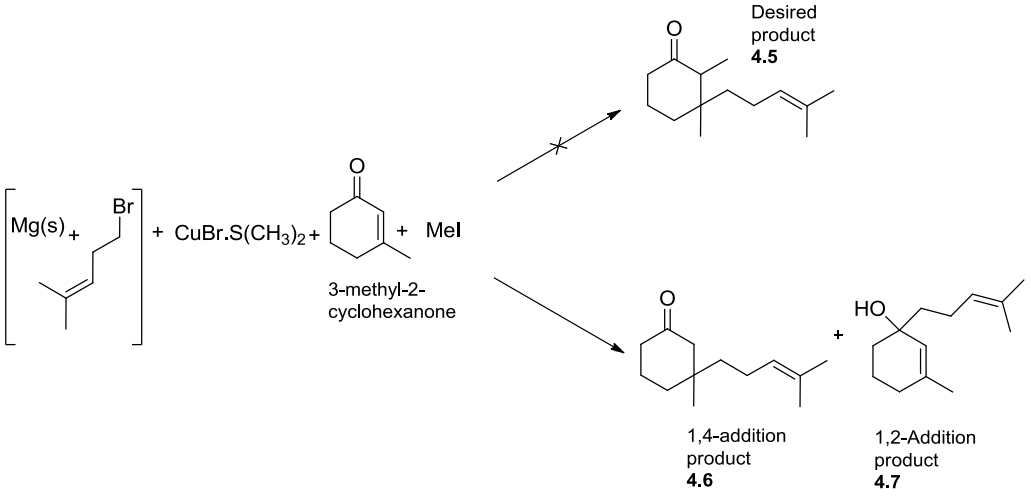


4.1.1. Model studies using 3-methyl-cyclohexenone and Grignard reagents: Trapping enolate with MeI

The traditional method of 1,4-additions using catalytic amounts of copper was first investigated. Kharasch and Tawney first showed in 1941[3] that selective 1,4-addition occurred when a Grignard and an α,β-unsaturated carbonyl were combined in the presence of catalytic CuCl. Test reactions were carried out to determine the success of this crucial step using MeI as a substitute for the indole moiety as it had not yet been synthesised as well as the fact that MeI is an excellent electrophile. The test system used was 3-methyl-2-cyclohexenone as it was readily available and has a fair resemblance to the actual intermediate to be used.

The initial procedure was based on a synthetic route by Williams *et al.*[4] with the exception that Williams *et al*. quenched the enolate instead of trapping it with another reactant. The alkenyl cuprate used was synthesised *in situ* from the brominated alkene, which was purchased relatively inexpensively, in a metal exchange reaction from the Grignard compound.

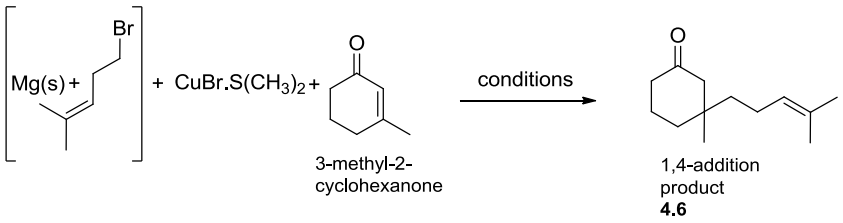
Scheme 4.4: Modified 1,4-addition test reactions



Reaction conditions were varied however the MeI failed to trap the enolate and no compound **4.5** was observed (*scheme 4.4*). After optimisation only compound **4.6** was isolated as well as trace amounts of the 1,2-addition reaction product **4.7**.

Despite this finding, the experiments carried out (*table 4.1*) have resulted in an increase of yield of the 1,4-addition step from 22% to 91%. It was discovered that doubling reaction times, 2 equivalents of Grignard reagent and only 10 mol% of the $CuBr.S(CH_3)_2$ reagent gave the highest yield (literature yield reported 85%). Any larger amount and the yield decreased accordingly as the cuprate and Grignard coupled together. Changing the electrophile to benzylbromide to trap the enolate also failed to give the desired product.

Table 4.1: Varying conditions for 1,4-addition reaction using test enone



Entry	Conditions	Yield of compound 4.6 %
1	Literature method* + 1.05 equiv MeI	22
2	Double reaction times after Grignard formation + 1.05 equiv MeI	23
3	2 equiv Grignard + 10 mol % Cu reagent and double reaction times + 2 equiv MeI	91
4	2 equiv Grignard + 2.1 equiv Cu reagent and double reaction times + 2 equiv MeI	12
5	2 equiv Grignard + 30 mol% Cu reagent and double reaction times + 2 equiv MeI	84
6	Repeat exp. **3** + 4 equiv MeI	No product**
7	Repeat exp. **3** + 4 equiv benzylbromide	No product**

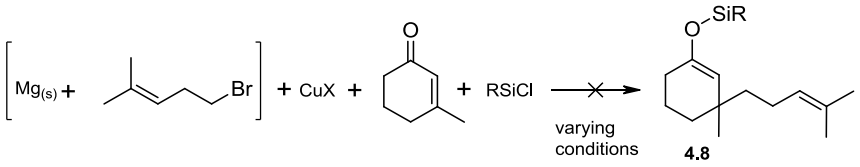
* Literature method: 1.05 equiv Grignard + 5 mol% $CuBr.S(CH_3)_2$ for ½ hr at ⁻20°c, add 1 equiv enone and stir 15 mins at -20 °C then warm to room temperature.

** Crude NMR spectroscopy and mass spectrometry indicated no desired product present so crude was not purified.

4.1.2. Model studies using 3-methyl-cyclohexenone and Grignard reagents: Trapping enolate with TBDMSCl/TMSCl

Difficulties have been encountered with conjugate additions of organocopper reagents with bulky groups or when there is steric hindrance at the reaction centre of the enone. To overcome this, addition of alkylsilanes is added to accelerate the conjugate additions by activating the carbonyl group.[5] As trapping of the enolate with MeI failed to succeed, it was thought that the enolate should be trapped with a more reactive species such as TBDMSCl or TMSCl. Alkylsilanes have a high affinity for oxygen therefore addition of TBDMSCl or TMSCl would alkylate the oxygen to form a more stable compound (silyl enol ether **4.8**) that can be isolated before reacting with an indole moiety. Several procedures were investigated (*table 4.2*).[6] Despite the varying conditions only starting materials were obtained for most, indicating that neither the 1,4-addition reaction was occurring nor the trapping of the enolate. Only the 1,4-addition product **4.6** was obtained with the previously described procedure when MeI was present (entry 4).

Table 4.2: Model compound reactions with Grignard reagents followed by trapping of enolate with silyl compounds



Entry	Conditions	Result
1	3.2 equiv Mg, 2.1 equiv. bromo-2-methyl-2-pentene, 10mol% $CuBr.S(CH_3)_2$ at -20 °C. At 0 °C add TBDMSCl, Et_3N, HMPA,	SM
2	5.6 equiv Mg, 1.1 equiv. bromo-2-methyl-2-pentene, 53mol% CuI	SM
3	Repeat of exp. **2** with extra-dried CuI and more concentrated solution	SM
4	3.2 equiv Mg, 2.1 equiv. bromo-2-methyl-2-pentene, 10mol% $CuBr.S(CH_3)_2$, 4 equiv. MeI	44% compound **4.6**
5	3.2 equiv Mg, 2.1 equiv. bromo-2-methyl-2-pentene, 10mol% $CuBr.S(CH_3)_2$ at -78 °C was added HMPA, then TBDMSCl with enone. 30 min at -40 °C followed by Et_3N.	SM
6	2.1 equiv. Grignard, 5mol% $CuBr.S(CH_3)_2$ at -78 °C, then HMPA, TMSCl and enone added together followed by addition of Et_3N at -40 °C.	SM

The formation of the quaternary carbon appears to require specific conditions and in this case, trapping of the enolate failed, possibly due to the steric hindrance of the alkyl chain that was added in the 1,4-addition.

Suzuki and Noyori[6] do mention the difficulty of alkylation of ketone enolates in cyclohexanone enolates and ascribe this to "proton exchange between the enolates and alkylated products leading to polyalkylation or other side reactions". HMPA is often added to the reaction medium in an attempt to solve this problem by creating a more polar medium. However this appeared to have no effect on the reactions carried out with only starting materials observed.

4.1.3. Model studies using 3-methyl-cyclohexenone and Gilman's reagents.

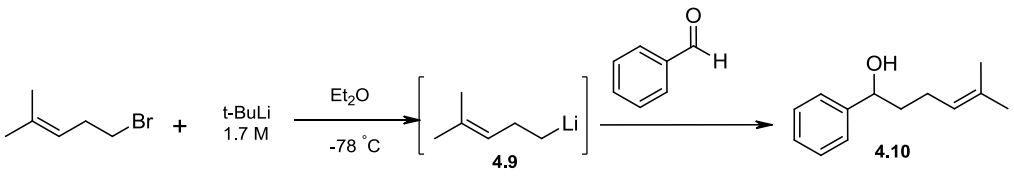
As the use of Grignard reagents failed to afford the desired product, the Gilman's reagents were then investigated. Several procedures describe the use of stoichiometric amounts of organocopper reagents known as Gilman's reagents (R_2CuLi), in a conjugate addition on similar compounds followed by trapping of the enolate with improved yields and regioselectivity compared to catalytic copper procedures. These compounds are prepared by the reaction of organolithium reagents (RLi) with copper(I) halides (CuX).

$$2\ RLi + CuX \longrightarrow R_2CuLi + LiX$$

The initially formed $(RCu)_n$ are polymeric and insoluble in Et_2O and THF but dissolve on addition of a second equivalent of RLi or RMgX. The resulting lower order organocuprates are thermally labile and therefore need to be prepared at low temperatures.

The first task was to synthesise 4-methyl-3-pentenyllithium **4.9**, from bromo-2-methyl-2-pentene, as it was not commercially available. Several procedures were carried out and reacted with benzaldehyde to confirm its success. Only two procedures were successful in forming compound **4.10**. The first[7] using lithium metal in Et_2O at -20 °C and 1,2-dibromoethane to initiate the reaction, gave only 8% product. The second[8] utilised tert-butyl lithium 1.5M in Et_2O at -78 °C and gave 44% product **4.10** (*scheme 4.5*). No product was observed with n-BuLi.

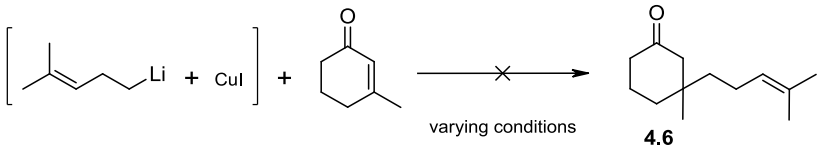
*Scheme 4.5: Confirmation of the formation of 4-methyl-3-pentenyllithium **4.9** by trapping with benzaldehyde*



Compound **4.9** was added to a suspension of CuI in Et_2O at 0 °C and then added to the model compound, warming to room temperature over two hours.[6] However, only starting material was detected. Subsequent reactions using further purified CuI and then a new bottle of 99.9 %

CuI, dried on the high-vac line for 24 hours gave no improvement to the reaction (*scheme 4.6*). Addition of di-n-butyl sulfide (twice the number of equivalents compared to CuI) was also added to aid solubility of the copper salt but this had no effect.

Scheme 4.6: Reaction of model compound with Gilmans reagent



If transmetallation with CuI did not occur, compound **4.9** could still react in a 1,2-addition but since no reaction is seen at all, it was deduced that the enone is not very active. It was also thought that any water present, in solvent or reagents would immediately quench compound **4.9** so every step was taken to ensure an anhydrous reaction.

The Lewis acid 10 mol% of $BF_3.OEt_2$ was chosen to activate the enone.[9] However, only starting materials were recovered. CuI was dissolved in di-n-butyl sulphide to increase its solubility and varying temperatures were tested, however no reaction occurred.

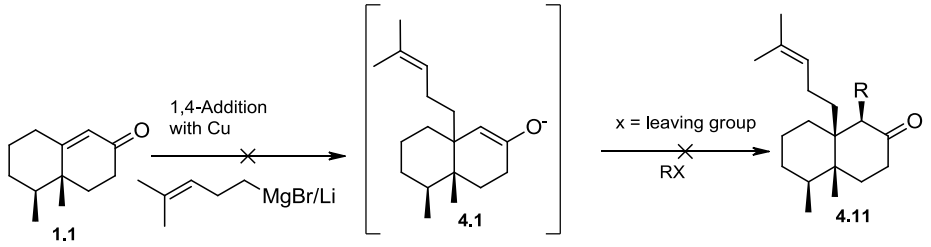
With compound **4.9** and the test enone, addition of TMSCl or even TBDMSCl/HMPA, no effect was found on the reaction. It was concluded that the reaction of compound **4.9** with this particular model system is particularly challenging.

It was also proposed that the failure of these 1,4-addition-alkylation reactions could have been due to the purity of the reagents. HMPA is often freshly distilled before use, however this process has been recently discouraged due to the hazards involved. While the TBDMSCl and TMSCl were obtained from commercial sources, they were used without further purification as the bottles were newly acquired.

4.1.4. Investigations of 1,4-addition reactions with enone 1.1

Despite the lack of success with the model compound, it was decided to carry out 1,4-addition-alkylation investigations on the actual enone **1.1** as it was thought that this system could react differently to the model (*scheme 4.7*). At this point in the investigations, there was an abundance of enone **1.1** from the large scale synthesis that was carried out. Enone **1.1** was investigated with both Grignard as well as Gilman reagents for the 1,4-addition.

*Scheme 4.7: Proposed 1,4-addition-alkylation reaction of enone **1.1**.*

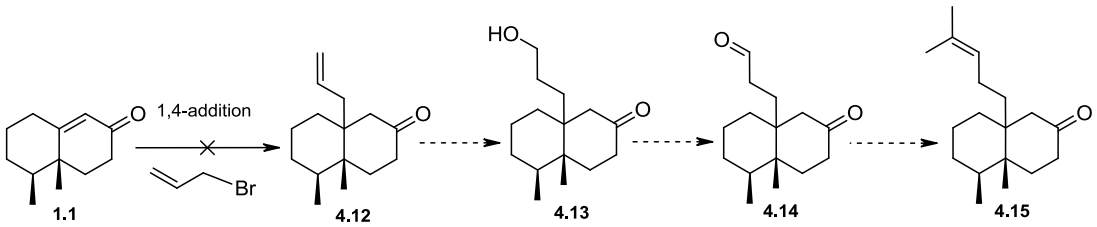


The reaction of enone **1.1** with Gilman reagent gave no reaction, despite the addition of Lewis acids to activate the carbonyl (such as $BF_3.OEt_2$, $AlCl_3$) or even the addition of tributylphosphine which was reported to be essential in the 1,4-addition of Gilman's reagents to sterically hindered enolates such as neopentylether-shielded *trans*-enolates.[10] Large excess of the reagents were used in both THF and Et_2O but no reaction occurred.

As the 1,4-addition with the Grignard reagent was found to be successful for the model compound, this procedure was carried out on enone **1.1**, however it was found that it was not suitable for this system as no product was obtained. The model compound is a flat system whereas enone **1.1** comprises of two rings which would be in a chair formation, creating more steric hindrance at the site of attack. Despite the addition of TMSCl and HMPA, or $BF_3.OEt_2$ to activate the enone,[9] or excesses of the Grignard and $CuBr.S(CH_3)_2$, only starting materials were obtained.

Due to the lack of positive results with bromo-2-methyl-2-pentene, it was thought that a smaller and more reactive species (allylbromide) could be used for the 1,4-addition and then converted to the desired moiety (*scheme 4.8*).

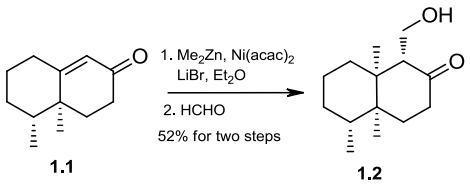
Scheme 4.8: Proposed route to compound 4.15 using allylbromide



The allylbromide was tested in both the Gilmans reagent[11] and the Grignard reagent[6] method of copper 1,4-addition (as described for the model compound) including the addition of HMPA and TMSCl, however all reactions recovered only starting materials. Compound **4.12** was not observed under any reaction conditions.

As previously mentioned, in the synthesis of (+)-nakamurol A Bonjoch *et al*.[2] successfully managed to add a methyl group to enone **1.1** via a 1,4-addition and trapping the enolate with formaldehyde. Dialkyzinc reagents were used instead of copper with a catalytic amount of $Ni(acac)_2$ for the 1,4-additon due to problems with reproducibility of results with the organocuprate conditions (*scheme 4.9*).

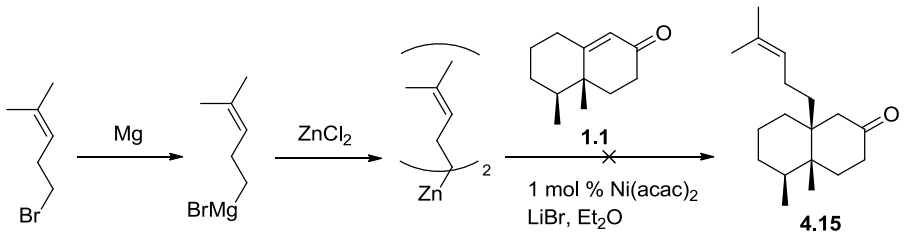
*Scheme 4.9: Successful 1,4-addition to enone **1.1** by Bonjoch et al. towards the synthesis of (+)-nakamurol A.*



These conditions were investigated in a stepwise manner to ensure its success. The 1,4-addition step was first adapted to suit our synthesis. The dialkylzinc reagent was synthesised using an adapted procedure by Schulz *et al.*[12] in which bromo-2-methyl-2-pentene was reacted with magnesium to form the Grignard reagent, which was added to a solution of $ZnCl_2$ in THF at room temperature and stirred overnight to form the dialkylzinc reagent. A premixed suspension of enone **1.1**, 1 mol% of $Ni(acac)_2$ and LiBr in Et_2O was added to the dialkylzinc solution at 0 °C and stirred at room temperature. Even after 24 hours, only starting material

was isolated; no reaction occurred (*scheme 4.10*). Repetition of these conditions on hydroxy enone **1.3** also failed to give any product.

Scheme 4.10: Bonjoch's conjugate addition conditions with the dialkyl zinc compound



It is uncertain whether the failure of the reaction was due to the lack of formation of the dialkylzinc compound or the sterically hindered position at the bicyclic ring junction and the size of the addition compound. While, there are several examples of the addition of a methyl group at this position in octalone compounds such as enone **1.1,** using both zinc reagents and copper reagents,[13] there is no literature indicating the successful addition of larger groups at this position.

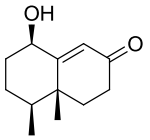
4.1.5. Conclusion to chapter 4.1

The 1,4-addition step followed by trapping of the enolate was thoroughly investigated both on a model compound and enone **1.1**, however these reactions failed to form any desired product. In many cases, starting material was isolated indicating the lack of reactivity in that system and despite the addition of activating Lewis acids, no product was formed. Had more time been available, the use of a more electrophilic reagent to trap the enolate such as formaldehyde (as used by Tokoroyama and Bonjoch) could have been tested as proof of concept that trapping of the enolate is possible with these systems.

Particularly for enone **1.1**, the site of 1,4-addition would be sterically hindered particularly for the long alkyl chain that is required for the synthesis of nominine. There have not been any literature precedent for conjugate addition at that hindered position of a decalin with anything larger than a single carbon group (ie. methyl or nitrile).

At this point, a new paper was discovered by Bonjoch *et al.*[14] who were also currently attempting the total synthesis of nominine. They had been investigating the addition of various organometallics to the hydroxy enone **1.3**, however they found the 1,4-addition to be unsuccessful also. As a result of this, investigations of the 1,4-addition reaction on these decalins was suspended while other routes were investigated.

4.2. Synthesis of hydroxy bicyclic enone 1.3

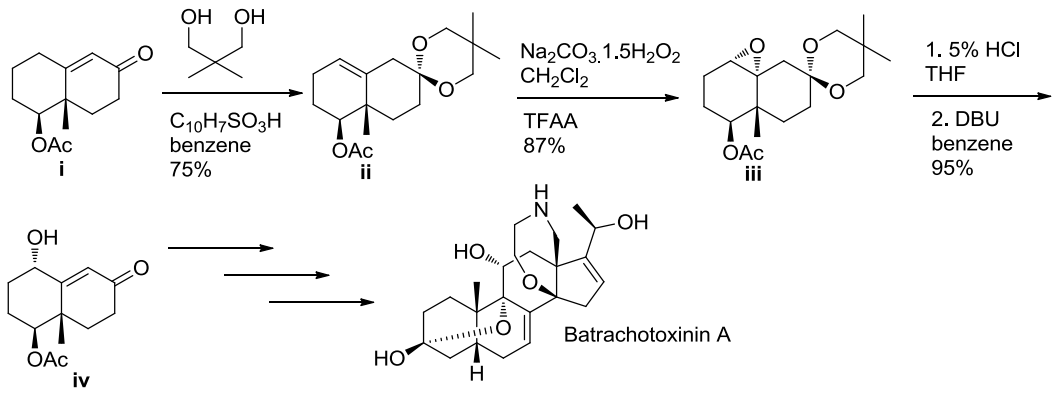


Several procedures were investigated towards the synthesis of hydroxy bicyclic enone **1.3**. Installation of the hydroxy group onto enone **1.1** was revealed to be a non-trivial step as investigations proceeded. The required *cis* orientation of the hydroxy to the methyl groups coupled with the conformation of the decalin rings resulted in difficulties with this step. The reported literature procedures tended to be low yielding, contain multiple steps and/or require very carefully controlled conditions.

4.2.1. Kishi's method

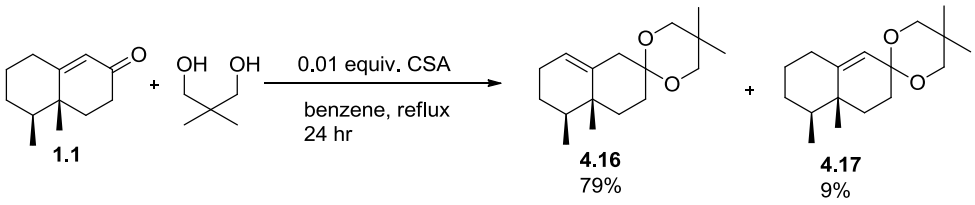
This method was based on a procedure by Kishi *et al.*[15] who installed a hydroxyl group on a similar intermediate (**i**) during their total synthesis of (±)-batrachotoxinin A (*scheme 4.11*). The carbonyl was protected with dimethyl propandiol causing the migration of the double bond to the β,γ-position (**ii**). Control of the alkene regiochemistry is determined by the acidity of the acid catalysts used in this step. Highly acidic catalysts (pK_a ~ 1) tend to cause the double bond to migrate whereas low acidity catalysts do not.[16] The migrated double bond is epoxidised (**iii**) and the carbonyl deprotected before DBU deprotonates to reinstall the double bond causing the opening of the epoxide to form the hydroxy group in the desired position (**iv**). Although we required the hydroxy to be in a *cis* position whereas Kishi obtained a *trans* hydroxy, we felt this could be remedied during the epoxidation step.

Scheme 4.11: Kishi's use of ketalisation to install a hydroxy group enroute to (±)-batrachotoxinin A



For the formation of the 1,3-dioxane with double bond migration to the β,γ-position **4.16**, we used camphorsulfonic acid (CSA) as 2-naphthalenesulfonic acid (NSA) was not readily available at the time of our investigations. We found a small percentage of the products obtained retained the double bond regiochemistry of the starting material (**4.17** 5-10%) and attributed this to the fact that CSA is not as acidic as NSA (*scheme 4.12*). However, as yields obtained for the desired product **4.16** were acceptable, this matter was not pursued. Out of interest, we also tested ethylene glycol and diethyl propanediol in this step and found that while they formed the desired product with migration of the double bond, higher yields were obtained with dimethyl propandiol. We varied the number of equivalents of dimethyl propandiol and the concentration used. Optimum yields were obtained with 2.5 equivalents of the diol in a 0.37 M solution for 24 hours in which 79% of the desired product **4.16** was obtained.

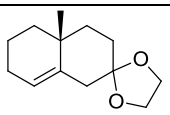
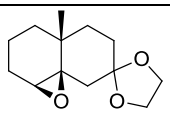
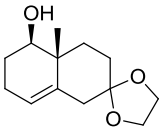
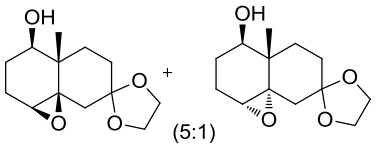
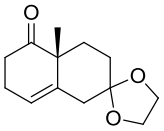
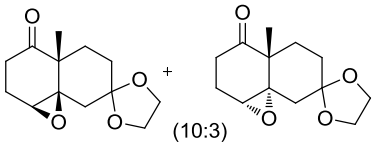
Scheme 4.12: Ketalisation of enone 1.1 using CSA resulted in two products



Kishi utilised the very powerful oxidising agent peroxy-trifluoroacetic acid (formed *in situ* from sodium percarbonate and trifluroacetic anhydride) to form the *trans* epoxide. However, as we required a *cis* epoxide, alternative reagents were investigated.

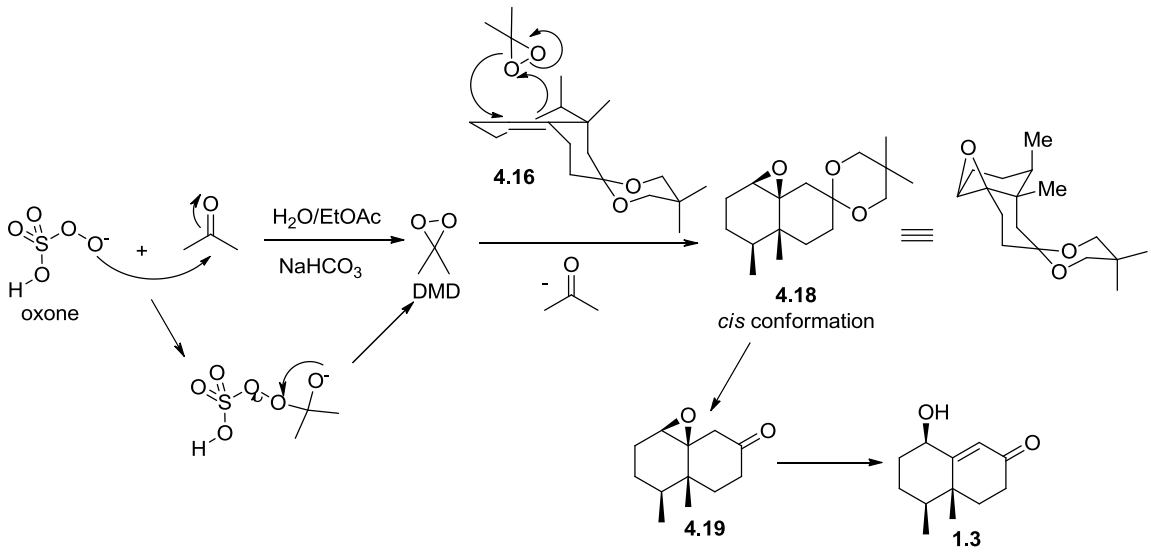
Dimethyldioxirane (DMD) is a common reagent for epoxidation along with mCPBA although it often shows superior yields and stereoselectivity in comparison. It has also been shown to be more tolerant of other functional groups which are sensitive to temperature or acid/base.[17] Whilst DMD is often synthesised and distilled before addition to the reaction mixture,[18] Ferraz *et al.* described a simple procedure for its synthesis and use *in situ*.[19] They also described the use of this procedure on substrates similar to that of enone **1.1** indicating a high ratio of the *cis* epoxide formation in high yields (*table 4.3*).

Table 4.3: Epoxidation of Δ^4-octalin derivatives by Ferraz et al.

Entry	Substrate	Products (ratio)	Yield
1			91%
2		 (5:1)	90%
3		 (10:3)	95%

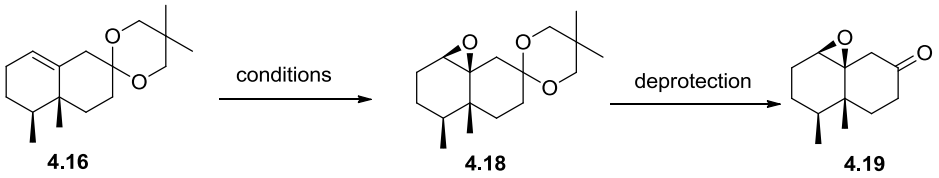
DMD is a three membered cyclic peroxide formed from addition of Oxone® (active component $KHSO_5$) to acetone in the presence of water and $NaHCO_3$. A by-product of the reaction is sulfuric acid therefore at least one equivalent of base is required as Oxone® will decompose at a pH lower then 7. DMD is used as an oxygen-transfer agent as well as an oxidising agent. In this case, DMD transfers an oxygen atom to the alkene forming the epoxide **4.18** and acetone. Epoxide **4.18** is then deprotected before a base is used to open the epoxide forming the desired hydroxy compound **1.3** (*scheme 4.13*). It was proposed that the small size of DMD would allow for attack of the top face of **4.16** resulting in the desired *cis* epoxide.

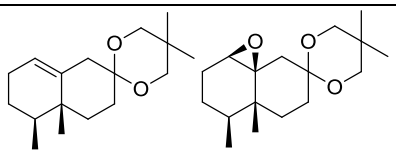
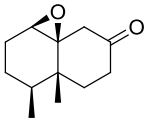
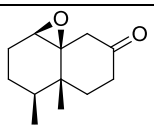
*Scheme 4.13: Use of DMD to form hydroxy compound **1.3***

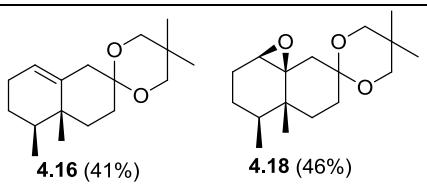
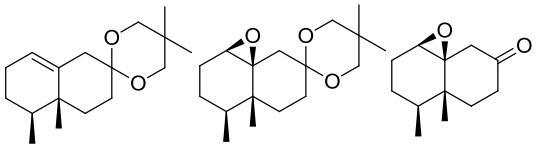
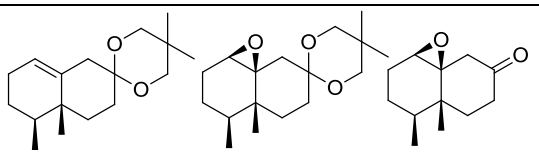
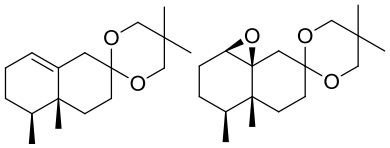
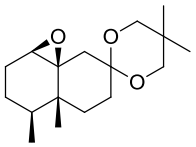
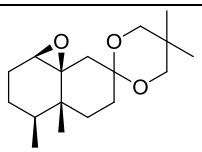


Ferraz *et al.*'s general procedure describe the dropwise addition of Oxone® in water to a stirred solution of the alkene and $NaHCO_3$ in acetone at 0 °C, and stirring of reaction mixture at room temperature until consumption of starting material. After overnight stirring, starting material was still recovered (entry 1 of *table 4.4*). Extended reaction times in entries 2 and 3 indicated no starting material by TLC although many other products were present. The crude reaction mixture was found to be only partially soluble in $CDCl_3$ which was puzzling as the desired product **4.18** was expected to be quite non-polar. This ^1H NMR spectra in $CDCl_3$ showed no identifiable products so a second extraction of the aqueous layer with addition of brine as well as copious washes with EtOAc was required to extract the products. After a long column with multiple products, compound **4.19** (confirmed by ^1H NMR spectroscopy in MeOD and ESI+) was identified as the major product in these reactions. This is a surprisingly polar compound preferring to stay in the aqueous layer during work up with an R_f = 0.12 in 50% EtOAc/hexane. These initial results indicated that deprotection of the ketal as well as decomposition of products occurred with time at room temperature.

*Table 4.4: Epoxidation of **4.16** with DMD*



Entry	Reagents & Conditions (addition of Oxone® over this period of time)	Products obtained (yields)
1	2 equiv. $NaHCO_3$ Acetone/H_2O 1.2 equiv. Oxone® (10 min) o/n, rt	 **4.16** (20%) **4.18** (60%)
2	1.8 equiv. $NaHCO_3$ Acetone/H_2O 1.1 equiv. Oxone® (10 min) 52 hr, rt	 **4.19** (85%)
3	2 equiv. $NaHCO_3$ Acetone/H_2O 1.2 equiv. Oxone® (10 min) 91 hr, rt	 **4.19** (59%)

4	2 equiv. $NaHCO_3$ Acetone/H_2O 1.2 equiv. Oxone® (10 min) 5 hr, 0 °C	 **4.16** (41%) **4.18** (46%)
5	2 equiv. $NaHCO_3$ Acetone/H_2O 1.2 equiv. Oxone® (10 min) 7 h, 0 °C	 **4.16** (10%) **4.18** (44%) **4.19** (~3%)
6	2 eq. $NaHCO_3$ Acetone/H_2O 1.2 eq. Oxone® (10 min) 5 hr, 0 °C then o/n rt	 **4.16** (20%) **4.18** (5%) **4.19** (~37%)
7	3 equiv. $NaHCO_3$ Benzene/Acetone/H_2O Phosphate buffer pH 7-8 0.2 equiv. 18-crown-6 (PTC) 2.3 equiv. Oxone® (30 min) Addition at 6-8 °C, o/n rt	 **4.16** (60%) **4.18** (31%)
8	1.1 equiv. **4.16** 5 equiv. $NaHCO_3$ EtOAc/Acetone/H_2O 0.9 equiv. Oxone® (1 hr) 2hr, rt	 **4.18** (95%)
9	1 equiv. **4.16** 5 equiv $NaHCO_3$ EtOAc/Acetone/H_2O 1 equiv. Oxone® (30 mins) 2.5hr, rt	 **4.18** (68%)

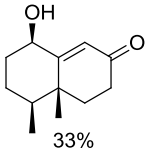
In light of the decomposition of the products at room temperature, the reaction temperature was reduced to 0 °C which slowed down the reaction as indicated by the recovery of 41% of starting alkene in entry 4. Extended reaction time at 0 °C reduced the amount of starting alkene recovered but deprotection of the ketal is also seen in entry 5 and 6.

In an attempt to increase yields of **4.18**, reaction conditions were modified[17] to include an organic solvent with PTC buffered to pH 7, however yields were still quite low at 31% (entry 7). Success was found using conditions developed by Hashimoto and Kanda[20] in which they show that DMD has a high affinity for EtOAc in a two-phase system and the addition of Oxone® in H_2O over a long period of time gives high yields of expoxidation without the need for temperature or pH control. When Oxone® was added over a period of one hour to a slight

excess of compound **4.16**, 95 % of **4.18** was formed (entry 8). A shorter addition time of 30 minutes and use of equimolar quantities of starting **4.16** and Oxone® reduced yields to 68% (entry 9). Only one isomer of the epoxide was observed by NMR analysis.

Opening of the epoxide was investigated using the batches of compound **4.19** formed from experiments in *table 4.4*. Kishi's procedure describes the addition of DBU to the epoxide in benzene at room temperature. However, the solubility of **4.19** was found to be very poor in benzene and required several drops of MeOH to solubilise. After overnight stirring, 33% of hydroxy enone **1.3** was isolated (entry 1 *table 4.5*). Initially, we proposed the low yields were due to solubility issues so we changed the solvent to acetone in which **4.19** dissolves well in. However, only starting material was isolated even when we changed the base. We eventually concluded that the base can also deprotonate acetone as the estimated pKa of **4.19** is similar to that of acetone. As the solvent, acetone would be easier and faster to deprotonate due to its abundance, therefore no reaction was seen in these experiments (entry 2 and 3). Changing the base and solvent in entries 4 and 5 only caused decomposition of starting material and products.

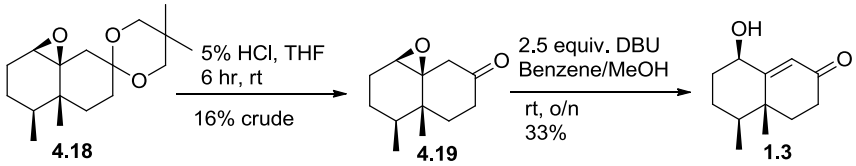
*Table 4.5: Investigating the ring opening of epoxide **4.19***

Entry	Base	Solvent	Conditions	Result
1	DBU	Benzene + drops of MeOH until **4.19** solubilised	Room temperature overnight	 33%
2	DBU	Acetone	Room temperature overnight	Starting material recovered
3	Et_3N	Acetone	Room temperature overnight	Starting material recovered
4	K^tOBu	t-butanol	Room temperature overnight	Decomposition
5	DBU	MeOH	Room temperature 24 hr	Decomposition

Concurrently, we were also investigating the deprotection of the ketal to form **4.19**. Using Kishi's method to form the hydroxy group using 5% HCl in THF followed by DBU in benzene gave poor yields (*scheme 4.14*). Increasing the reaction time (24 hours and 48 hours) of the

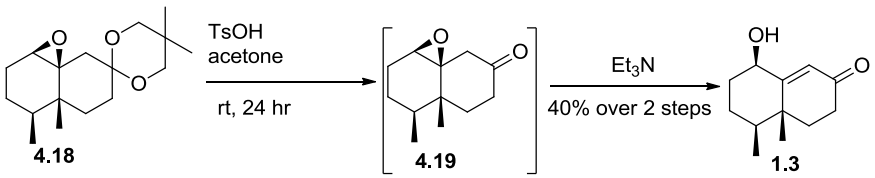
deprotection step (**4.18** to **4.19**) caused decomposition of products and starting material with no increase in yield.

*Scheme 4.14: Formation of enone **1.3** via Kishi conditions*



Screening of conditions revealed the use of 0.02 equivalents TsOH in anhydrous acetone for the hydrolysis of the protecting group[21] which was then quenched with Et_3N. Concentration of this reaction mixture to remove the acetone caused the epoxide to ring open giving enone **1.3** in up to 40% yields over the two steps (*scheme 4.15*). Only the *cis* hydroxy enone was obtained (by comparison of data with literature)[22] which confirmed that the *cis* epoxide was formed exclusively in the previous step.

*Scheme 4.15: Formation of enone **1.3** via adapted Kishi conditions to give higher yields*



Although it would appear to be beneficial for the epoxidation step to also deprotect the ketal so that compound **4.19** could be formed from **4.16** in one step, it was found that the product formed was not 100% pure and was often very difficult to isolate, so a crude form of **4.19** had to be taken onto the next step. The highest yield achieved over the three steps from alkene **4.16** to hydroxy enone **1.3** was 34%.

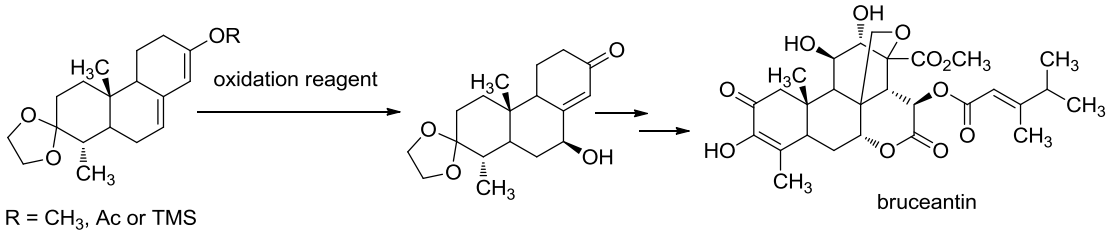
4.2.2. Dienol ether intermediate

The installation of a 6β-hydroxy group onto bicyclic enones via dienol ether intermediates has been reported in literature since the 1950's.[23] This two step transformation occurs through dienol ether intermediates which are oxidised to give the hydroxy compound.

4.2.2.1. Dienol ether intermediate

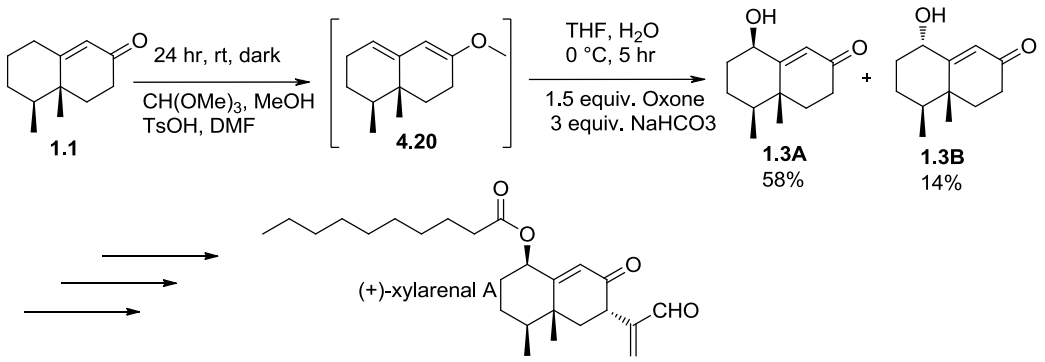
Suryawanshi and Fuchs[24] investigated optimum conditions for the installation of the 6β-hydroxy group onto bicyclic intermediates during their investigations towards the total synthesis of bruceantin. The corresponding dienol ether, dienyl acetate and silyldienyl ether intermediates were prepared and different oxidation reagents (MCPBA, O_2 in presence of *h*υ, iodosobenzene and Oxone®) were evaluated (*scheme 4.16*). Oxone® was found to afford the highest yields of axial hydroxy group in mild and efficient conditions.

Scheme 4.16: Investigating optimal conditions for the installation of a 6β-hydroxy group by Suryawanshi and Fuchs towards the total synthesis of bruceantin



Based on this work, Bonjoch *et al.*[22] installed a hydroxy group onto enone **1.1** to form **1.3** enroute to the total synthesis of (+)-xylarenal A (*scheme 4.17*).

*Scheme 4.17: Bonjoch's formation of hydroxy enone **1.3** from enone **1.1** enroute to (+)-xylarenal A.*



This two step transformation involved the oxidation of compound **1.1** to install the hydroxyl group which was carried out through its dienol ether intermediate[25] **4.20** with Oxone®. Although Suryawanshi and Fuchs did not report the isolation of the equatorial epimer, Bonjoch obtained a 4:1 ratio of axial:equatorial epimers (**1.3A**:**1.3B**) for this particular substrate.

Bonjoch reported the use of trimethyl orthoformate, MeOH and DMF with TsOH for 24 hours in the dark to form the dienol ether intermediate which was isolated but not purified due to its instability. Selected signals from the ^{1}H NMR spectrum were reported. Oxone® in H_2O was then added to the crude dienol ether in THF at 0 °C over half an hour and the reaction mixture stirred for five hours. This method was carried out with initially poor results due to the sensitivity of the reaction and the need for extremely carefully controlled conditions. However, upon repetition and modification of some reagents/conditions, higher yields were obtained (*table 4.6*).

*Table 4.6: Optimising yields for the formation of hydroxy enone **1.3A***

Entry	Conditions	Result
1	Step 1 – 0.95 mmol **1.1**, 4:4:1 $C(OCH_3)_3$:DMF:MeOH, 0.2 equiv. TsOH, 24 hr, dark Step 2 – THF, 0 °C, 3 equiv. $NaHCO_3$, 1.5 equiv. Oxone® in H_2O dropwise, 5.5 hr at 0 °C	**1.3A** 6%
2	Step 1 –2 mmol **1.1**, 5:5:1 $C(OCH_3)_3$:DMF:MeOH, 0.2 equiv. TsOH, 24 hr, dark Step 2 – THF, 0 °C, 3 equiv. $NaHCO_3$, 1.5 equiv. Oxone® in H_2O dropwise, 5 hr at 0 °C	**1.3A** 20% **1.3B** 5%
3	Step 1 – 1.4 mmol **1.1**, 6:6:1 $C(OCH_3)_3$:DMF:MeOH, 0.2 equiv. TsOH, 24 hr, dark Step 2 – THF, 0 °C, 3 equiv. $NaHCO_3$, 1.5 equiv. Oxone® in H_2O dropwise, 7 hr at 0 °C followed by 1 hr at rt	**1.3A** 18% **1.3B** 5%
4	Step 1 – 1.1 mmol **1.1**, 6:6:1 $C(OCH_3)_3$:DMF:MeOH, 0.2 equiv. TsOH, 46 hr, dark – new bottles of solvent and freshly dried TsOH Step 2 – THF, 0 °C, 3 equiv. $NaHCO_3$, 2 equiv. Oxone® in H_2O dropwise, 5.5 hr at 0 °C	**1.3A** 21% **1.3B** 9%
5	Step 1 – 1.1 mmol **1.1**, 6:6:1 $C(OCH_3)_3$:DMF:MeOH, 0.2 equiv. TsOH, 24 hr, dark – new bottles of solvent and freshly dried TsOH Step 2 – THF, 0 °C, 3 equiv. $NaHCO_3$, 2 equiv. Oxone® in H_2O dropwise, 5.5 hr at 0 °C	**1.3A** 28% **1.3B** 6%
6	Step 1 – 1.1 mmol **1.1**, 6:6:1 $C(OCH_3)_3$:DMF:MeOH, 0.2 equiv. TsOH, 24 hr, dark – new bottles of solvent, freshly dried TsOH and freshly distilled $C(OCH_3)_3$ Step 2 – THF, 0 °C, 3 equiv. $NaHCO_3$, 2 equiv. Oxone® in H_2O dropwise, 5.5 hr at 0 °C	**1.3A** 31% **1.3B** 5%

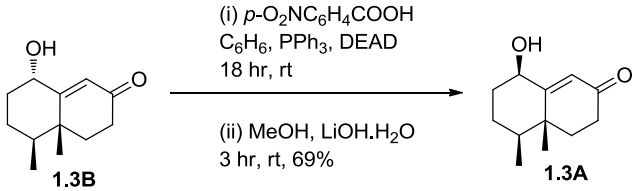
7	Step 1 – 7.9 mmol **1.1**, 4:5:1 $C(OCH_3)_3$:DMF:MeOH, 0.2 equiv. TsOH, 28 hr, dark – new bottles of solvent, freshly dried TsOH and freshly distilled $C(OCH_3)_3$ Step 2 – THF, 0 °C, 3 equiv. $NaHCO_3$, 1.5 equiv. Oxone® in H_2O over 35 mins then 6 hr at 0 °C	**1.3A** 38% **1.3B** 23%
8	Step 1 – 8.2 mmol **1.1**, 4:5:1 $C(OCH_3)_3$:DMF:MeOH, 0.2 equiv. TsOH, 24 hr, dark Step 2 – THF, 0 °C, 3 equiv. $NaHCO_3$, 0.02 equiv. PTC, 2 equiv. Oxone® in H_2O over 30 mins then 3 hr at 0 °C, 2 hr at rt	**1.3A** 32% **1.3B** 11%
9	Step 1 – 7.8 mmol **1.1**, 4:5:1 $C(OCH_3)_3$:DMF:MeOH, 0.2 equiv. TsOH, 24 hr, dark Step 2 – 3:1 EtOAC:acetone, 0 °C, 5 equiv. $NaHCO_3$, 1 equiv. Oxone® in H_2O over 30 mins then 1 hr rt	**1.3A** 41% **1.3B** 13%

An increase in scale appeared to increase yields of product (see experiment 1, 2 and 7). Increasing reaction time of step 1 did not increase yields; it increased the ratio of **1.3B** (see experiment 4 and 5). It was observed that trimethyl orthoformate required fresh distillation prior to each experiment for optimal yields as with prolonged storage yields decreased.

Changing solvent ratios did not seem to affect yields. The optimum yield was achieved in experiment 9 where EtOAc and acetone was used instead of THF at room temperature for only one hour. The most important condition observed was that very slow addition of Oxone® was required. 41% of the desired **1.3A** epimer was obtained in a 3:1 ratio with **1.3B**. Although these yields were considered moderate, they were comparable with literature results.[25] Also, the results were sufficient to obtain enough material for use in the next step of the project.

Compound **1.3B** corresponds to the natural product (**±**)-1α-hydroxyisoondetianone which was first isolated from the aerial parts of the South African plant *Ondetia linearis* in 1989.[26] Although it is possible to convert the equatorial epimer **1.3B** to the axial **1.3A** via the Mitsunobu process[22] (*scheme 4.18*), this was not carried out due to the fact that we had substantial amounts of enone **1.1** available.

*Scheme 4.18: Bonjoch's conversion of stereochemistry to form **1.3A***



4.2.2.2. Dienol acetate intermediate

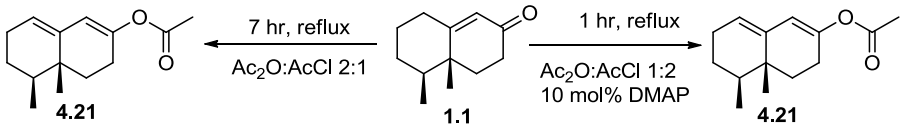
An alternative to the dienol ether intermediate was the formation of the dienol acetate. It was anticipated the dienol acetate could be formed from enone **1.1** and this intermediate would be stable enough to be isolated so a yield could be obtained to ascertain which step, formation of the dienol ether or the oxidation, caused the low overall yields of enone **1.3**.

Suryawanshi and Fuchs[24] reported the use of acetic anhydride, triethylamine and DMAP at 80 °C for 18 hours to form 90% of the enol acetate derivatives of their intermediate although no procedure was published. The procedure originated from a paper by Cousineau, Cook and Secrist III in 1979,[27] however they reported that yields for these conditions on ketones to form enol acetates were not satisfactory and therefore did not disclose the yields.

Further research into the literature revealed alternative methods of formation of the dienol acetate. Dienol acetate intermediate **4.21** was formed from enone **1.1** (*scheme 4.19*) using two methods; firstly using acetic anhydride: acetyl chloride 2:1 reflux[28] for a total of seven hours. Secondly using acetic anhydride: acetyl chloride 1:2 and 10 mol% DMAP reflux for one hour.[29]

For both methods, no starting material was observed either by TLC or ^{1}H NMR spectroscopy of the crude which appeared clearer than that of the previously synthesised dienol ethers. However, after purification by column chromatography on basic alumina less than 10% of the dienol acetate **4.21** was isolated along with approximately 50% of starting enone **1.1**. It was concluded that the dienol acetate was not stable enough to withstand purification as it hydrolysed back to starting material. In further attempts at this procedure, the dienol acetate was assumed quantitative in yield (after ensuring no starting material was present by ^{1}H NMR spectroscopy) and used crude immediately in the next step.

*Scheme 4.19: Formation of dienol acetate intermediate **4.21***



De Groot *et al.*[25] reported the formation of dienol acetate intermediates on similar structures to enone **1.1** to give good yields (**4.23** 80% although no procedure was published). These were immediately oxidised with MCPBA in a mixture of pH 8 buffer solution with 1,4-dioxane to give moderate yields of hydroxy enones **4.24** and **4.25** (*scheme 4.20* and *table 4.7*). It is interesting to note that with a methyl group alpha to the carbonyl (entries c and d) some epoxidation occurred at the alpha double bond forming compound **4.26**.

Scheme 4.20: Formation of hydroxy enones on similar bicyclic systems by de Groot et al.

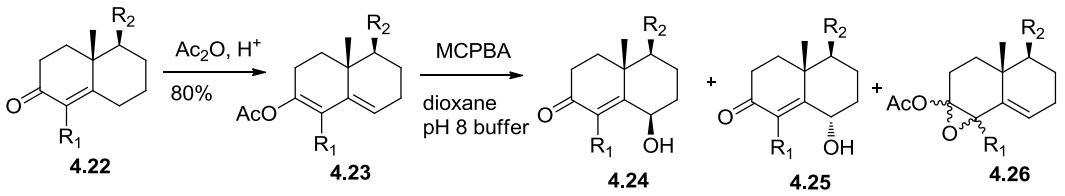
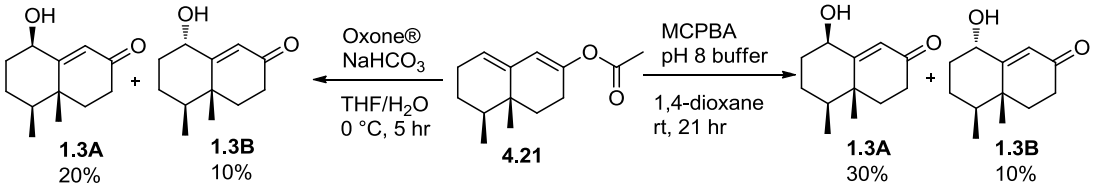


Table 4.7: MCPBA oxidation of dienol acetate intermediates by Groot et al.

Reactant **4.23**	**Reaction time, hr**	**Products %**		
		4.24	**4.25**	**4.26**
a. $R_1 = R_2 = H$	16	57	18	-
b. $R_1 = H$ $R_2 = OAc$	24	51	17	-
c. $R_1 = CH_3$ $R_2 = H$	16	62	25	7
d. $R_1 = CH_3$ $R_2 = OAc$	16	57	28	12

The crude dienol acetate **4.21** was consequently oxidised with MCPBA using this procedure as well as using the Oxone® procedure, however only low yields of **1.3** were achieved (scheme 4.21).

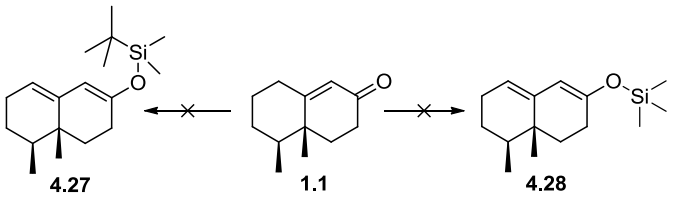
*Scheme 4.21: Oxidation of dienol acetate **4.21***



4.2.2.3. Dienol silylether intermediates

The formation of dienol silylether intermediates were briefly explored (*scheme 4.22*). Various bases (^{t}BuOK, KH, imidazole, DBU) were employed at room temperature in THF, however no success was found in forming either **4.27** or **4.28**. Since Suryawanshi and Fuchs reported lower yields of hydroxy enone products from dienol silylethers (compared to dienol acetates and dienol ethers), the formation of **4.27**/**4.28** was not pursued.

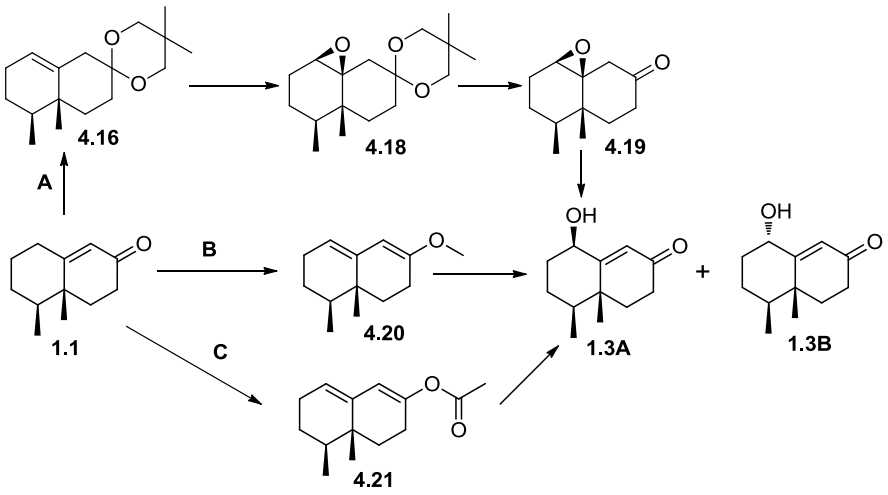
Scheme 4.22: Attempted formation of dienol silylether intermediates



4.2.3. Conclusion to chapter 4.2

Three successful methods for the formation of hydroxy enone **1.3** were established (*scheme 4.23*).

*Scheme 4.23: Three methods of forming hydroxy enone **1.3** from enone **1.1***



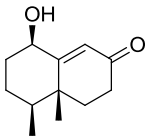
Method A (Kishi's method) utilises the migration of the double bond in the protection of the carbonyl with a ketal (**4.16**) to install the hydroxy group. Although this method formed only the desired diastereoisomer **1.3A**, the yield was inadequate and required four steps to obtain.

Formation of hydroxy enone **1.3** via the dienol ethers (methods B and C) also forms the undesired diastereoisomer in a 3:1 ratio (**1.3A**:**1.3B**) which is consistent with that observed in similar bicyclic systems.[25] Method B achieved the highest overall yield of **1.3A** (*table 4.8*) over two steps therefore this was the selected method employed to synthesise hydroxy enone **1.3**.

*Table 4.8: Overall yields obtained from three methods of formation of **1.3***

Method	**Yield 1.3A (%)**	**Yield 1.3B (%)**
A Kishi method	34	-
B via dienol ether	41	13
C via dienol acetate	30	10

4.3. Investigating the reactions of hydroxy enone 1.3



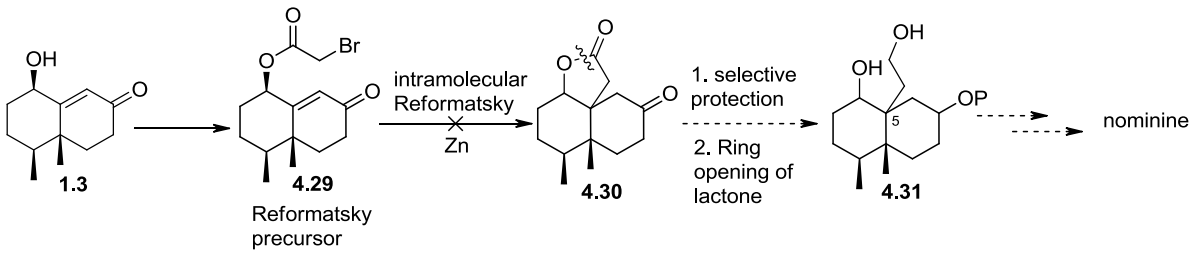
1.3

With this substrate in hand, we decided to investigate its scope of reactions given that the copper catalysed intermolecular 1,4-addition reactions investigated in chapter 4.1 were found to be unsuccessful on these cyclic enone compounds. Our strategy was to develop and test alternative or novel methodology on compound **1.3**; for example, Michael addition or intramolecular Reformatsky reactions, as well as synthesise new analogues which could be tested in biological assays in the quest for a new insecticide. Hence, a number of reactions of hydroxy enone **1.3** were concurrently investigated.

4.3.1. Modified-Reformatsky reaction

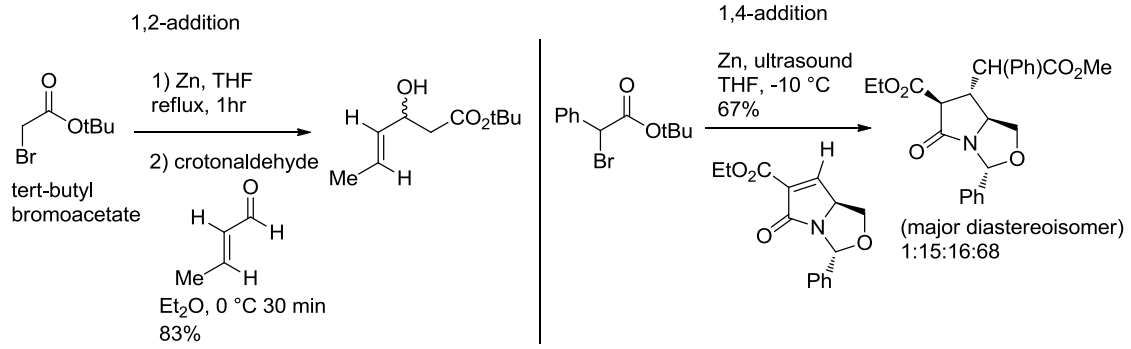
As the intermolecular 1,4-additions had proved to be very challenging for enone **1.1**, it was proposed that an intramolecular 1,4-addition could be attempted, based on the Reformatsky reaction. These are generally described as "reactions resulting from metal insertions into carbon-halogen bonds activated by carbonyl or carbonyl-derived groups in vicinal or vinylogeous positions with practically all kinds of electrophiles".[30] The metal most commonly associated with Reformatsky reactions is zinc. There have been several examples of intramolecular Reformatsky reactions, most commonly with aldehydes and ketones, and several examples of intermolecular Reformatsky reactions with α,β-unsaturated carbonyls.[31] However, there had yet to be reported an intramolecular Reformatsky type reaction on α,β-unsaturated carbonyls. This novel concept was therefore of interest. Tricyclic **4.30** could then be utilised to install a handle at the quaternary centre by ring opening of the lactone to give intermediate **4.31** which could be further elaborated into nominine (*scheme 4.24*).

Scheme 4.24: Proposed series of reactions utilising a novel intramolecular Reformatsky to install handle at C5.



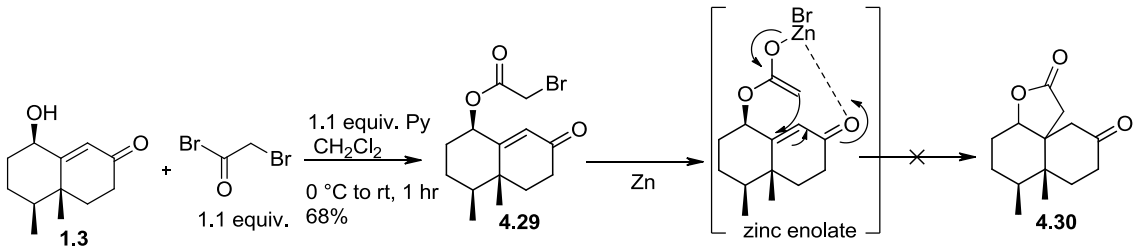
Although both 1,2-additions and 1,4-conjugate additions have been reported in literature for intermolecular Reformatsky reactions with α,β-unsaturated carbonyls, there does not appear to be a definitive method of predicting which outcome will occur. However, it has been noted that it is more common for 1,2-addition to occur with aldehydes, and 1,4-conjugate additions with bulky Reformatsky reagents (*scheme 4.25*).

Scheme 4.25: Examples of a 1,2-addition of a Reformatsky reagent to an aldehyde[32] and a 1,4-addition to an activated lactam[33]



Bromo acetylbromide undergoes nucleophilic acyl substitution with hydroxy enone **1.3** to give the precursor **4.29** to the proposed intramolecular Reformatsky reaction. It was proposed that the insertion of activated zinc into the carbon-bromine bond of Reformatsky precursor compound **4.29** would form the intermediate (zinc enolate). The close proximity of the reacting partners, with the zinc enolate also coordinating to the enone carbonyl, could increase the chances of an intramolecular 1,4-addition reaction to give tricyclic compound **4.30** (*scheme 4.26*).

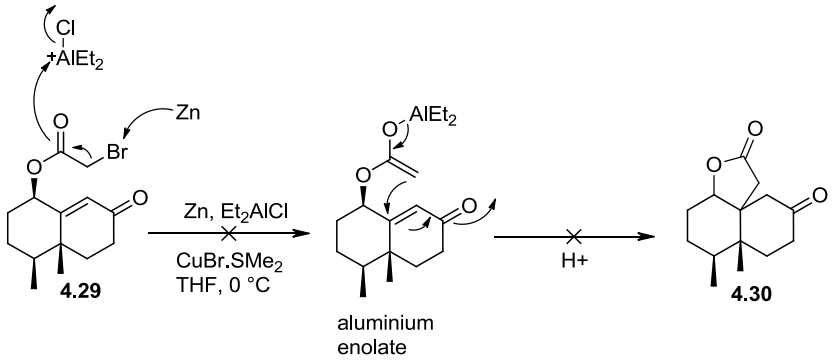
*Scheme 4.26: Proposed intramolecular Reformatsky reaction on compound **4.29***



For the formation of Reformatsky reactions, activated zinc is required for which there are two main methods of formation; either by removal of the oxide layer (washing with acid) or by creating a fine distribution of zinc typically by reduction of anhydrous zinc halides.

For the former method, zinc dust was washed with 5% HCl, H_2O, acetone then Et_2O before storing in a desiccator under vacuum overnight.[34] Compound **4.29** in THF was added to a slurry of this activated zinc (3 equivalents) in combination with 5 mol% CuBr.SMe_2 and two equivalents Et_2AlCl in THF at 0 °C over half an hour.[35] Et_2AlCl is reported to be essential for these mild conditions[36] forming the aluminium enolate which is sufficiently activated for addition to the enone partner (*scheme 4.27*). Without the use of Et_2AlCl, reflux conditions would be required for the insertion of zinc into the α-bromoester as depicted in *scheme 4.24*.

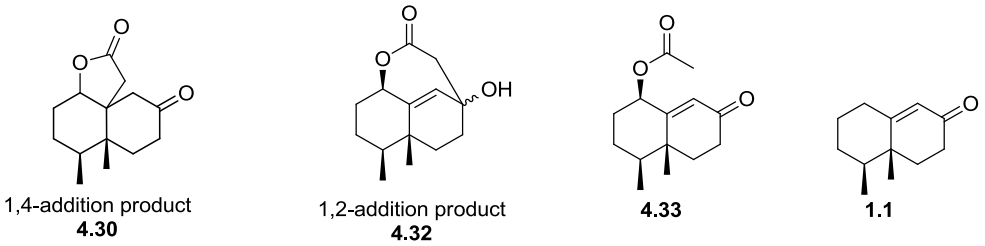
*Scheme 4.27: Mild conditions for the intramolecular Reformatsky reaction of compound **4.29**.*



After overnight stirring at room temperature, no starting material **4.29** was observed by TLC or ESI+. TLC indicated many products, however after column purification no desired product **4.30** was isolated. 20% of the parent enone **1.1** was isolated as well as trace amounts of compound **4.33** indicating insertion of zinc did occur to some degree. The ^{1}H NMR spectra was too

complex for the characterisation of the remaining fractions isolated. While it is possible that 1,2-addition occurred instead of 1,4-addition, compound **4.32** was not detected either (*figure 4.1*). These results indicated that the zinc was activated to some degree as reactions did occur, however it was unselective and the desired product was not observed in any detectable yields.

*Figure 4.1: Possible products from the Reformatsky reaction of compound **4.29**.*

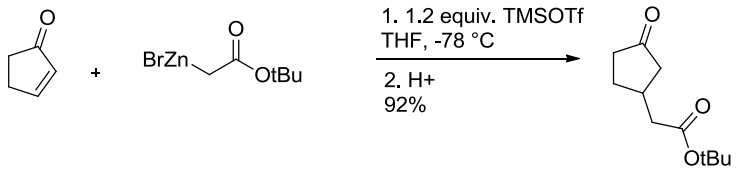


An alternative method of forming activated zinc is the reduction of $ZnCl_2$ by lithium known as Rieke zinc.[37] 2.1 equivalents of lithium wire was weighed in hexane in a two neck flask and the hexane replaced with 1,2-dimethoxyethane. 10 mol% naphthalene was added followed by 1 equivalent of 1.0 M $ZnCl_2$ in THF. The resulting mixture was stirred at room temperature overnight before leaving to settle for two hours. White solid settled at the bottom of the flask in a pale yellow liquid which was removed by syringe. Compound **4.29** in THF was added and the resulting mixture stirred at room temperature overnight, however no reaction was seen. Only starting **4.29** was isolated. No other compounds were isolated indicating that the activated Rieke zinc was not formed. Rieke's procedure reports a fine black powder formed whereas we observed a white solid.

However, in an alternative method of Rieke zinc formation, a fine gray dispersion of zinc was obtained by Boudjouk *et al.*[38] when $ZnCl_2$ and lithium were sonicated in THF for one hour. This method was carried out to obtain a dark gray solid which was suspended in Et_2O before compound **4.29** in Et_2O was added. The resulting mixture was stirred overnight at room temperature to give several compounds although none appeared to be the desired product **4.30** or starting material **4.29** after purification. Trace amounts of compound **4.33** was detected (from the $COCH_3$ peak in ^1H NMR spectra) but once again, NMR spectra were too complex for conclusive identification with multiple compounds present after purification.

Although only trace amounts of compound **4.33** were identified, conditions could have been optimised to increase the insertion of the activated zinc but no evidence of 1,4 or even 1,2-addition compounds was found. This could be a result of steric hindrance of the bicylic molecule in which the reacting orbitals are not able to align appropriately due to the conformation of the molecule. Alternatively, compound **4.29** may not have been activated enough for a reaction to occur. In comparison to other organometallic compounds derived from Li, Mg or Cu to enones, the zinc enolate compound is considered only a mildly reactive species. Although addition of Et_2AlCl was used, perhaps it was not the appropriate Lewis acid for this particular reaction. Kim *et al*.[39] reported the use of trimethyl silyltriflate (TMSOTf) as an excellent Lewis acid for the activation of the addition of a Reformatsky reagent to 2-cyclopenten-1-one (*scheme 4.28*) to give only the 1,4-addition product.

Scheme 4.28: Kim et al.'s use of TMSOTf for the addition of Reformatsky reagents to enones



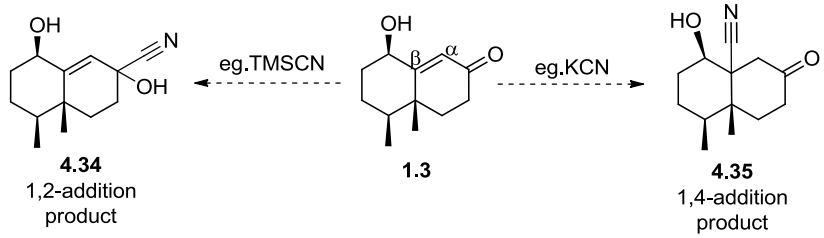
As we were concurrently looking at other reactions of hydroxy enone **1.3**, we decided at this point to focus on the hydrocyanation reactions as they appeared to have more scope so these conditions were not tested. However, it is something to consider for future work.

4.3.2. Hydrocyanation reaction

In consideration of the congestion and steric hindrance at the β-carbon on hydroxy enone **1.3**, it was proposed that a small nucleophile could be added in a Michael addition type reaction at that position. The nitrile group is a versatile functional group which would allow for further functional group modification and extension, hence this was the nucleophile chosen for the Michael addition investigations.

Addition of the CN^- nucleophile to an α,β-unsaturated ketone can give either a direct addition 1,2-product (α-cyanohydrin) or a 1,4-addition product (β-cyano ketone) depending on the substrate, reaction conditions and source of CN^- (*scheme 4.29*). Both the 1,2 and 1,4-addition reactions are reversible so it is possible to obtain both types of products with some substrates. Formation of 1,2-addition products tend to occur in low temperature, acidic conditions as cyanohydrins are stabilised in acid medium, whereas high temperature, basic conditions favour the 1,4-addition product. Lewis acid cyanides, such as TMSCN, favour 1,2-addition whereas the use of alkali metal cyanides, such as KCN, have been shown to form 1,4-addition products as a result of the basic medium. Literature indicated the most popular reagents for 1,4-addition of CN^- were the use of Et_2AlCN or KCN. Both reagents were concurrently investigated.[40]

*Scheme 4.29: Possible products obtained from the addition of CN^- to hydroxy enone **1.3**.*



4.34
1,2-addition product

1.3

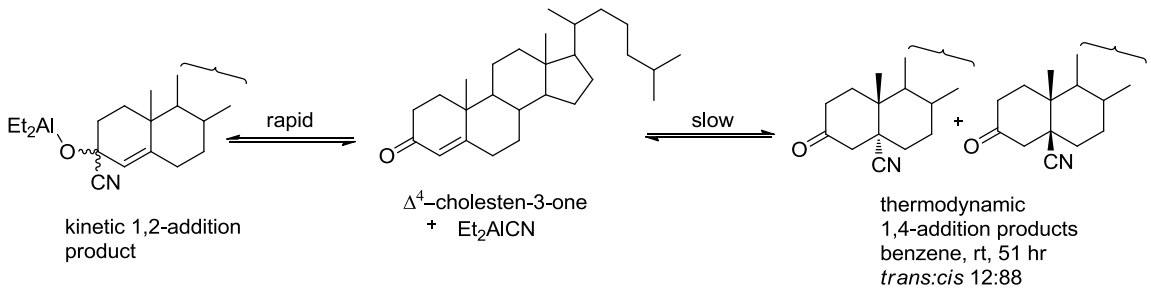
4.35
1,4-addition product

4.3.2.1. Et_2AlCN reagent

Nagata *et al.*[41] carried out some of the most influential early work on the addition of CN nucleophile to α,β-unsaturated ketones. In 1972, they first introduced use of the neutral reagent Et_2AlCN along with R_3Al-HCN as superior reagents for the introduction of CN. As HCN is extremely toxic, Et_2AlCN was the preferred choice of reagent to investigate for our substrate **1.3**.

Nagata *et al.* illustrated the use of Et_2AlCN on cyclic α,β-unsaturated ketones, such as cholesterone. They were shown to afford good yields and stereoselectivity under mild conditions and high efficiency. At least two equivalents of Et_2AlCN were required. The first equivalent activates the enone system by coordinating with the oxygen and the second introduces the cyano group at the β-position. Aprotic solvents such as benzene, toluene, CH_2Cl_2 or THF are required. Nagata's mechanistic studies on the addition of Et_2AlCN on cholesterone showed that the reaction is reversible. The 1,2-addition product is initially formed, followed by thermodynamic equilibrium to the 1,4-addition product via the starting material. The organoaluminium reagent activates the carbonyl and the cyanide nucleophile attacks. With cholesterone, the *cis*-isomer was found to be the major product after 51 hours (*scheme 4.30*).

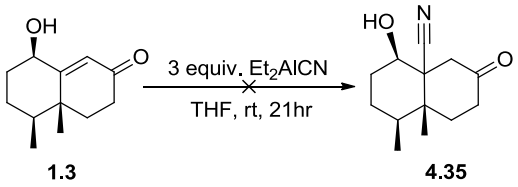
Scheme 4.30: Nagata's mechanistic studies on the addition of Et_2AlCN to cholesterone



Three equivalents of Et_2AlCN was added to a solution of hydroxy enone **1.3** in THF at 0 °C and stirred at room temperature for 21 hours (*scheme 4.31*). The reaction mixture was found to be very complex with several overlapping products by TLC. Trace amounts of product **4.35** was identified by crude ^1H NMR spectroscopy but after column chromatography, no pure fractions could be isolated. It was suspected that a mixture of the 1,2-addition and 1,4-addition products (possibly all *cis*/*trans* isomers) were present as well as the starting material. It has

been reported that with sterically hindered substrates, the reaction does not go to completion. It is possible that with a longer reaction time, the equilibrium would be in favour of the 1,4-addition product however, this was not further investigated as more success was observed with the use of KCN.

*Scheme 4.31: Use of Et_2AlCN on compound **1.3***



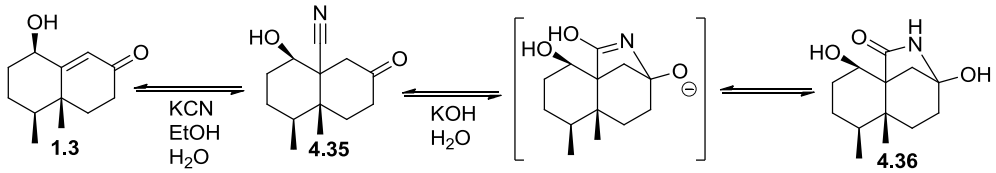
1.3 **4.35**

4.3.2.2. KCN reagent

For substrates which display poor *cis/trans* selectivity with the addition of Et_2AlCN, Nagata[41] advised the use of KCN which could give higher ratios of *cis*-products as a result of solvation of the polar solvent to the cyanide ion increasing the steric bulk of the cyanating moiety. Due to the larger *syn*-axial cyano-hydrogen interactions in the *trans*-isomer transition state than in the *cis*, the increase in steric bulk of the cyanating moiety causes a decrease of formation of *trans* isomers.

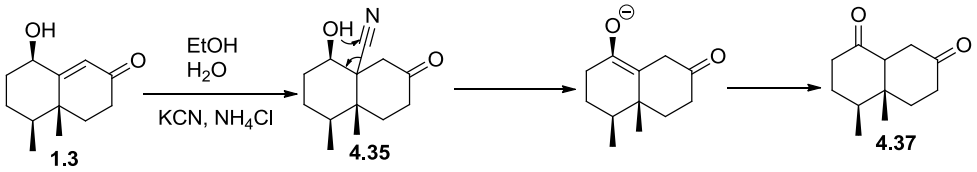
Addition of NH_4Cl was reported to be essential in the KCN cyanating conditions in aqueous ethanolic conditions to reduce side reactions such as reaction reversal or hydrolysis of the product cyanides to lactamols.[42, 43] The strong base KOH formed from the initial CN addition in the presence of H_2O can potentially hydrolyse the product **4.35** to form lactamol **4.36** (*scheme 4.32*). NH_4Cl which is mildly acidic in solution acts as a buffer to prevent this from occurring by neutralising the KOH formed.

*Scheme 4.32: In the absence of NH_4Cl, lactamol product **4.36** would be formed.*



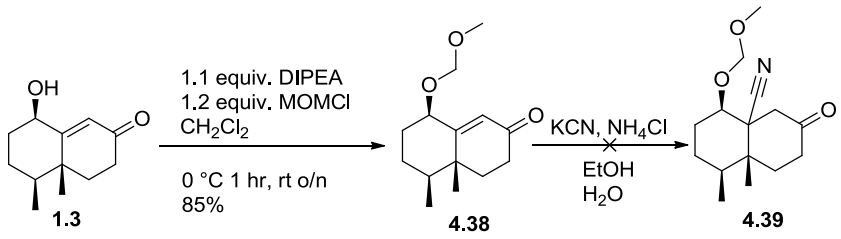
Two equivalents of KCN and one point eight equivalents of NH_4Cl in H_2O was added to a solution of hydroxy enone **1.3** in EtOH and heated to reflux[43](*table 4.9, experiment 1*). After four and eight hours, starting material was found to be prominent by TLC so the reaction was heated to reflux overnight. After purification, the main compound isolated (40%) was found to be diketone compound **4.37** which was proposed to arise from the elimination of HCN from the desired product due to prolonged refluxing (*scheme 4.33*). Starting material was also isolated (20%) indicating that the reaction did not go to completion despite prolonged reaction times.

*Scheme 4.33: Elimination of HCN from compound **4.35** to form diketone **4.37**.*



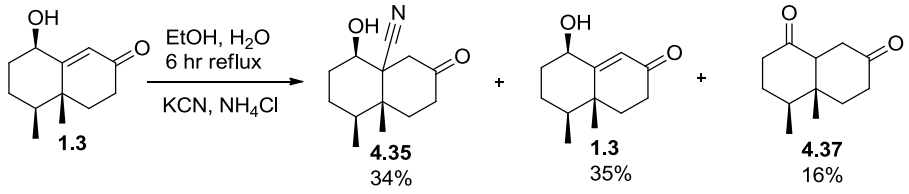
In order to prevent the hydroxy group from participating in the reaction, it was protected with MOMCl to give compound **4.38** in good yields.[44] However, the subsequent reaction with KCN yielded no product **4.39** despite varying reaction times and addition of excessive amounts of KCN/NH_4Cl (*scheme 4.34*). A possible explanation for the lack of reaction is that the MOM-group appears to cause too much steric hindrance for the addition of CN^- to occur. No 1,2-addition product was observed either; only starting material was isolated. The nitrile group was unable to attack from the opposite face from the mom group either, presumably due to steric hindrance cause by the conformation of the compound.

*Scheme 4.34: Attempted CN^- addition to MOM-protected hydroxy enone **4.38**.*



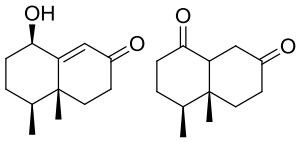
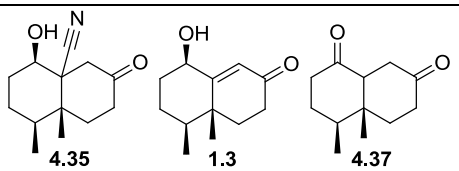
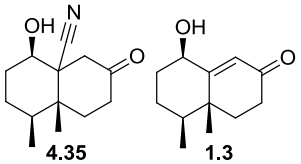
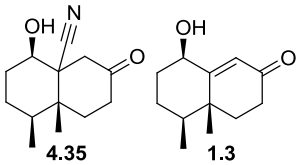
As a result, investigations on the cyanation reaction resumed with hydroxy enone **1.3**. The initial reaction conditions were repeated with a reduced reaction time of six hours and this afforded 34% of the desired product **4.35** as a single isomer, 35% of the starting hydroxy enone **1.3** and 16% of the diketone **4.37** (*scheme 4.35 and table 4.9 experiment 2*). The R_f of the product was found to be very similar to that of the starting hydroxy enone **1.3** causing complications in the isolation of pure product. However, they could be distinguished by TLC by the fact that the starting enone **1.3** is UV active whereas the product **4.35** is not, but can be visualised with ceric stain as a spot overlapping the starting material. Pure product was isolated successfully by recrystallisation with Et_2O after column chromatography.

*Scheme 4.35: Formation of cyano-ketone compound **4.35***



With longer reaction times, the reaction mixture became more complex and the starting hydroxy enone **1.3** never disappeared by TLC. Increasing the number of equivalents of KCN/NH_4Cl and addition of the phase-transfer catalyst (to aid solvation of KCN), 30 mol% of 18-crown-6, did not improve yields. It was concluded that under these conditions, the reaction does not go to completion as starting hydroxy enone **1.3** was always observed by TLC.

Table 4.9: Summary of results of cyanation with KCN reagent

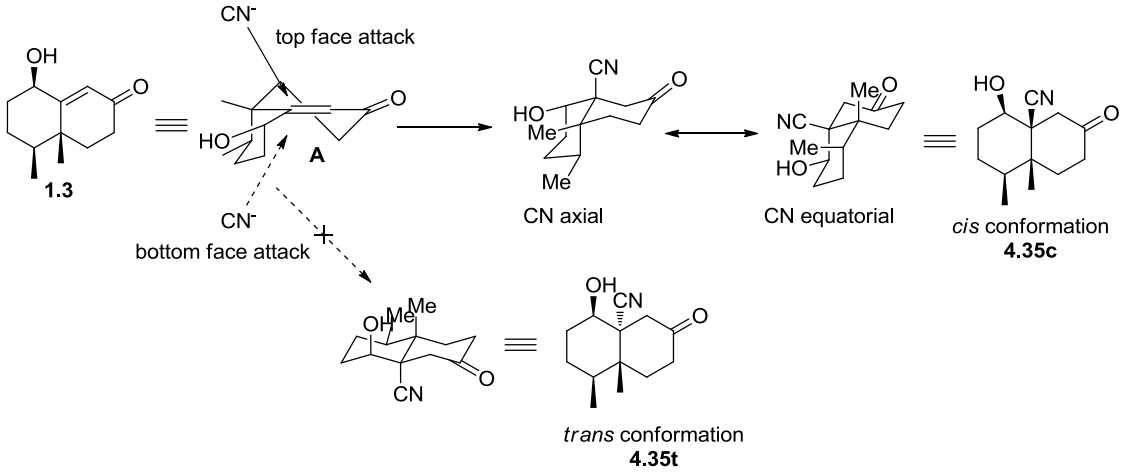
Exp.#	Conditions	Result (main products isolated)
1	2 equiv. KCN, 1.8 equiv.NH_4Cl, 1:1 EtOH:H_2O, reflux 20 hr	 1.3 20% **4.37** 40%
2	2 equiv. KCN, 1.8 equiv.NH_4Cl, 1:1 EtOH:H_2O, reflux 6 hr	 **4.35** 34% **1.3** 35% **4.37** 16%
3	3 equiv. KCN, 2 equiv. NH_4Cl, 1:1 EtOH:H_2O, reflux 6 hr	 **4.35** 10% **1.3** 15%
4	2 equiv. KCN, 1.8 equiv. NH_4Cl, 30 mol% 18-C-6, 1:1 EtOH:H_2O, reflux 4 hr 45min	 **4.35** 21% **1.3** 10%

The unoptimised yield of compound **4.35** from these test runs was 34% (entry 2, *table 4.9*). The cyano compound **4.35** was confirmed by CIMS (GCMS: (CI) *m/z* 221 $[M]^+$; 239 $[M+NH_4]^+$) and IR spectroscopy (IR (film) ν_{max} = 2227 cm^{-1} (C≡N)), and was obtained as a single diastereoisomer as shown by ^1H NMR and ^{13}C NMR spectroscopy.

*Stereochemistry of cyano compound **4.35***

Compound **1.3** exists as a decalin ring with one six membered chair attached to the second six membered ring in a twisted half chair conformation as a result of the sp^2 atoms (*scheme 4.36*, structure **A**). From conformational considerations, the single diastereoisomer obtained from these reactions was proposed to be the *cis* isomer **4.35c**. Attack of the cyanide nucleophile occurs axially (in order to achieve maximum overlap with the p orbitals of the enone) onto the top face (convex face) as it is more exposed resulting in the *cis* isomer **4.35c**, with both rings in the stable chair conformation. The *cis* isomer can exist as two possible conformers, one in which the nitrile group is axial, and the second in which the nitrile group is in the equatorial position. The two conformers are able to interconvert by bond rotation (ring flipping). At room temperature, the NMR spectrum displays an average of the signals from the two conformers.

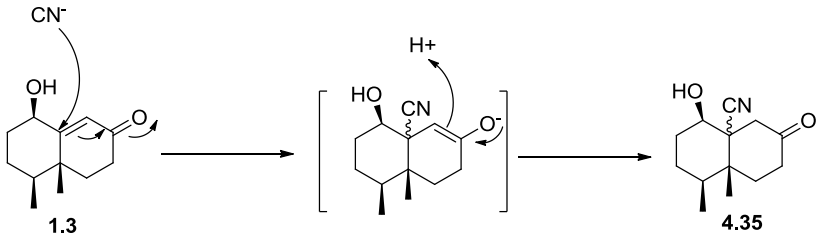
Scheme 4.36: Attack of the CN nucleophile onto the top face resulting in the cis product



Attack of the bottom face (concave face) is prevented by the steric hindrance from the twisted half chair so the *trans* isomer **4.35t** is not formed. Experimental evidence to support this proposal is observed in the experiment in which the MOM protected starting material **4.38** failed to yield any product, neither *cis* addition nor *trans* addition of the nitrile. The large MOM group caused excessive steric hindrance on the top face and the conformation of the starting material itself blocked attack from the bottom face resulting in no reaction (*scheme 4.34*).

The mechanism of this reaction is a conjugate addition in which the nucleophilic CN^- attacks the β-carbon of the enone followed by protonation of the α-carbon by the protic solvent (*scheme 4.37*).

*Scheme 4.37: Mechanism of hydrocyanation of compound **1.3***



The hydroxy group adjacent to the β-carbon could provide stereocontrol by chelating to the potassium ion which is also chelating to the π-system of C≡N thereby ensuring its *cis* addition by positioning it on the same side of the decalin ring. Metalated nitriles have been shown to exhibit stereocontrol in previous reactions.[45]

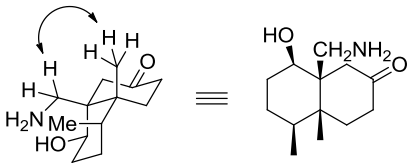
4.3.2.3. Future work for hydrocyanation of compound 1.3

For the optimisation of reaction conditions for hydrocyanation using KCN method and Et_2AlCN reagent, the temperature, solvent and concentration would be systematically modified on reactions of the same scale in order to increase yields of product. Other aprotic solvents have been used in hydrocyanations such as DMF, CH_2Cl_2 and benzene (toluene). As the *cis* product is the thermodynamically favourable product using KCN, longer reaction times should be employed with a reduced temperature to avoid side reactions.

Use of a HPLC chiral column would further confirm the compound as a single diastereoisomer and its high purity product could be used to grow a single crystal for X-ray crystallography, which would also give valuable additional conformational data.

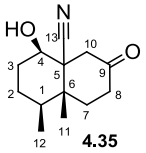
Further spectroscopic analysis is required, particularly the use of 2D NMR spectroscopy. If the cyano group was reduced (either to an alkyl amine **4.40** with Raney nickel under high pressure H_2, or to an aldehyde with DIBAL), a NOESY experiment should show correlations[46] between these new protons and the quaternary methyl group if the compound was in a *cis* conformation (*figure 4.2*).

Figure 4.2: NOE correlation between –CH_2NH_2 and quat.CH_3 would confirm cis isomer



cis conformation
4.40

A range of spectroscopic methods have been used to distinguish between *cis* and *trans* isomers of decalones in previously published literature. However, both the *cis* and *trans* isomer of each substrate is required pure in order to compare the data. In order to determine the stereochemistry of the cyano group without doubt, the *trans* isomer should be synthesised (by optimising the Et_2AlCN method and isolating the products by HPLC) and the following spectroscopic methods could be applied.

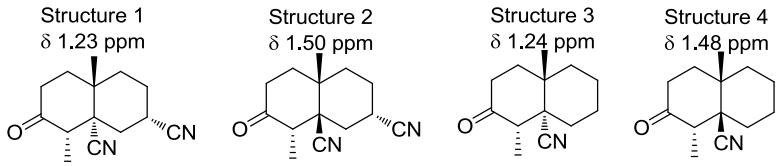


4.35

1. ^{1}H NMR spectroscopy

Rodig and Johnston[43] observed that the chemical shift of the quaternary methyl group in their bicyclic compounds (*figure 4.3*) was found to be consistently upfield for the *trans* isomer compared to the *cis*. This is a result of the dihedral angle between the quaternary methyl group and the cyano group at the other ring junction. In the *cis* isomer, the dihedral angle is approximately 60° whereas in the *trans* isomer, it is much larger at approximately 180°. This relates to the deshielding effect of the cyano group on the methyl. With the cyano group further away in the *trans* isomer, it exerts less of a deshielding effect on the CH_3, therefore the chemical shift is lower (upfield).

Figure 4.3: Chemical shift of quaternary methyl group of Rodig and Johnston's bicyclic cyano compounds

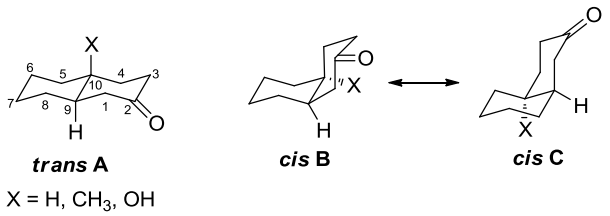


For our cyano compound **4.35**, C11 CH_3 has a chemical shift of δ 1.41 ppm which is similar to that of structure 4. This method of comparison could aid compound identification if we had the *trans* cyano compound **4.35t**.

2.^{13}C NMR spectroscopy

In the analysis of 10-substituted decal-2-ones (*figure 4.4*) by 2D NMR spectroscopic techniques, Vecchi *et al.*[47] observed several distinguishing features in the NMR spectra of the *cis* and *trans* isomers. They noted that the best criterion to distinguish a *cis* from a *trans* isomer is the presence in the *cis* isomer ^{13}C NMR spectra of some skeletal carbon signals (in their case, C-4, C-5 and C-7) with broadened line width and low intensity. This is a result of the two *cis* conformers inter-converting and indicates exchanging sites. In contrast, all the signals of the *trans* isomer were sharp and typical.

Figure 4.4: 10-substituted decal-2-ones analysed by Vecchi et al.

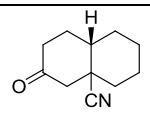
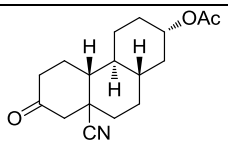
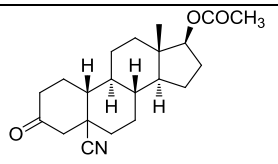
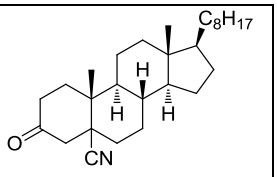


In the ^{13}C NMR spectra of compound **4.35**, C1 (CHOH) is of noticeably reduced intensity and broadened linewidth to the point where it cannot be observed unless extra scans were implemented or a 100 MHz spectrometer was used. C2 (CH_2) and C11 (quat.CCH_3) also show half the signal intensity expected (when compared to neighbouring CH_2 and CH_3). These observations indicate the *cis* isomer as expected but a comparison of the ^{13}C NMR spectra of the *trans* isomer is required to confirm this absolutely.

3. Infrared stretching bands comparison

Nagata *et al.*[48] observed slightly higher C≡N stretching bands for *cis* isomers of polycyclic cyano compounds when compared to their *trans* counterpart (*table 4.10*). The C≡N IR band for cyano **4.35** was observed at 2227 cm^{-1}. Rodig and Johnston also used this method among others to confirm their compound identification.

Table 4.10: Selection of C≡N stretching infrared absorption data from Nagata et al.

Structure				
Cis cm^{-1}	2238	2236	2238	2236
Trans cm^{-1}	2236	2234	2237	2235

4.3.3. Conclusion to chapter 4.3

Modified Reformatsky reaction

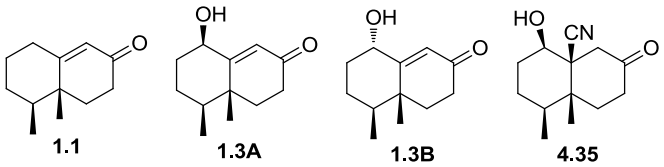
Although our initial results failed to produce the desired tricyclic compound **4.30**, we did obtain evidence that insertion of zinc was occurring. Reaction conditions were not fully explored as more promising results were obtained from the hydrocyanation investigations. However, the concept of forming a third ring and utilising it to install a handle at the quaternary centre is similar to that of Nicolaou's recent work (published several years after our investigations).[49] While Nicolaou employed an Ueno-Stark radical cyclisation, our investigations focused on a novel intramolecular Reformatsky reaction with an enone as the electrophile. If hydrocyanation yields could not be improved, this concept would be worth revisiting.

Hydrocyanation

Initial results have shown hydrocyanation is successful with hydroxy enone **1.3**. The regiospecific 1,4-addition of KCN to compound **1.3** was achieved in which a single diastereoisomer **4.35** was isolated. We have assigned the cyano stereocentre as *cis* as a result of the consideration of the conformation of starting enone **1.3**. Diastereoselectivity has been known to be achieved in conformationally restricted compounds.

Although yields obtained were unsatisfactory, there was insufficient time to optimise conditions. Our plan was to continue optimising hydrocyanation with KCN reaction conditions, as well as the alternative method utilising the Et_2AlCN reagent in order to synthesise and isolate the *trans* isomer in addition to the *cis* isomer. Only small amounts of the *trans* isomer would be required for spectroscopic studies in order to confirm absolutely that the product of the KCN hydrocyanation is indeed *cis*.

4.4. Conclusion to Chapter 4



1.1 1.3A 1.3B 4.35

The proposed key step to the total synthesis of nominine (1,4-addition of bromo-2-methyl-2-pentene followed by trapping of the enolate) was thoroughly investigated with a model compound then with enone **1.1**. However, no desired product was obtained with many conditions investigated resulting in no reaction observed. It was suspected that the β-carbon of the enone was too sterically hindered particularly for the long alkyl chain that was required for the natural product. Both Bonjoch and Nicolaou reported poor results with their attempts at 1,4-additions with similar intermediates towards the total synthesis of (a)nominine.

Three methods of installing the hydroxy group at C4 to give compound **1.3** were carried out. The highest yielding was found to be via a dienol ether intermediate yielding 41% of the desired *cis* isomer **1.3A** and 13% of the *trans* isomer **1.3B** which could be separated without difficulty. This was a sufficient yield to synthesise gram quantities of hydroxy enone **1.3**.

In the investigations of reactions of hydroxy enone **1.3**, hydrocyanation was found to be successful with the use of KCN. Although there was insufficient time to optimise yields, this 1,4-addition Michael type reaction was found to afford compound **4.35** as a single diastereoisomer with scope for elaboration into the desired natural product nominine.

4.5. References for Chapter 4

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Chapter 5. Future work towards the total synthesis of nominine and beyond

5.1. Towards the total synthesis of nominine

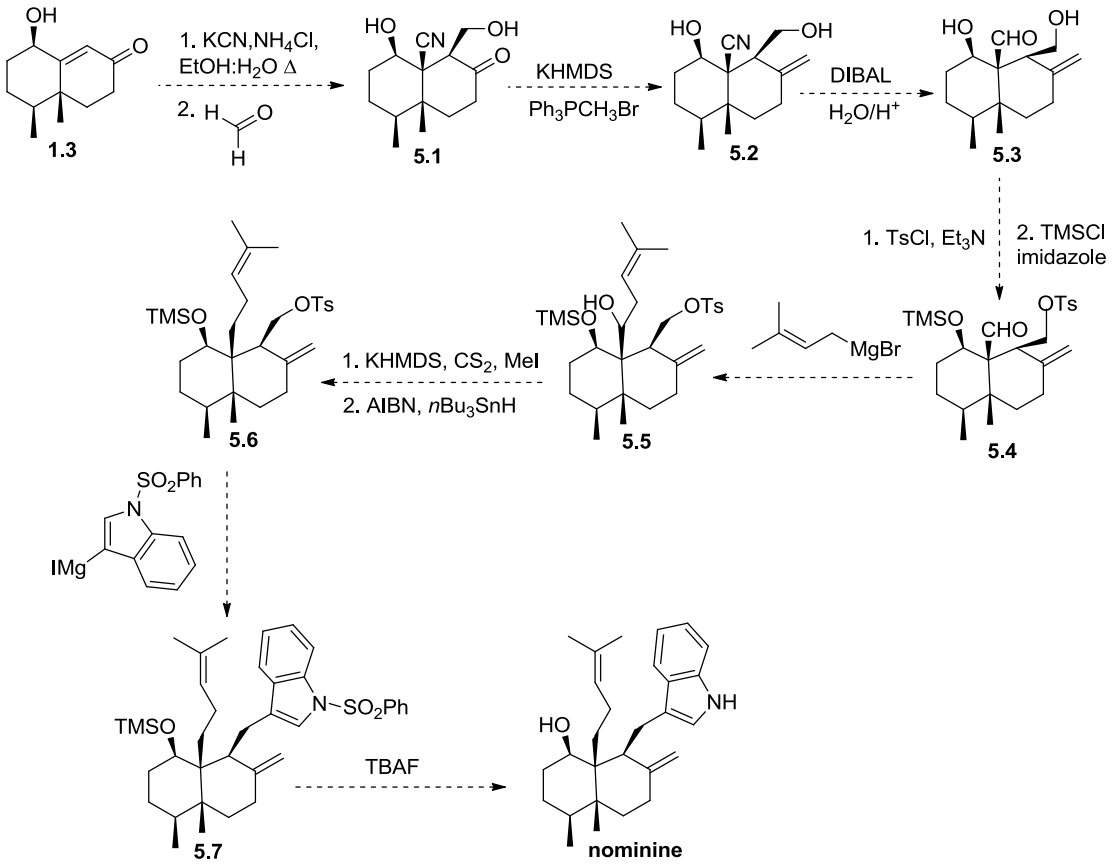
With initial studies demonstrating the success of the stereospecific hydrocyanation of hydroxy enone **1.3** to give cyano compound **4.35**, the main steps required towards the total synthesis are the extension of the nitrile group into the 2-methyl-petene fragment and installation of the indole at C10.

A one pot reaction consisting of the 1,4-addition of KCN followed by trapping of the enolate with formaldehyde to give compound **5.1** would be preferred. This alcohol at C10 would provide the necessary handle to install the indole group. However if problems arise with this one pot reaction, Nicolaou[1] has shown that deprotonation with LiHMDS was regiospecific and use of Mukiyama aldol conditions allowed the installation of an alcohol at C10. Epimerisation may be required to afford the core of the natural product with all the correct stereocentres in place.

A Wittig olefination with methyltriphenylphsophonium bromide would convert the carbonyl into alkene **5.2** followed by a DIBAL reduction of the nitrile group and subsequent hydrolysis into aldehyde **5.3**. The primary alcohol would then be selectively protected with 4-toluenesulfonyl chloride followed by protection of the secondary alcohol with a silylether (for example, TMSCl) to give compound **5.4**.

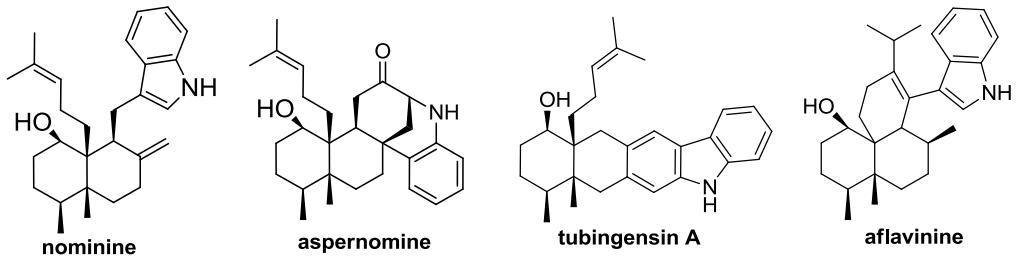
Using carefully controlled reaction conditions, a Grignard reaction between the aldehyde and bromo-3-methylbutene would elongate the quaternary carbon chain **5.5** but the resulting hydroxy group would need to be removed via xanthate formation and radical deoxygenation[1] to complete the alkenyl chain at quaternary carbon C5 to afford compound **5.6**. Coupling of the indole Grignard and tosylate[2] would give compound **5.7** and deprotection with TBAF would furnish the natural product nominine (*scheme 5.1*). Installing the alkenyl chain and indole via Grignard reactions allows for various coupling partners to be used in order to generate analogues for the discovery of a novel pesticide. The total number of steps is 22 which is comparable to Bonjochs' and Nicoloau's route to nominine.

*Scheme 5.1: Proposed route to nominine from hydroxy enone **1.3***



5.2. Beyond nominine

Nominine has been proposed to be the precursor to a family of indole diterpenoids for example, aspernomine, tubingensin A and aflavinine. With nominine in hand, the biosynthetic pathway to these other natural products could be explored.

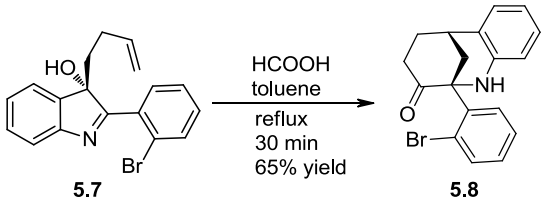


For example, aspernomine was also isolated from the sclerotia of *Aspergillus nomius*. Spectral data indicated similarities with nominine, however differences in UV and ^{13}C NMR spectra indicated the lack of an indole moiety. Further NMR experiments determined the structure of aspernomine containing a previously unreported ring system, so named 1,4,5,6-tetrahydro-2,6-methano-1-benzazocin-3(2H)-one.

Aspernomine was found to exhibit similar activity against *Heliothis zea* as nominine, in addition to exhibiting cytotoxicity against three human solid tumour cell lines, lung carcinoma, breast adenocarcinoma and colon adenocarcinoma. A synthetic approach has yet to be reported for the total synthesis of aspernomine.

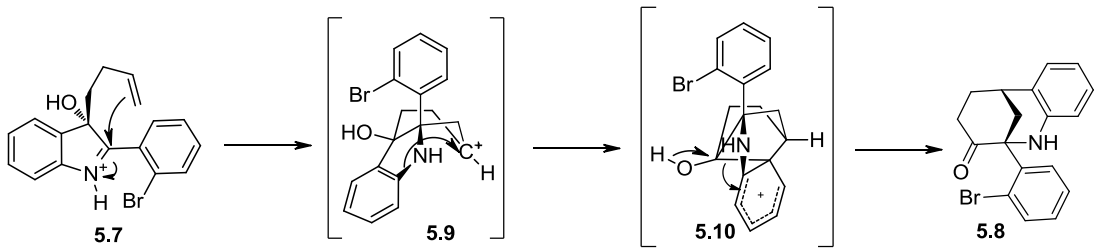
During the total synthesis of hinckdentine A, McWhorter and coworkers[4] observed the rearrangement of 2-(2-bromophenyl)-3-(3-butenyl)-3H-indol-3-ol **5.8** to the uncommon ring system containing **5.9**, also found in aspernomine (*scheme 5.2*).

*Scheme 5.2: Novel rearrangement of **5.7** to the uncommon ring system in **5.8***



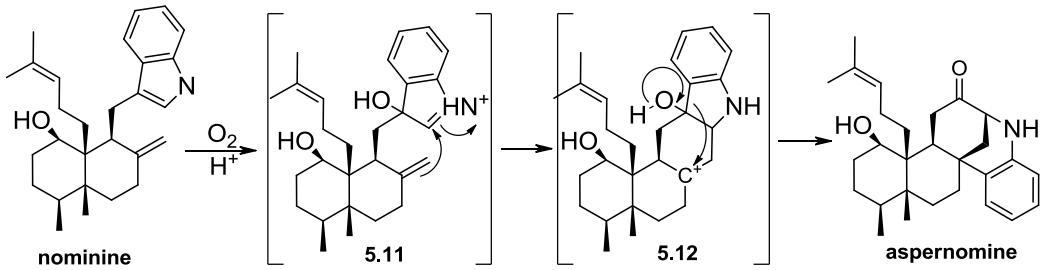
The proposed mechanism by McWhorter and co-workers suggested a Markovnikov addition of the protonated imine to the double bond in **5.7** forming a boat like intermediate **5.9**. The electron rich aromatic ring attacks the secondary carbocation to form intermediate **5.10** which breaks down to form the new ring system in compound **5.8** (*scheme 5.3*).

Scheme 5.3: Mechanism of novel rearrangement



This mechanism suggests a possible similar rearrangement of nominine to aspernomine. Nominine could be oxidized to form 3H-indol-3-ol **5.11** and would then contain the necessary functionalities to undergo the novel rearrangement in the presence of acid via intermediate **5.12** to form aspernomine (*scheme 5.4*). Tantillo *et al.*[5] carried out quantum chemical calculations which confirmed this proposed mechanism is energetically feasible. Investigations into the conditions required for this biomimetic conversion would result in the natural product synthesis of another active indole alkaloid.

Scheme 5.4: Proposed mechanism of nominine conversion to aspernomine



5.3. References for Chapter 5

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Chapter 6. Conclusion

At the commencement of this project, the total synthesis of (a)nominine had yet to be achieved. However, a year after practical work had ceased on this project, Bonjoch *et al.* published the first total synthesis of *ent*-anominine in 2010, followed by a second total synthesis in 2012 by Nicolaou *et al*.

Similarities between our synthetic route and that of Bonjoch and Nicolaou's strategy include the use of enone **1.1** and hydroxy enone **1.3** as a vital intermediate at some point in their investigations. Both groups investigated 1,4-addition reactions to install the alkene chain at the quaternary centre but also failed to yield the desired product. Bonjoch's solution was to install a propene moiety within their key Wieland-Miescher ketone analogue at the desired quaternary centre prior to cyclisation, and Nicolaou used hydroxy enone **1.3** to form a pentacycle/lactol at that junction (similar to our modified Reformatsky investigations). Our approach was to install a small nucleophile (the nitrile group) at that junction on hydroxy enone **1.3** which would allow for modification at a later stage.

The key intermediate bicyclic enone **1.1** had proven to be quite problematic where several synthetic routes had been explored. Several of the published procedures were found to be irreproducible despite several attempts. However, the discovery of a paper by Paquette *et al.* led to promising results as the published procedures were found to be reproducible and scalable. Large scale synthesis with the aid of Pfizer laboratories was successful, stockpiling more than 30 g of this racemic compound. Two natural products, dehydrofukinone and fukinone were synthesised using this key intermediate showcasing its versatility.

Continuing on with the total synthesis of nominine, 1,4-addition reactions on model compounds as well as enone **1.1** with the long chain alkenyl moiety was thoroughly investigated but failed to give the desired product. It was suspected that the β-carbon of the enone was too sterically hindered particularly for the long alkyl chain that was required for the natural product. Success was found with initial studies on the 1,4-addition of KCN to the intermediate hydroxy enone **1.3** which formed cyano compound **4.35** as a single diastereoisomer which we proposed to be the desired *cis* isomer. Further work towards the total synthesis of nominine has been outlined with scope to synthesise other active indole alkaloids.

Chapter 7. Experimental Section

7.1. General Experimental

^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker AC300, Bruker AM300 or Bruker DPX400 spectrometers in deuterated chloroform unless otherwise stated with chloroform (δ_H 7.27 ppm ^{1}H, δ_C 77.00 ppm ^{13}C) as the internal standard. Chemical shift values δ are quoted in ppm (parts per million). Multiplicities are described using the abbreviations s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet and br, broad.

Infrared spectra were recorded on a Nicolet 380 FT-IR (Thermo Electron Corporation). Infrared peaks are quoted in cm^{-1}.

Mass spectra were obtained on a Waters ZMD Single quadrupole mass spectroscopy with an electrospray ion source or a ThermoQuest TraceMS Single quadrupole GC-MS in either chemical ionisation or electron impact ionisation mode.

Melting points were determined using the Electrothermal melting point apparatus and are uncorrected.

All air and/or moisture sensitive reactions were carried out under argon atmosphere, in oven-dried glassware.

Reactions were monitored by thin layer chromatography using aluminium-backed plates coated with silica gel 60 containing a fluorescence indicator active at 254 nm; the chromatograms were visualised under UV light (254 nm) and by staining with 20% phosphomolybdic acid in ethanol (PMA) or cerium sulphate/ ammonium molybdate in 2M H_2SO_4(aq).

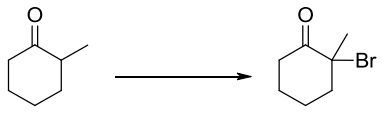
Flash chromatography was performed with 40-63 μm silica gel (Merck).

“Brine” refers to a saturated aqueous solution of sodium chloride.

Dichloromethane was dried by distillation from CaH_2 and THF was distilled from Na/benzophenone prior to use. All other solvents and reagents were used directly as supplied unless otherwise stated.

7.2. Experimental details

2-Bromo-2-methyl-1-cyclohexanone 2.45



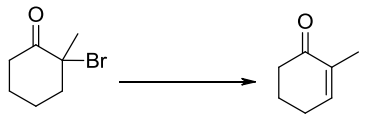
2.45

A solution of 2-methyl-1-cyclohexanone (3.30 mL, 27.0 mmol, 1 equiv.) and *N*-bromosuccinimide (4.81 g, 27.0 mmol, 1 equiv.) in CCl_4 (30 mL) was stirred at reflux overnight. The reaction mixture was cooled to room temperature and filtered through celite to remove succinimide and the filter cake washed with Et_2O (20 mL). The filtrate was concentrated to afford the title compound (R_f = 0.36, 30% EtOAc in hex) (5.17 g, quantitative yield) as a brown oil and taken on without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 3.21 (1H, td, *J* = 17, 8 Hz, 1H from CH_2CO); 2.42-2.31 (2H, m, CH_2); 2.16-2.0 (2H, m, CH_2); 1.82 (3H, s, CH_3); 1.78-1.72 (2H, m, CH_2); 1.68-1.52 (1H, m, 1H from CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 204.7 (C=O); 65.8 (quat.C); 43.6 (CH_2); 36.7 (CH_2); 28.1 (CH_3); 26.8 (CH_2); 22.3 (CH_2).[1] MS: ESI+ 215.0 [^{81}Br M+Na]$^+$; 213.0 [^{79}Br M+Na]$^+$.

Data consistent with literature: Hua, D.H.; Chen, Y.; Sin, H.; Maroto, M.J.; Robinson, P.D.; Newell, S.W.; Perchellet, E.M.; Ladesich, J.B.; Freeman, J.A.; Perchellet, J-P.; Chiang, P.K. *J. Org. Chem*. **1997**, *62*, 6888-6896.

2-Methyl-2-cyclohexen-1-one 2.31



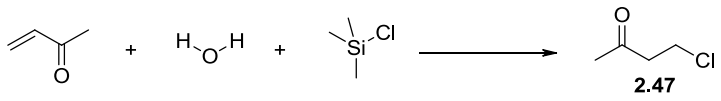
2.45 **2.31**

To a solution of compound **2.45** (5.47 g, 27.0 mmol, 1 equiv.), used without further purification, in DMF (60 mL) was added Li_2CO_3 (6.00 g, 81.0 mmol, 3 equiv.) and LiBr (7.03 g, 81.0 mmol, 3 equiv.). The resulting mixture was heated at 130 °C for three hours. The reaction mixture was cooled to room temperature, diluted with H_2O (60 mL) and extracted with Et_2O (3 x 40 mL). The mixture was filtered to remove insoluble foam as separation of phases was not clear. The organic extracts were combined, dried over $MgSO_4$ and concentrated to yield 2.03 g of a crude yellow oil which was purified by column chromatography (20% EtOAc in hexane) to afford the title compound (R_f = 0.24, 20% EtOAc in hex) (1.37 g, 46%) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 6.68 (1H, br. s, C=<u>CH</u>); 2.36 (2H, t, *J* = 7 Hz, CH_2); 2.30-2.23 (2H, m, CH_2); 1.97-1.88 (2H, m, CH_2); 1.71 (3H, q, *J* = 2 Hz, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 199.8 (C=O); 145.5 (C=<u>CH</u>); 135.6 (<u>C</u>=CH); 38.3 (CH_2); 26.0 (CH_2); 23.2 (CH_2); 15.9 (CH_3). MS: ESI+ 133.2 $[M + Na]^+$.

Data consistent with literature: Hua, D.H.; Chen, Y.; Sin, H.; Maroto, M.J.; Robinson, P.D.; Newell, S.W.; Perchellet, E.M.; Ladesich, J.B.; Freeman, J.A.; Perchellet, J-P.; Chiang, P.K. *J. Org. Chem*. **1997**, *62*, 6888-6896.

4-Chloro-2-butanone 2.47



2.47

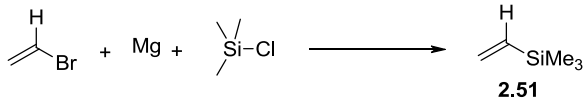
Water (0.44 mL, 24.0 mmol, 1.0 equiv.) was added to methyl vinyl ketone (2.70 mL, 32.0 mmol, 1.3 equiv.) and the reaction mixture stirred for five minutes before chlorotrimethylsilane (6.14 mL, 49.0 mmol, 2.0 equiv.) was added slowly dropwise as reaction was exothermic. The reaction mixture was stirred overnight at room temperature with the colour turning from clear to a yellow/brown over time. The trimethylchlorosilane and hexamethyldisiloxane were removed on the rotary evaporator and the residual taken up in CH_2Cl_2 (5 mL). The solution was stirred with $MgSO_4$ for half an hour to remove water and the mixture concentrated for half an hour with the water bath at room temperature. This afforded the crude title compound (R_f = 0.6, 20% EtOAc in hex) (2.20 g, 86%) as a dark brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 3.70 (2H, t, *J* = 7 Hz, CH_2Cl); 2.89 (2H, t, *J* = 7 Hz, $C{=}OCH_2$); 2.18 (3H, s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 205.0 (C=O); 45.8 ($C{=}O\underline{CH_2}$); 38.2 (CH_2Cl); 30.2 (CH_3). MS: ESI+ 129.6 $[M + Na]^+$.

^{1}H NMR data is consistent with literature (no literature ^{13}C NMR data was available):

Boudjouk, P.; Kim, B-K.; Han, B-H. *Synth. Commun.* **1996**, *26* (18), 3479-3484.

Trimethyl-vinyl-silane 2.51

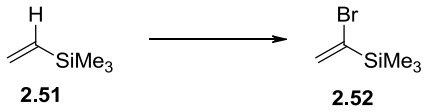


2.51

A 3-neck flask was fitted with a condenser, stirrer and charged with $Mg_{(s)}$ (0.48 g, 20.0 mmol, 1.0 equiv.) and heated with a heat gun under Ar atmosphere to activate Mg. Mg was allowed to cool for 15 minutes before anhydrous THF (16 mL) and one small iodine crystal was added. The flask was swirled to disperse the brown colour. A portion of 1.0 M vinyl bromide in THF (20 mL, 20.0 mmol, 1.0 equiv.) was added and heated gently, with no stirring until reflux was attained with solution turning colourless. Gentle heating was required whilst stirring to maintain reflux as remaining vinyl bromide solution was added dropwise. The solution remained stirring at reflux for one hour before slow dropwise addition of 1.0 M chlorotrimethylsilane in THF (19.9 mL, 20.0 mmol, 1.0 equiv.) over half an hour. The solution was stirred at reflux for two hours then stirred at room temperature overnight. Product was isolated by distillation with a Vigreux column (bp. 60-65 °C) to afford the title compound (12.7 g, 38% yield by ^{1}H NMR) as a colourless liquid.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 6.15 (1H, m, C=<u>CH</u>); 5.91 (1H, dd, *J* = 15, 4 Hz, HC=<u>CH_2</u>); 5.65 (1H, dd, *J* = 20, 4 Hz, HC=<u>CH_2</u>); 0.07 (9H, s, 3 x CH_3).

(1-Bromo-vinyl)-trimethyl-silane 2.52



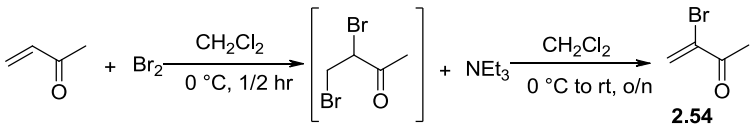
2.51 **2.52**

Bromine (0.77 mL, 15.0 mmol, 1.5 equiv) was added dropwise over half an hour to compound **2.51** (1.0 g, 10.0 mmol, 1.0 equiv.) at -78 °C whilst stirring to form an orange solution which was allowed to warm to room temperature. Et_2NH (6.75 mL, 65.0 mmol, 6.5 equiv.) was added dropwise whilst stirring to dissipate the yellow precipitate that formed. The reaction mixture was stirred at reflux overnight, cooled to room temperature and the diethylamine hydrochloride precipitate filtered off and the solid washed with Et_2O (5 mL). The organic solution was washed with 10 % HCl until aqueous layer remained acidic, then washed with portions of H_2O and brine. The organic layer was dried over $MgSO_4$ and concentrated to afford the title compound crude (0.55 g, approx. 29%) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 6.27 (1H, d, *J* = 2 Hz, C=$\underline{CH_2}$); 6.18 (1H, d, *J* = 2 Hz, C=$\underline{CH_2}$); 0.20 (9H, s, $SiMe_3$).

^{1}H NMR data is consistent with literature: Boeckman, R.K. Jr.; Blum, D.M.; Ganem, B.; Halvey, N. *Org*. *Synth*. **1978**, *58*, 152-156.

3-Bromo-but-3-en-2-one 2.54

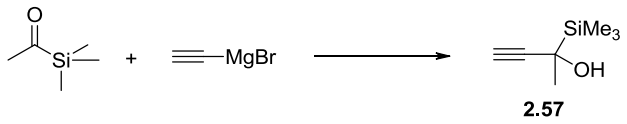


Bromine (4.10 mL, 80.0 mmol, 1.0 equiv.) in anhydrous CH_2Cl_2 (10 mL) was added dropwise over an hour to a stirring solution of methyl vinylketone (6.6 mL, 80.0 mmol, 1.0 equiv.) in anhydrous CH_2Cl_2 (40 mL) at 0 °C. The solution turned from colourless to a brown colour and was left stirring at 0 °C for half an hour. Triethylamine (28 mL, 200 mmol, 2.5 equiv.) in anhydrous CH_2Cl_2 (20 mL) was added slowly forming a creamy yellow mixture with precipitate and reaction was left stirring overnight at room temperature. The reaction mixture was dissolved in CH_2Cl_2 (10 mL), washed with 2M HCl (5 mL) and H_2O (5 mL). The combined organic layers were dried over $MgSO_4$ and evaporated to afford the crude title compound (R_f = 0.32, 100% CH_2Cl_2) (10.7 g, 90%) as a dark yellow liquid.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 6.80 (1H, d, *J* = 2 Hz, C=C<u>H$_2$</u>); 6.42 (1H, d, *J* = 2 Hz, C=C<u>H$_2$</u>); 2.48 (3H, s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 192.1 (C=O); 132.2 (quat.C); 129.8 (CH_2); 26.3 (CH_3). MS: ESI+ 172.9 [^{81}Br M + Na]$^+$; 170.9 [^{79}Br M + Na]$^+$.

Data consistent with literature: Murphy, J.A.; Scott, K.A.; Sinclair, R.S.; Martin, C.G.; Kennedy, A.R.; Lewis, N. *J. Chem. Soc. Perkin Trans. 1* **2000**, 2395-2408.

2-(trimethylsilyl)but-3-yn-2-ol 2.57

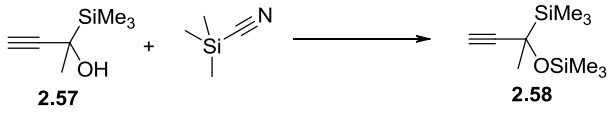


2.57

A solution of 0.5 N ethynylmagnesiumbromide in THF (24 mL, 12.0 mmol, 1.2 equiv.) in anhydrous THF (20 mL) was treated dropwise at room temperature with a solution of acetyltrimethylsilane (1.43 mL, 10.0 mmol, 1.0 equiv.) in THF (20 mL) over half an hour and stirred for 20 minutes. The reaction mixture was hydrolysed with dilute aqueous NH_4Cl, extracted with pentane and dried over $MgSO_4$ to afford the title compound crude (1.42 g with 30% THF, 69%) as a brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.59 (1H, s, C≡<u>CH</u>); 1.46 (3H, s, CH_3); 0.13 (9H, s, $SiMe_3$).

Trimethyl((2-(trimethylsilyl)but-3-yn-2-yl)oxy)silane 2.58

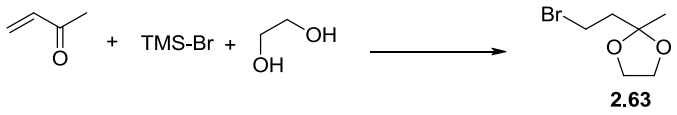


Trimethylsilyl cyanide (1.7 mL, 12.6 mmol, 2.0 equiv.) was added dropwise to compound **2.57** (0.9g, 6.3 mmol, 1.0 equiv. with 30% THF) and the reaction mixture heated to 60 °C overnight. The reaction mixture was cooled and placed on a rotary evaporator at 40 °C for one hour to remove excess trimethylsilyl cyanide to afford the title compound crude (1.10 g, 85%) as a light brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.6 (1H, s, C≡CH); 1.42 (3H, s, CH_3); 0.16 (9H, s, $OSiMe_3$); 0.07 (9H, s, $SiMe_3$).

^{1}H NMR data is consistent with literature: Cunico, R.F. *Tetrahedron Lett.* **1994**, *35*, 2291-2294.

2-(2-Bromoethyl)-2-methyl-1,3-dioxolane 2.63



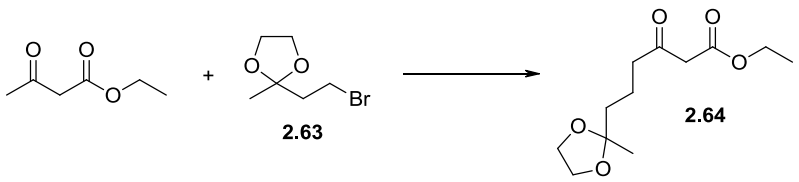
2.63

Methyl vinyl ketone (1.66 mL, 20.0 mmol, 1.0 equiv.) was added dropwise to a solution of bromotrimethylsilane (3.16 mL, 24.0 mmol, 1.2 equiv.) in benzene (30 mL) at 0 °C. The resulting mixture was then stirred at 0 °C for 30 minutes and at room temperature for an additional one hour. To the reaction mixture was added ethylene glycol (1.6 mL, 28.0 mmol, 1.4 equiv.) and *para*-toluenesulfonic acid (100 mg, catalytic amount). The mixture was azeotropically distilled for four hours. After cooling, the reaction mixture was diluted with benzene (20 mL) and washed with $NaHCO_3$ (saturated) and H_2O. The organic layer was dried with $MgSO_4$ and concentrated to afford the title compound (R_f = 0.46, 30% EtOAc in hex.) (3.0 g, 77%) as a dark brown/green liquid.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 3.99-3.88 (4H, m, dioxolane 2 x CH_2); 3.44-3.39 (2H, m, Br$\underline{CH_2}$); 2.29-2.24 (2H, m, CH_2); 1.33 (3H, s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 109.1 (quat.C); 64.6 (dioxolane 2xOCH_2); 42.8 (CH_2); 26.8 ($BrCH_2$); 24.0 (CH_3). MS: ESI+ 219.0 [^{81}Br M + Na]$^+$; 217.0 [^{79}Br M + Na]$^+$.

^{1}H NMR data is consistent with literature (No published ^{13}C NMR data): Hsung, R.P. *Synth. Commun*. **1990**, *20*, 1175-1179.

Ethyl 6-(2-methyl-1,3-dioxolan-2-yl)-3- oxohexanoate 2.64

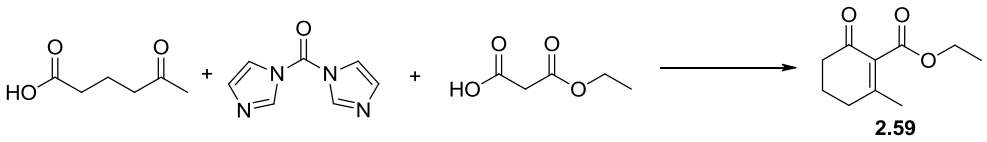


To NaH 60% suspension in mineral oil (0.18 g, 4.4 mmol, 3 equiv.) was added THF (5 mL) and the suspension was cooled in an ice-water bath and anhydrous hexamethylphosphoramide (0.3 mL, 2.2 mmol, 0.5 equiv.) was added. Ethyl acetoacetate (0.2 mL, 1.5 mmol, 1.0 equiv.) was added dropwise to the above suspension which was stirred at 0 °C for one hour before the dropwise addition of *n*-butyllithium (2.5 mL, 4.2 mmol, 2.8 equiv.). The resulting solution was stirred at 0 °C for 30 mins forming a yellow colour. Compound **2.63** (0.82g, 4.2 mmol, 2.8 equiv.) in THF (1 mL) was added and the reaction mixture stirred for an additional hour at 0 °C. The reaction mixture was quenched with aqueous NH_4Cl, washed with $NaHCO_{3(sat)}$ and extracted with CH_2Cl_2 (2 x 3 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to give 1.1 g of a crude yellow oil which was purified by column chromatography to afford the title compound (R_f = 0.15, 30% EtOAc in hex) (0.24 g, 65%) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 4.19 (2H, q, *J* = 7 Hz, $CO_2\underline{CH_2}CH_3$); 3.97-3.87 (4H, m, dioxolane 2 x CH_2); 3.42 (2H, s, $COCH_2CO$); 2.57 (2H, t, *J* = 7 Hz, $CO\underline{CH_2}CH_2$); 1.77-1.61 (4H, m, 2 x CH_2); 1.30 (3H, s, CH_3); 1.27 (3H, t, *J* = 7 Hz, $CO_2CH_2\underline{CH_3}$). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 202.5 (C=O); 167.2 ($\underline{CO_2}CH_2CH_3$); 109.8 (quat.C); 64.6 (dioxolane CH_2); 61.3 ($\underline{CH_2}CH_3$); 49.3 ($CO\underline{CH_2}CO$); 42.8 ($CO\underline{CH_2}CH_2$); 38.0 (CH_2); 23.7 (CH_3); 18.0 (CH_2); 14.1 ($CH_2\underline{CH_3}$). MS: ESI+ 267.3 $[M + Na]^+$.

Data consistent with literature: Rychnovsky, S.D.; Mickus, D.E. *J.Org.Chem.* **1992**, *57*, 2732-2736.

Ethyl 2-methyl-6-oxocyclohex-1-enecarboxylate 2.59



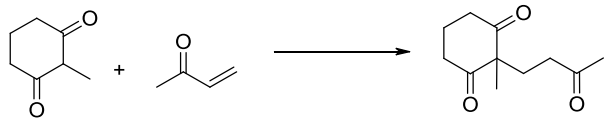
2.59

To a solution of acetobutyric acid (1.13 mL, 10.0 mmol, 1.0 equiv.) in THF (50 mL) was added carbonyldiimidazole (1.94 g, 12.0 mmol, 1.1 equiv.). After stirring at room temperature for six hours, the magnesium salt prepared from magnesium ethoxide (0.68 g, 6.0 mmol, 0.5 equiv.) and monoethyl malonate (1.41 mL, 12.0 mmol, 1.2 equiv.) was added. The reaction mixture was stirred for 18 hours. After filtration and evaporation, the residue was partitioned between Et_2O (20 mL) and 0.5M HCl (10 mL). The organic layer was washed with $NaHCO_{3(sat)}$, H_2O, brine, dried over $MgSO_4$ and evaporated to yield 1.8 g of a crude oil which was purified by column chromatography (gradient 20-50% EtOAc in hexane) to afford the title compound (R_f = 0.4, 50% EtOAc in hex) (1.4 g, 74%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 4.23 (2H, q, *J* = 7 Hz, $\underline{CH_2}CH_3$); 2.37-2.31 (4H, m, 2 x CH_2); 1.99-1.90 (2H, m, CH_2); 1.92 (3H, s); 1.26 (3H, t, *J* = 7 Hz, $CH_2\underline{CH_3}$). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 194.9 (C=O); 166.8 (CO_2); 159.9 (C=$\underline{C}CH_3$); 133.3 ($\underline{C}$=CCH_3); 61.2 ($\underline{CH_2}CH_3$); 36.9 (CO$\underline{CH_2}$); 31.6 (CH_2); 22.0 (CH_2); 21.7 (C=C-$\underline{C}H_3$); 14.2 ($CH_2\underline{CH_3}$). MS: ESI+ 205.3 $[M + Na]^+$.

^{1}H NMR data is consistent with literature (No published ^{13}C NMR data): Nishizuka, T.; Hirosawa, S.; Kondo, S.; Ikeda, D.; Takeuchi, T. *J. Antibio*. **1997**, *50*, 755-765.

2-methyl-2-(3-oxobutyl)cyclohexane-1,3-dione 2.65

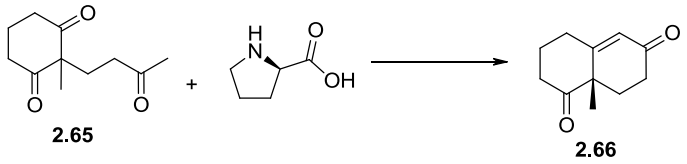


2.65

To a well stirred suspension of 2-methyl-1,3-cyclohexanedione (12.6 g, 0.1 mol, 1.0 equiv.) in distilled water (90 mL) was added acetic acid (0.3 mL), hydroquinone (100 mg) and methyl vinyl ketone (16.6 mL, 0.2 mmol, 2.0 equiv.). The reaction mixture was stirred at 74 °C for one hour, cooled to room temperature, treated with NaCl (1 g) and poured into a separating funnel containing EtOAc (20 mL). The organic phase was collected and the aqueous phase was re-extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and evaporated to afford the title compound (R_f = 0.36, 60% EtOAc in hex) (19.1 g, 97%) as a crude yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.75-2.56 (4H, m, cyclohex. 2 x CH_2); 2.32 (2H, t, *J* = 6 Hz, $CO\underline{CH_2}CH_2$); 2.08 (3H, s, $CO\underline{CH_3}$); 2.03 (2H, t, *J* = 6 Hz, $COCH_2\underline{CH_2}$); 1.98-1.81 (2H, m, cyclohex. CH_2); 1.22 (3H, s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 209.9 (2 x C=O); 207.5 (C=O); 64.3 (quat.C); 38.3 (CH_2); 37.7 (2 x cyclohex CH_2); 29.9 (CH_2); 29.5 ($CO\underline{CH_3}$); 20.1 (cyclohex CH_2); 17.6 (CH_3). MS: ESI+ 291 $[M + Na]^+$.

(*S*)-8a-methyl-3,4,8,8a-tetrahydronaphthalene-1,6(2H,7H)-dione 2.66



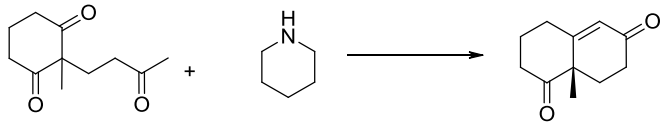
L-Proline (0.24 g, 2.1 mmol, 5 mol%) was added to a stirring solution of compound **2.65** (8.15 g, 42 mmol, 1.0 equiv.) in anhydrous DMSO (40 mL) at room temperature under N_2 and stirred for five days. The reaction mixture was extracted with EtOAc and washed with H_2O (6 x 100 mL) to remove the DMSO. The organic layer was dried over $MgSO_4$ and the solvent evaporated to yield 6.7 g of a purple viscous liquid which was distilled under high vacuum using short path cold finger distillation equipment (0.005mm Hg, 78-100 °C) to yield 5.03 g of a red oil. Et_2O (30 mL) was added and the solution was seeded with a few pure crystals of (*S*)-(+)-Wieland-Miescher ketone (Sigma Aldrich, (*S*)-(+)-3,4,8,8a-Tetrahydro-8a-methyl-1,6(2H,7H)-naphtha-lenedione) at 0 °C and left in -20 °C freezer overnight. The resulting crystals were filtered off and washed with 0 °C hexane and dried over the high vacuum pump for three hours to afford the title compound (R_f = 0.24, 50% EtOAc in hex) (3.10 g, 42%) as grey crystals (65% ee).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.78 (1H, d, *J* = 2 Hz, C=CH); 2.73-2.60 (2H, m, C=CHCOCH$_2$); 2.48-2.36 (4H, m, $COCH_2$ + CH_2); 2.14-2.02 (3H, m, CH_2); 1.72-1.56 (1H, m, CH_2); 1.39 (3H, s, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 210.9 (C=O); 198.1 (C=CHC=O); 165.8 (C=CH); 125.7 (C=CH); 50.6 (quat.CCH_3); 37.6 (COCH_2); 33.6 (CH_2); 31.7 (CH_2); 29.7 (CH_2); 23.2 (CH_3); 22.9 (CH_2). MS: ESI+ 179.3 $[M+H]^+$; 201.3 $[M+Na]^+$. Mpt 48 °C. $[a]^{25}_D$ +65.1 (c 1.00 toluene); published value of the pure crystals $[\alpha]_D^{25}$ +97.3 (toluene, *c* 1.0) Buchschacher, P.; Fürst, A.; Gutzwiller, J. *Org. Synth.* **1985**, *63*, 37-41.

^{1}H NMR data is consistent with literature: Fuhshuku, K.; Funa, N.; Akeboshi, T.; Ohta, H.; Hosomi, H.; Ohba, S.; Sugai, T. *J. Org. Chem.* **2000,** *65,* 129-135.

^{13}C NMR data is consistent with literature: Bonjoch, J.; Díaz, S.; González, A.; Bradshaw, B.; Cuesta, J.; *J. Org. Chem*. **2005**, *70*, 3749-3752.

(±)-(S)-8a-Methyl-3,4,8,8a-tetrahydro-1,6(2H, 7H)-naphthalenedione 2.66



2.65 **2.66**

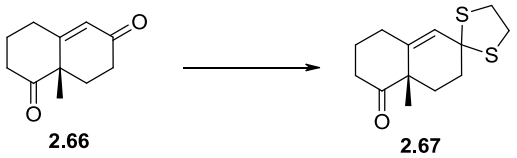
Pyrrolidine (0.82 mL, 9.8 mmol, 10 mol%) was added dropwise to a stirring solution of compound **2.65** (19.3 g, 98 mmol, 1.0 equiv.) in toluene (80 mL) with a colour change from yellow to orange/red. The reaction was azeotropically distilled for one and a half hours during which all water collected was removed and reflux continued to remove an additional 10 mL solvent. The resulting brown/black mixture was cooled to room temperature, diluted with Et_2O and washed with a solution made of 10% HCl: H_2O (1:6). The aqueous layer was extracted with Et_2O and the combined organic extracts were washed with H_2O, brine, dried over $MgSO_4$ and evaporated to yield 12.7 g of a crude brown liquid which was purified by column chromatography (50% EtOAc in hexane) to afford the title compound (R_f = 0.24, 50% EtOAc in hex) (12.5g, 72%) as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.85 (1H, d, *J* = 2 Hz, C=CH); 2.79-2.64 (2H, m, C=CHCOCH$_2$); 2.56-2.40 (4H, m, $COCH_2$ + CH_2); 2.22-2.06 (3H, m, CH_2); 1.80-1.62 (1H, m, CH_2); 1.45 (3H, s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 210.9 (C=O); 198.1 (C=CHC=O); 165.7 (C=CH); 125.8 (C=CH); 50.6 (quat.CCH_3); 37.6 ($COCH_2$); 33.6 (CH_2); 31.7 (CH_2); 29.7 (CH_2); 23.2 (CH_3); 22.9 (CH_2). MS: ESI+ 179.3 $[M+H]^+$; 201.3 $[M + Na]^+$.

^{1}H NMR data is consistent with literature: Fuhshuku, K.; Funa, N.; Akeboshi, T.; Ohta, H.; Hosomi, H.; Ohba, S.; Sugai, T. *J. Org. Chem.* **2000,** *65,* 129-135.

^{13}C NMR data is consistent with literature: Bonjoch, J.; Díaz, S.; González, A.; Bradshaw, B.; Cuesta, J.; *J. Org. Chem*. **2005**, *70*, 3749-3752.

(±)-(S)--4a'-Methyl-4',4a',7',8'-tetrahydro-3'H-spiro[[1,3]dithiolane-2,2'-naphthalen]-5'(6'H)-one 2.67



2.66 **2.67**

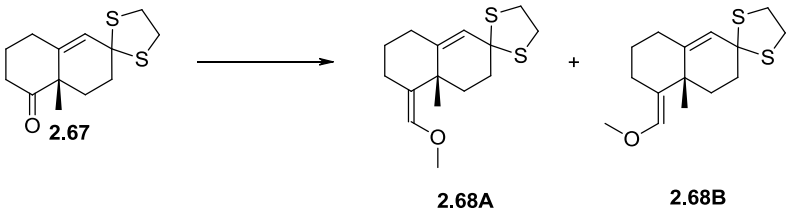
To a solution of compound **2.66** (20.2 g, 0.11 mol, 1.0 equiv.) in glacial acetic acid (45 mL) was added 1,2-ethanedithiol (10.5 mL, 0.12 mol, 1.1 equiv.), *p*-toluenesulfonic acid (10.15 g, 0.05 mol, 47 mol%) and glacial acetic acid (120 mL). The mixture was stirred at room temperature for six hours, poured into H_2O (100 mL) and stirred for 15 minutes. The solid was filtered off, washed successively with dilute aqueous $NaHCO_3$ and H_2O and then dried over $MgSO_4$ to yield 28.0 g of a crude yellow solid which was purified by column chromatography (5% EtOAc in hexane) to afford the title compound (R_f = 0.35, 20% EtOAc in hex) (26.7 g, 95%) as a colourless amorphous solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.66 (1H, s, C=CH); 3.38-3.31 (3H, m, CH_2's); 3.30-3.18 (1H, m, CH_2's); 2.67-2.45 (2H, m, CH_2); 2.39-2.31 (1H, m, from CH_2); 2.25-2.12 (4H, m, 2 x SCH_2); 2.05-1.95 (1H, m, from CH_2); 1.81-1.50 (2H, m, CH_2); 1.28 (3H, s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 212.9 (C=O); 141.3 (C=CH); 128.1 (C=CH); 64.9 (quat.C dithiane); 49.5 (quat.CCH_3); 40.2 (SCH_2); 39.7 (SCH_2); 38.0 ($COCH_2$); 37.7 (CH_2); 30.9 (CH_2); 30.8 (CH_2); 24.8 (CH_2); 24.6 (CH_3). MS: ESI+ 255.3 $[M + H]^+$; 531.3 $[2M + Na]^+$.

Data consistent with literature: Paquette, L.A.; Wang, T-Z.; Philippo, C. M. G.; Wang, S. *J. Am. Chem. Soc.* **1994**, *116*, 3367-3374.

(±)-(S,*Z*)-5'-(Methoxymethylene)-4a'-methyl-4',4a',5',6',7',8'-hexahydro-3'H-spiro[[1,3]dithiolane-2,2'-naphthalene] 2.68A

(±)-(S,*E*)-5'-(Methoxymethylene)-4a'-methyl-4',4a',5',6',7',8'-hexahydro-3'H-spiro[[1,3]dithiolane-2,2'-naphthalene] 2.68B

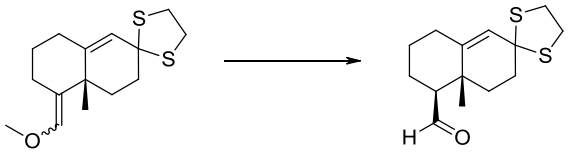


To a cold (-30 °C) solution of (methoxymethyl) triphenylphosphonium chloride (18.8 g, 55 mmol, 3.0 equiv.) in THF (160 mL) was added potassium hexamethyldisilazane (0.5 M in toluene, 90.0 mL, 45 mmol, 2.5 equiv.). The resulting red solution was stirred at 0 °C for 30 minutes before being treated with a solution of compound **2.67** (4.65 g, 18 mmol, 1.0 equiv.) in THF (40 mL). The reaction mixture was stirred at room temperature for 24 hours, quenched with aqueous $NaHCO_3$ and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with H_2O, brine, dried over $MgSO_4$ and concentrated to yield 26 g of a crude brown liquid which was first purified through a short silica plug (60% CH_2Cl_2 in hex) to yield 7.83 g of a yellow liquid. This was further purified by column chromatography (gradient 10-50% CH_2Cl_2 in hexane) to afford the title compounds **2.68A** (1.54 g) (R_f = 0.6, 20% CH_2Cl_2 in hex), **2.68B** (2.43 g) (R_f = 0.5, 20% CH_2Cl_2 in hex) and mixed fractions (0.92 g); total Wittig product formed (4.9 g, 96%) as a yellow oil.

Wittig 2.68A product: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.65 (1H, s, C=<u>CH</u>OCH_3); 5.51 (1H, s, C=<u>CH</u>); 3.48 (3H, s, OCH_3); 3.39-3.31 (3H, m, from SCH_2); 3.28-3.18 (1H, m, from SCH_2); 2.33-2.13 (5H, m, from CH_2); 2.10-1.97 (2H, m, from CH_2); 1.93-1.84 (1H, m, from CH_2); 1.73-1.61 (1H, m, from CH_2); 1.54-1.40 (1H, m, from CH_2); 1.27 (3H, s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 144.9 (<u>C</u>=CH); 140.8 (C=<u>CH</u>CH_3); 125.5 (C=<u>CH</u>); 122.6 (<u>C</u>=CHCH_3); 65.8 (quat.C dithiane); 59.5 (OCH_3); 39.9 (SCH_2); 39.6 (SCH_2); 39.2 (<u>quat.C</u>CH_3); 38.4 (CH_2); 35.2 (CH_2); 31.3 (CH_2); 28.6 (CH_2); 26.3 (CH_2); 24.1 (CH_3). MS: ESI+ 283.3 $[M + H]^+$. IR (film): ν_{max} = 2926, 2836 (OCH_3), 1660, 1437 cm^{-1}.

Wittig 2.68B product: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.81 (1H, d, *J* = 2 Hz, C=<u>CH</u>OCH_3); 5.46 (1H, s, C=<u>CH</u>); 3.55 (3H, s, OCH_3); 3.40-3.32 (3H, m, from SCH_2); 3.28-3.18 (1H, m, from SCH_2); 2.83-2.76 (1H, m, from CH_2); 2.33-2.22 (3H, m, from CH_2); 2.09-1.68 (5H, m, from CH_2); 1.34-1.24 (1H, m, from CH_2); 1.21 (3H, s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 145.0 (<u>C</u>=CH); 139.9 (C=<u>CH</u>CH_3); 125.2 (<u>C</u>=CHCH_3); 124.2 (C=<u>CH</u>); 65.9 (quat.C dithiane); 59.4 (OCH_3); 40.0 (SCH_2); 39.5 (SCH_2); 38.1 (CH_2); 37.3 (<u>quat.C</u>CH_3); 34.6 (CH_2); 32.7 (CH_2); 27.4 (CH_2); 26.6 (CH_3); 21.9 (CH_2). MS: ESI+ 283.3 $[M + H]^+$. IR (film): ν_{max} = 2926, 2837 (OCH_3), 2360, 1664 cm^{-1}**.**

(±)-(4a'R,5'S)-4a'-Methyl-4',4a',5',6',7',8'-hexahydro-3'H-spiro[[1,3]dithiolane-2,2'-naphthalene]-5'-carbaldehyde 2.69



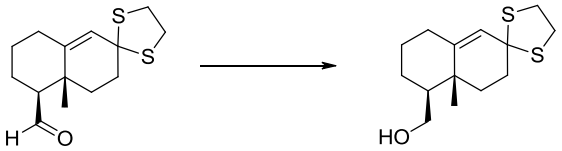
2.68A & 2.68B **2.69**

A solution of MeOH in THF (1:1, 30 mL) and 4N HCl (30 mL) was added to a solution of compound **2.68A** and **2.68B** (3.56g, 12.6 mmol, 1.0 equiv.) in THF (30 mL) at 0 °C and the resulting solution was stirred at room temperature for 48 hours, forming precipitate. The reaction was poured into H_2O (40 mL) and extracted with Et_2O (4 x 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to yield 3.53 g of a yellow solid which was purified by column chromatography (gradient 20-70% CH_2Cl_2 in hexane) to afford the title compound (R_f = 0.37, 70% CH_2Cl_2 in hex) (3.24 g, 96%) as a colourless amorphous solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 9.81 (1H, d, *J* = 2 Hz, CHO); 5.56 (1H, s, C=CH); 3.41-3.33 (3H, m, from SCH_2); 3.28-3.18 (1H, m, from SCH_2); 2.23-2.10 (4H, m, CHCHO + from CH_2); 2.06-1.97 (3H, m, from CH_2); 1.92-1.83 (1H, m, from CH_2); 1.77-1.72 (2H, m, from CH_2); 1.40-1.21 (1H, m, from CH_2); 1.14 (3H, s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 204.4 (CHO); 143.3 (C=CH); 125.9 (C=CH); 65.1 (quat.C dithiane); 60.6 (CHCHO); 40.1 (SCH_2); 39.6 (SCH_2); 37.3 (CH_2); 37.2 (CH_2); 36.8 (CCH_3); 31.7 (CH_2); 25.9 (CH_2); 22.1 (CH_2); 19.6 (CH_3). MS: ESI+ 291.3 $[M + Na]^+$.

Data consistent with literature: Paquette, L.A.; Wang, T-Z.; Philippo, C. M. G.; Wang, S. *J. Am. Chem. Soc.* **1994**, *116*, 3367-3374.

(±)-((4a'R,5'S)-4a'-Methyl-4',4a',5',6',7',8'-hexahydro-3'H-spiro[[1,3]dithiolane-2,2'-naphthalen]-5'-yl)methanol 2.70

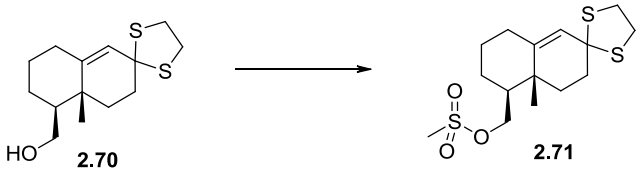


To a cold solution (0 °C) of compound **2.69** (1.38 g, 5.0 mmol, 1.0 equiv.) in MeOH (25 mL) and THF (20 mL) was added sodium borohydride (0.4 g, 10.0 mmol, 2.0 equiv.) portionwise. The reaction mixture was warmed to room temperature until disappearance of starting material by TLC then quenched with saturated aqueous NH_4Cl and concentrated. The residue was taken up in EtOAc, washed with H_2O, dried over $MgSO_4$ and concentrated to afford the title compound (R_f = 0.46, 50% EtOAc in hex) (1.5 g, quantitative yield) as a colourless amorphous solid and used in the next step without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.52 (1H, s, C=CH); 3.82 (1H, d, *J* = 9 Hz, from CH_2OH); 3.40-3.32 (4H, m, from CH_2OH + from SCH_2); 3.27-3.19 (1H, m, from SCH_2); 2.19-2.11 (3H, m, from CH_2); 2.04 (1H, m, CH_2); 1.91-1.68 (4H, m, $CHCH_2OH$ + from CH_2); 1.36-1.33 (3H, m, from CH_2); 0.98 (3H, s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 145.5 (C=CH); 124.9 (C=CH); 65.5 (quat.C dithiane); 63.7 (CH_2OH); 51.4 ($CHCH_2OH$); 40.0 (SCH_2); 39.6 (SCH_2); 37.8 (CH_2); 37.3 (CH_2); 36.4 (CCH_3); 32.6 (CH_2); 26.8 (CH_2); 25.5 (CH_2); 18.7 (CH_3). MS: ESI+ 271.3 $[M + H]^+$; 293.3 $[M + Na]^+$.

Data consistent with literature: Paquette, L.A.; Wang, T-Z.; Philippo, C. M. G.; Wang, S. *J. Am. Chem. Soc.* **1994**, *116*, 3367-3374.

(±)-((4a'R,5'S)-4a'-Methyl-4',4a',5',6',7',8'-hexahydro-3'H-spiro[[1,3]dithiolane-2,2'-naphthalen]-5'-yl)methyl methanesulfonate 2.71

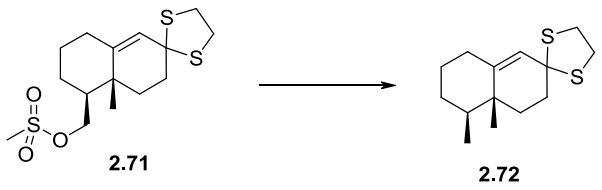


To a cold (0 °C) solution of compound **2.70** (1.20 g, 4.4 mmol, 1.0 equiv.) in CH_2Cl_2 (22 mL) and triethylamine (1.26 mL, 9.1 mmol, 2.0 equiv.) was added methanesulfonyl chloride (0.65 mL, 3.4 mmol, 1.9 equiv.). The reaction mixture was warmed to room temperature for 30 minutes and washed with water and brine prior to drying over $MgSO_4$. Evaporation of the solvent afforded the title compound crude (R_f = 0.36, 20% EtOAc in hex) (1.6 g, quantitative yield) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.54 (1H, s, C=CH); 4.34 (1H, dd, *J* = 10, 4 Hz, from $CH_2SO_3CH_3$); 3.99 (1H, t, *J* = 10 Hz, from $CH_2SO_3CH_3$); 3.40-3.32 (3H, m, from SCH_2); 2.27-3.18 (1H, m, from SCH_2); 3.00 (3H, s, SO_3CH_3); 2.19-2.00 (4H, m, from CH_2's); 1.89-1.70 (3H, m, $CHCH_2OH$ + from CH_2's); 1.65 (1H, m, from CH_2); 1.48-1.27 (3H, m, from CH_2); 1.01 (3H, s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 144.2 (C=CH); 125.7 (C=CH); 70.6 (CH_2SO_3); 65.2 (quat.C dithiane); 48.0 (SO_3CH_3); 40.1 (SCH_2); 39.6 (SCH_2); 37.6 (CH_2); 37.4 ($CHCH_2OH$); 37.2 (CH_2); 36.3 (CCH_3); 31.5 (CH_2); 26.4 (CH_2); 25.5 (CH_2); 18.7 (CH_3). MS: ESI+ 349.3 $[M + H]^+$; 371.3 $[M + Na]^+$.

Data consistent with literature: Paquette, L.A.; Wang, T-Z.; Philippo, C. M. G.; Wang, S. *J. Am. Chem. Soc.* **1994**, *116*, 3367-3374.

(±)-(4a'R,5'S)-4a',5'-Dimethyl-4',4a',5',6',7',8'-hexahydro-3'H-spiro[[1,3]dithiolane-2,2'-naphthalene] 2.72

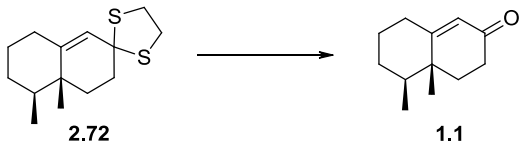


To a cold (0 °C) solution of compound **2.71** (20.3g, 58.0 mmol, 1.0 equiv.) in THF (200 mL) was added Superhydride® (167 mL, 1.0M in THF, 3.0 equiv.). The reaction mixture was stirred at reflux for two hours, cooled and quenched with H_2O and extracted with Et_2O. The organic layers were combined, washed with H_2O, brine, dried over $MgSO_4$ and concentrated to yield 17.8 g of a crude viscous yellow oil which was purified by column chromatography (gradient 0-60% EtOAc in hex) to afford the title compound (R_f = 0.69, 50% EtOAc in hex) (14.2 g, 96%) as a colourless amorphous solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.50 (1H, s, C=CH); 3.42-3.31 (3H, m, from SCH_2); 3.29-3.18 (1H, m, from SCH_2); 2.20-2.07 (3H, m, from CH_2); 2.03-1.94 (1H, m, from CH_2); 1.84-1.68 (2H, m, $CHCH_3$ + from CH_2); 1.65-1.51 (1H, m, from CH_2); 1.47-1.26 (4H, m, CH_2's); 0.94 (3H, s, quat.CCH_3); 0.84 (3H, d, *J* = 6 Hz, CHCH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 146.5 (C=CH); 124.4 (C=CH); 66.0 (quat.C dithiane); 43.4 ($CHCH_3$); 39.9 (SCH_2); 39.5 (SCH_2); 38.0 (CH_2); 37.1 (CH_2); 33.2 (CCH_3): 32.5 (CH_2); 30.9 (CH_2); 27.4 (CH_2); 17.2 (quat.CCH_3); 15.5 ($CHCH_3$). GCMS (CI) *m/z* 255 [M+H$^+$].

Data consistent with literature: Paquette, L.A.; Wang, T-Z.; Philippo, C. M. G.; Wang, S. *J. Am. Chem. Soc.* **1994**, *116*, 3367-3374.

(±)-(4aR,5S)-4a, 5-Dimethyl-4,4a, 5, 6, 7, 8-hexahydronaphthalen-2(3H)-one 1.1



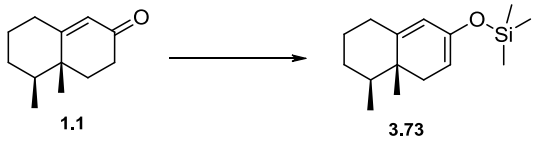
2.72 **1.1**

To a solution of **2.72** (1.00g, 3.9 mmol, 1.0 equiv.) in MeOH/H_2O (22 mL, 10:1) was added methyl iodide (0.73 mL, 11.7 mmol, 3.0 equiv.) and the reaction mixture was heated to reflux for 24 hours. The resulting solution was cooled to room temperature and concentrated to give 0.69 g of a crude yellow oil which was purified by column purification (gradient 10-50% EtOAc in hex) to afford the title compound (R_f = 0.24, 20% EtOAc in hex) (0.62 g, 90%) as a clear oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.70 (1H, s, C=C<u>H</u>); 2.47-2.19 (3H, m, from CH_2's); 2.04-1.97 (1H, m, from CH_2); 1.87-1.37 (7H, series of m, CH_2's); 1.08 (3H, s, quat.C<u>CH_3</u>); 0.89 (3H, d, *J* = 6 Hz, CH<u>CH_3</u>). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 199.6 (C=O); 171.3 (<u>C</u>=CH); 124.0 (C=<u>CH</u>); 43.1 (<u>CH</u>CH_3); 39.0 (<u>quat.C</u>CH_3); 35.5 (CH_2); 34.0 (CH_2); 33.3 (CH_2); 30.5 (CH_2); 26.5 (CH_2); 16.0 (quat.C<u>CH_3</u>); 15.2 (CH<u>CH_3</u>). MS: ESI+ 395.4 $[2M + K]^+$.

Data consistent with literature: Paquette, L.A.; Wang, T-Z.; Philippo, C. M. G.; Wang, S. *J. Am. Chem. Soc.* **1994**, *116*, 3367-3374.

(±)-((4aR,5S)-4a,5-Dimethyl-4,4a,5,6,7,8-hexahydro-naphthalen-2-yloxy)-trimethyl-silane 3.73

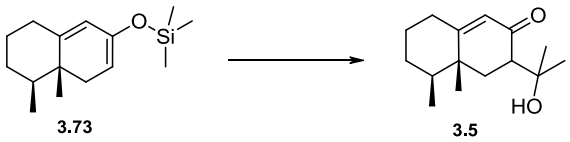


1.1 3.73

To a solution of 1.78 M LDA (3.37 mL, 6.0 mmol, 3.0 equiv.) in THF (10 mL) at -78 °C was slowly added compound **1.1** (340 mg, 1.9 mmol, 1.0 equiv.) in THF (10 mL). The resulting solution was stirred at -78 °C for 45 min followed by the dropwise addition of trimethylsilyl chloride (0.80 mL, 6.3 mmol, 3.2 equiv.). The reaction mixture was subsequently warmed to room temperature over one and a half hours and quenched with H_2O (2 mL). The reaction mixture was concentrated and Et_2O (20 mL) was added. The organic layer was extracted with ice cold saturated aqueous $NaHCO_3$ (5 mL) and brine (2 mL), dried over $MgSO_4$ and concentrated to yield 910 mg of a crude brown oil (R_f = 0.83, 30% EtOAc in hex) to afford the title compound which was used without purification in the next step.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.13 (1H, m, C=CH); 4.53 (1H, m, C=<u>CH</u>CH_2); 0.00 (9H, s, $SiMe_3$).

(±)-(4aR,5S)-3-(2-hydroxypropan-2-yl)-4a,5-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one 3.5



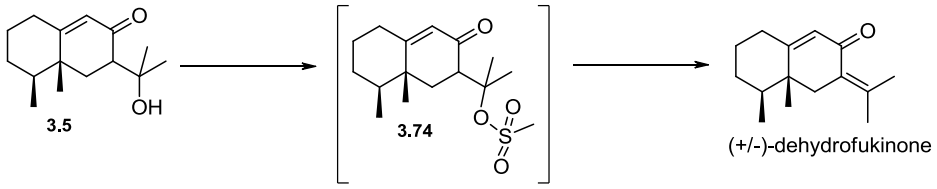
3.73 3.5

To a stirred solution of anhydrous acetone (0.15 mL, 2.0 mmol, 1.0 equiv.) and titanium chloride (0.22 mL, 2.0 mmol, 1.0 equiv.) in CH_2Cl_2 (2 mL) at 0 °C was added compound **3.73** (500 mg, 2.0 mmol, 1.0 equiv.) dropwise. The solution turned from a bright yellow solution to a dark brown/black colour. This was stirred at 0 °C for two hours and a following one hour at room temperature. The reaction solution was quenched with H_2O (2 mL) and stirred for 15 minutes at room temperature. The organic layer was isolated with CH_2Cl_2 (10 mL), washed with H_2O, brine, dried over $MgSO_4$ and concentrated to yield 420 mg of a crude brown oil which was purified by column chromatography (0-10% EtOAc in hex) to afford the title compound (R_f = 0.37, 30% EtOAc in hex) (220 mg, 48%) as a brown oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.71 (1H, s, C=CH); 5.20 (1H, s, OH); 2.53 (1H, dd, *J* = 15, 4 Hz C<u>H</u>C$(CH_3)_2$OH); 2.40-2.23 (2H, m, CH_2); 2.02 (1H, dd, *J* = 13, 4 Hz, C<u>H</u>CH_3); 1.92-1.82 (1H, m, from CH_2); 1.63-1.39 (5H, m, from CH_2); 1.23 (6H, s, C<u>$(CH_3)_2$</u>OH); 1.14 (3H, s, quat.C<u>CH_3</u>); 0.93 (3H, d, *J* = 6 Hz, CH<u>CH_3</u>). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 203.4 (C=O); 172.0 (CH<u>C</u>$(CH_3)_2$OH); 124.6 (C=<u>CH</u>); 72.5 (<u>C</u>=CH); 51.2 (<u>CH</u>C$(CH_3)_2$OH); 43.6 (<u>CH</u>CH_3); 39.6 (quat C.CH_3); 38.6 (CH_2); 32.9 (CH_2); 30.3 (CH_2); 28.3 (CH_3); 26.2(CH_2); 24.6 (CH_2); 15.9 (quat.C<u>CH_3</u>); 15.1 (CH<u>CH_3</u>). MS: ESI+ 259.2 $[M + Na]^+$.

Data consistent with literature: Torii, S.; Inokuchi, T.; Yamafuji, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2640-2645.

(±)-Dehydrofukinone

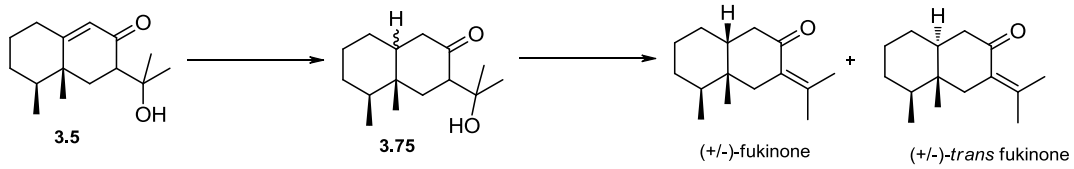


To a cold (0 °C) solution of compound **3.5** (0.17 g, 0.72 mmol, 1.0 equiv.) in CH_2Cl_2 (5.0 mL) and triethylamine (0.40 mL, 2.8 mmol, 4.0 equiv.) was added methanesulfonyl chloride (0.22 mL, 2.7 mmol, 3.8 equiv.). The reaction mixture was warmed to room temperature for five and a half hours during which time the solution went from clear to cloudy yellow. The reaction mixture was washed with H_2O, dilute HCl, H_2O and brine prior to drying with $MgSO_4$ and concentrated to yield 0.25 g of a crude brown oil which was purified by column chromatography (0-5% EtOAc in hex) to afford the title compound (R_f = 0.6, 30% EtOAc in hex) (0.1 g, 66%) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.71 (1H, s, C=C<u>H</u>); 2.86 (1H, d, *J* = 13 Hz, from CH_2); 2.36-2.19 (2H, m, CH_2); 2.12 (1H, m, from CH_2); 2.07 (3H, d, *J* = 2 Hz, C=C(C<u>H</u>$_3$)$_2$); 1.82 (4H, s within m, C=C(C<u>H</u>$_3$)$_2$ + from CH_2); 1.55-1.33 (4H, m, C<u>H</u>CH_3 + from CH_2); 0.95 (3H, s, quat.CC<u>H</u>$_3$); 0.94 (3H, d, *J* = 6 Hz, CHC<u>H</u>$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 192.2 (C=O); 168.6 (<u>C</u>=CH); 142.1 (C=<u>C</u>(CH$_3$)$_2$); 128.1 (C=<u>C</u>(CH$_3$)$_2$); 126.1 (C=<u>CH</u>); 42.5 (<u>CH</u>CH$_3$); 41.8 (<u>quat.C</u>CH$_3$); 41.0 (CH_2); 32.5 (CH_2); 30.5 (CH_2); 26.5 (CH_2); 22.5 (C=C(<u>CH</u>$_3$)$_2$); 22.0 (C=C(<u>CH</u>$_3$)$_2$); 16.0 (quat.CC<u>H</u>$_3$); 15.4 (CH<u>CH</u>$_3$). GCMS (EI) *m*/*z* 219 [M^+]. IR (film): ν_{max} = 3020, 1665, 1220, 1040 cm^{-1}.

Data consistent with literature: Tenius, B. S. M.; Schenato, R. A.; dos Santos, E. M.; Costa, P. R. R.; Caracelli, I.; Zukrtman-Schpector, J. *Tetrahedron: Asymmetry* **2001**, *12*, 579-584.

(±)-Fukinone



Pd/C (15 mg, 15wt%) was added to a solution of compound **3.5** (100 mg, 0.42 mmol, 1.0 equiv.) in EtOH (2 mL) and stirred under H_2 atmosphere at room temperature for 16 hours. The reaction mixture was filtered through celite to remove the catalyst and concentrated to afford compound **3.75** crude (R_f = 0.54, 30% EtOAc in hex) as a clear oil which was used without purification in the next step. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.18 (1H, s, OH); 1.21 (6H, d, *J* = 3 Hz, C($\underline{CH_3}$)$_2$OH); 0.95 (3H, s, quat.C$\underline{CH_3}$); 0.87 (3H, d, *J* = 6 Hz, CH$\underline{CH_3}$). MS: ESI+ 261 $[M+Na]^+$.

To a cold (0 °C) solution of crude compound **3.75** (100 mg, 0.42 mmol, 1.0 equiv.) in CH_2Cl_2 (3.0 mL) and triethylamine (0.23 mL, 1.68 mmol, 4.0 equiv.) was added methanesulfonyl chloride (0.12 mL, 1.6 mmol, 3.8 equiv.). The mixture was warmed to room temperature for six hours during which time the solution went from clear to cloudy yellow. The crude was washed with H_2O, dilute HCl, H_2O and brine prior to drying with $MgSO_4$ and concentrated to yield 90 mg of a crude orange oil which was purified by column chromatography (0-5% EtOAc in hex) to afford the title compound as the minor compound in a mixture of two isomers (R_f = 0.6, 30% EtOAc in hex) (49 mg, 1:3 ratio 53%) as a pale yellow oil.

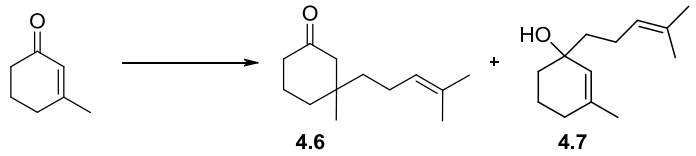
^{1}H NMR of minor product, *cis* isomer (13%) (300 MHz, $CDCl_3$) δ_H 2.75 (1H, d, *J* = 15 Hz, from $\underline{CH_2}$CO); 2.55 (1H, dd, *J* = 16, 11 Hz, from $\underline{CH_2}$CO); 2.28-2.23 (1H, m, from $\underline{CH_2}$C=C); 1.94 (3H, s, C=C($\underline{CH_3}$)$_2$); 1.78 (3H, s, C=C($\underline{CH_3}$)$_2$); 1.72-1.15 (9H, series of m, $\underline{CH}CH_3$, quat.CH, CH_2's); 0.96 (3H, s, quat.CCH_3); 0.85 (3H, d, *J* = 6 Hz, CH$\underline{CH_3}$). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 206.2 (C=O); 139.9 (C=$\underline{C}$(CH$_3$)$_2$); 131.2 ($\underline{C}$=C(CH$_3$)$_2$); 44.1 ($\underline{CH_2}$CO); 41.4 (quat.CH); 40.6 ($\underline{CH_2}$C=C); 36.7 ($\underline{quat.C}CH_3$); 32.2 ($\underline{CH}CH_3$); 30.1 (CH_2); 27.2(CH_2); 22.6 (C=C($\underline{CH_3}$)$_2$); 21.6 (C=C($\underline{CH_3}$)$_2$); 21.6 (CH_2); 20.4 (Quat.C$\underline{CH_3}$); 16.0 (CH$\underline{CH_3}$).[15] MS: ESI+ 243 $[M+Na]^+$; 463 $[2M+Na]^+$. IR (film) 2930, 2870, 1670, 1605, 1460 cm $^{-1}$.

Data consistent with literature of minor product for fukinone: Kozmin, S.A.; Reddy, D.S. *J. Org. Chem.* **2004**, *69*, 4860-4862.

^{1}H NMR of major product, *trans* isomer (40%) (300 MHz, $CDCl_3$) δ_H 2.76 (1H, d, *J* = 14 Hz, from $\underline{CH_2}CO$); 2.25-2.11 (2H, m, from $\underline{CH_2}CO$ + $\underline{CH_2}C{=}C$); 1.98 (3H, d, *J* = 2 Hz, $C{=}C(\underline{CH_3})_2$); 1.77 (3H, d, *J* = 2 Hz, $C{=}C(\underline{CH_3})_2$); 1.72-1.15 (9H, series of m); 0.89 (3H, d, *J* = 6 Hz, $CH\underline{CH_3}$); 0.74 (3H, s, quat.$C\underline{CH_3}$). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 204.5 (C=O); 142.6 ($C{=}\underline{C}(CH_3)_2$); 131.5 ($C{=}\underline{C}(CH_3)_2$); 45.5 ($\underline{CH_2}CO$); 44.0 (quat.CH); 43.0 ($\underline{CH_2}C{=}C$); 42.5 ($\underline{CH}CH_3$); 36.9 ($\underline{\text{quat.C}}CH_3$); 30.7 ($CH_2$); 29.0 ($CH_2$); 26.2 ($CH_2$); 23.0 ($C{=}C(\underline{CH_3})_2$); 22.0 ($C{=}C(\underline{CH_3})_2$); 15.7 ($CH\underline{CH_3}$); 10.1 (quat.$C\underline{CH_3}$).

3-Methyl-3-(4-methylpent-3-en-1-yl)cyclohexanone 4.6

3-Methyl-1-(4-methylpent-3-en-1-yl)cyclohex-2-enol 4.7



4.6 **4.7**

A 3-neck flask was fitted with a condenser, stirrer and charged with $Mg_{(s)}$ (272 mg, 11.4 mmol, 3.2 equiv.) then heated with a heat gun under Ar atmosphere to activate Mg. Mg was allowed to cool for 15 minutes before one small iodine crystal was added followed by anhydrous THF (10.0 mL). The flask was swirled to disperse the brown colour. A few drops of bromo-2-methyl-2-pentene (1.00 mL, 7.46 mmol, 2.1 equiv.) was added and the reaction mixture was heated to 60 °C until solution turned colourless indicating reaction was activated. The remaining bromo-2-methyl-2-pentene in anhydrous THF (1.00 mL) was added dropwise over 10 minutes. The reaction mixture was stirred at reflux for one and a half hours to form the Grignard compound, then allowed to cool to room temperature.

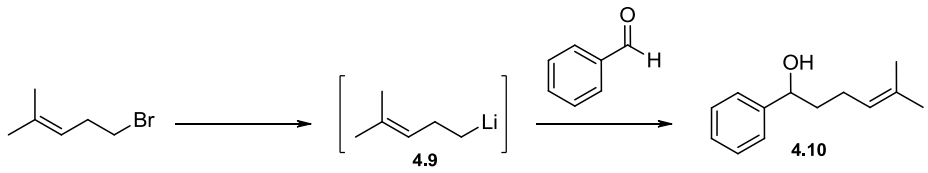
Copper bromide dimethylsulphide complex (74.0 mg, 0.36 mmol, 10 mol%) was suspended in anhydrous THF (6.00 mL) and cooled to -20 °C and the Grignard solution added via syringe over five minutes. After 30 minutes at -20 °C 3-methyl-2-cyclohexenone (0.40 mL, 3.55 mmol, 1.0 equiv.) was added over 10 minutes and the reaction mixture stirred for 15 minutes and allowed to warm to room temperature. MeI (0.44 mL, 7.10 mmol, 2.0 equiv.) in anhydrous THF (1.00 mL) was added and the mixture stirred for 30 minutes before reaction was quenched with aqueous saturated NH_4Cl and the organic layer separated. The aqueous solution was extracted with Et_2O and the organic layers combined, washed with brine, dried over $MgSO_4$ and concentrated to give 99 mg of a crude yellow liquid which was purified by column chromatography (2% EtOAc in hex) to afford the title compound **4.6** (R_f = 0.62, 50% EtOAc in hex) (630 mg, 91%) as a colourless oil, followed by the minor 1,2-addition product **4.7** (R_f = 0.45, 50% EtOAc in hex) (7.00 mg, 1%) as a colourless oil.

^{1}H NMR of compound **4.6** (300 MHz, $CDCl_3$) δ_H 5.06 (1H, tt, *J* = 1, 7 Hz, C=CH); 2.26 (2H, t, *J* = 7 Hz, CH_2); 2.22–2.05 (2H, m, CH_2); 1.97-1.79 (4H, m, from CH_2); 1.69-1.49 (8H, m including 2 s, C=C(CH_3)$_2$ + CH_2); 1.30-1.21 (2H, m, CH_2); 0.92 (3H, s, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 212.0 (C=O); 131.4 (C=CH); 124.3 (C=CH); 53.6 (cyclohex. CH_2); 41.6 (cyclohex. CH_2); 40.9 (cyclohex. CH_2); 38.5 (quat.C); 35.8 (CH_2); 25.6 (C=C(CH_3)$_2$); 24.8 (C=C(CH_3)$_2$); 22.1 (cyclohex.CH_2); 22.0 (CH_2); 17.5(CH_3). GCMS (EI) *m*/*z* 194 [M^+].

Data consistent with literature: Williams, C.M.; Tilly, D.P.; Bernhardt, P.V. *Org. Lett*. **2005**, *7*, 5155-5157.

^{1}H NMR of compound **4.7** (300 MHz, $CDCl_3$) δ_H 5.36 (1H, s, CH=CCH_3); 5.17-5.09 (1H, m, (CH_3)$_2$C=CH); 2.12-2.00 (2H, m, cyclohex. CH_2); 1.95-1.85 (2H, m, CH_2); 1.74-1.42 (7H, m, CH_2's + OH); 1.68 (6H, s, CH=C(CH_3)$_2$); 1.62 (3H, s, CH=CCH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 137.8 (CH_3C=CH); 131.5 (CH=C(CH_3)$_2$); 127.2 (CH_3C=CH); 124.7 (CH=C(CH_3)$_2$); 70.6 (quat.COH); 42.5 (CH_2); 35.1 (cyclohex. CH_2); 30.3 (cyclohex. CH_2); 25.7 (CH=C(CH_3)$_2$); 23.7 (CH=C(CH_3)$_2$); 22.4 (CH_2); 19.4 (cyclohex. CH_2); 17.7 (CH=CCH_3). GCMS (EI) *m*/*z* 194 [M^+].

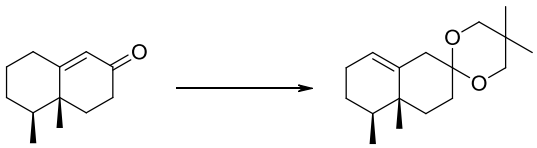
5-Methyl-1-phenylhex-4-en-1-ol 4.10



To a solution of 5-bromo-2-methyl-2-pentene (0.10 mL, 0.75 mmol, 1.4 equiv.) in anhydrous Et_2O (2.0 mL) at -78 °C was slowly added *tert*-butyllithium 1.5 M (0.80 mL, 1.2 mmol, 2.2 equiv.) over five minutes. This mixture was stirred at -78 °C for five minutes, followed by the slow addition of benzaldehyde (0.05 mL, 0.55 mmol, 1.0 equiv.) in Et_2O (1 mL) over five minutes. The mixture was subsequently warmed to room temperature over 15 minutes and hydrolysed with brine (2 mL). The aqueous layer was extracted with Et_2O (2 x 2 mL) and the combined organic layers were washed with brine (2 mL), dried over $MgSO_4$ and concentrated to yield 190 mg of a clear oil which was purified by column chromatography (0-20% EtOAc in hex) to afford the title compound (R_f = 0.35, 20% EtOAc in hex) (44.0 mg, 44%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.39 - 7.27 (5H, m, phenyl H); 5.16 (1H, tt, *J* = 7 Hz, $(CH_3)_2C=\underline{CH}$); 4.69 (1H, dd, *J* = 7, 5 Hz, $\underline{CH}OH$); 2.16 – 2.00 (2H, m, $CH\underline{CH_2}$); 1.93 – 1.73 (3H, m, OH + $CHOH\underline{CH_2}$); 1.71 (3H, s, $CH=C(\underline{CH_3})_2$); 1.60 (3H, s, $CH=C(\underline{CH_3})_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 144.7 (phenyl quat.CCHOH); 132.3 ($(CH_3)_2\underline{C}=CH$); 128.4 (2 x phenyl CH); 127.4 ($(CH_3)_2C=\underline{CH}$); 125.9 (2 x phenyl CH); 123.8 (phenyl CH); 74.2 ($\underline{CH}OH$); 39.0 ($CHOH\underline{CH_2}$); 25.7 ($(\underline{CH_3})_2C=CH$); 24.5 ($\underline{CH_2}CH=C$); 17.7 ($(\underline{CH_3})_2C=CH$). GCMS (EI) *m/z* 190 [M^+].

(±)-(4a'R,5'S)-4a',5,5,5'-tetramethyl-3',4',4a',5',6',7'-hexahydro-1'H-spiro[[1,3]dioxane-2,2'-naphthalene] 4.16

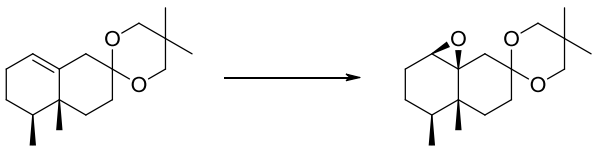


1.1 4.16

To a solution of compound **1.1** (2.00 g, 11.2 mmol, 1.0 equiv.) in benzene (30 mL) was added 2,2-methyl-1,3-propanediol (2.92 g, 28 mmol, 2.5 equiv.) and camphorsulfonic acid (13.0 mg, 0.11 mmol, 0.01 equiv.) The reaction mixture was stirred at reflux and water was removed using Dean-Stark apparatus for 24 hours. The resulting solution was cooled to room temperature and quenched with solid $NaHCO_3$. The solids were filtered off and the precipitate was washed with 20:1 hex:EtOAc (20 mL). The filtrates were combined and concentrated to give 3.81 g of a crude yellow solid which was purified by column chromatography (gradient 0-30% EtOAc in hex) to afford the title compound (R_f = 0.93, 50% EtOAc in hex) (2.58 g, 79%) as a colourless amorphous solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.38 (1H, ddd, *J* = 5, 2, 2 Hz, C=CH); 3.54 (2H, ABq, *J* = 11 Hz, OCH_2); 3.51 - 3.41 (2H, m, OCH_2); 2.58 (1H, dd, *J* = 14, 3 Hz, from CH_2); 2.20 - 2.36 (2H, m, from CH_2); 2.03 - 2.17 (1H, m, from CH_2); 1.99 – 1.68 (1H, m, $CHCH_3$); 1.71 (1H, dt, *J* = 13, 3 Hz, from CH_2); 1.50 - 1.61 (1H, m, from CH_2); 1.48 – 1.36 (3H, m, from CH_2); 1.25 (1H, dt, *J* = 13, 4 Hz, from CH_2); 1.01 (3H, s, quat.CCH_3); 0.94 (s, 3 H, CCH_3); 0.92 (s, 3 H, CCH_3); 0.88 (3H, d, *J* = 6 Hz, CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 139.8 (C=CH); 123.0 (C=CH); 98.5 (quat.C$(OCH_2)_2$); 70.2 (OCH_2); 69.9 (OCH_2); 40.2 (CH_3CH); 39.9 (CH_2); 37.1 (quat.CCH_3); 34.8 (CH_2); 30.1 (quat.C$(CH_3)_2$); 27.6 (CH_2); 27.2 (CH_2); 25.8 (CH_2); 22.8 (CH_3); 22.7 (CH_3); 17.4 (CCH_3); 15.8 (CH_3CH). MS: ESI+ 287.5 $[M+Na]^+$. IR (film): ν_{max} = 2920, 2840, 1660, 868 cm^{-1}.

(±)-(1a'R,4'S,4a'R,8a'S)-4',4a',5,5-tetramethyloctahydrospiro[[1,3]dioxane-2,7'-naphtho[1,8a-b]oxirene] 4.18

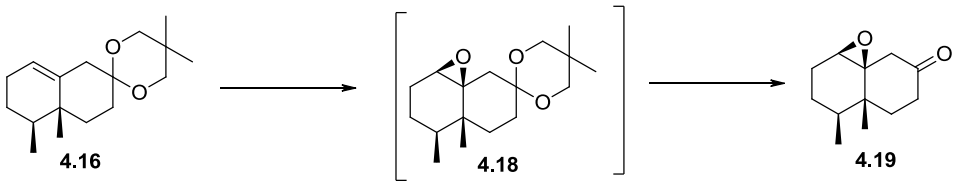


4.16 4.18

To compound **4.16** (1.45 g, 5.48 mmol, 1.1 equiv.) in EtOAc (24 mL) was added sodium bicarbonate (2.08 g, 24.8 mmol, 5 equiv.), water (23 mL) and acetone (10 mL). This biphasic mixture was stirred vigorously as an aqueous Oxone® solution (3.05 g, 4.96 mmol, 1.0 equiv.) in water (21 mL) was added dropwise over one hour at room temperature. The reaction mixture was stirred vigorously for an additional two hours. The organic layer was separated, washed with brine, dried over $MgSO_4$ and concentrated to give 1.51 g of a crude colourless oil which was purified by column chromatography (gradient 0-30% EtOAc in hex) to afford the title compound (R_f = 0.84, 50% EtOAc in hex) (1.32 g, 95%) as a colourless amorphous solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 3.54-3.40 (4H, m, 2 x OCH_2); 3.05 (1H, t, *J* = 2 Hz, epoxide CH); 2.08 (1H, d, *J* = 14 Hz, from CH_2); 2.04 - 1.91 (2H, m, $\underline{CH}CH_3$ + from CH_2); 1.82 – 1.53 (5H, m, from CH_2's); 1.39 – 1.28 (m, from CH_2); 1.27 – 1.10 (2H, m, from CH_2); 1.00 (3H, s, quat.C$\underline{CH_3}$); 0.95 (3H, s, C($\underline{CH_3}$)$_2$); 0.91 (3H, s, C($\underline{CH_3}$)$_2$); 0.83 (3H, d, J = 7 Hz, CH$\underline{CH_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 99.1 ($\underline{quat.C}(OCH_2)_2$); 70.3 ($OCH_2$); 70.2 ($OCH_2$); 63.1 (epoxide CH); 62.6 (quat.C epoxide); 38.8 ($CH_3\underline{CH}$); 38.5 (CH_2); 35.5 ($\underline{quat.C}(CH_3)_2$); 33.7 ($CH_2$); 30.1 ($\underline{quat.C}CH_3$); 29.4($CH_2$); 25.5 ($CH_2$); 24.2 ($CH_2$); 22.7 ($CH_3$); 22.6 ($CH_3$); 16.2 (quat.C$\underline{CH_3}$); 16.1 ($\underline{CH_3}$CH). MS: ESI+ 303 $[M+Na]^+$. IR (film): ν_{max} = 3055 (epoxide CH), 2900, 2843, 1642 cm^{-1}.

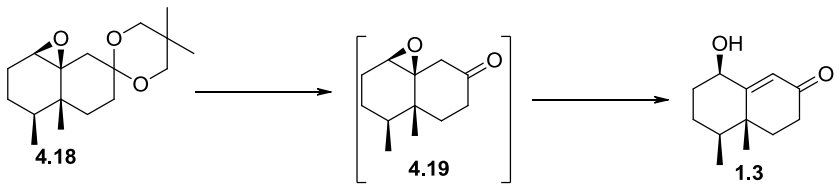
(±)-(1aR,4S,4aR,8aS)-4,4a-dimethylhexahydro-1aH-naphtho[1,8a-b]oxiren-7(8H)-one 4.19



An aqueous Oxone® solution (6.31 g, 10.2 mmol, 1.1 equiv.) in water (38 mL) was added dropwise to a stirring solution of sodium bicarbonate (1.44 g, 17.1 mmol, 1.8 equiv.) and compound **4.16** (2.50 g, 9.46 mmol, 1.0 equiv.) in acetone (20 mL). The reaction mixture was stirred for 52 hours at room temperature and then extracted with EtOAc (5 x 20 mL). Brine (20 mL) was added to the aqueous layer to aid separation of organic compounds. The organic fractions were combined, dried over $MgSO_4$ and concentrated to give 2.84 g of a crude yellow solid which was purified by column chromatography (gradient 20-50% EtOAc in hex) to afford the title compound (R_f = 0.12, 50% EtOAc in hex) (1.55 g, 85%) as a colourless amorphous solid.

^{1}H NMR (300 MHz, MeOD) δ_H 3.45 (1H, t, *J* = 3 Hz, epoxide CH); 3.18 (1H, d, *J* = 15 Hz, from CH_2); 2.56 – 2.41 (1H, m, from CH_2); 2.29 – 2.19 (1H, m, from CH_2); 2.17 – 2.07 (1H. m, from CH_2); 2.03 (1H, dd, *J* = 15, 2 Hz, from CH_2); 1.99 – 1.83 (2H, m, from CH_2); 1.76 – 1.62 (2H, m, from CH_2); 1.61 – 1.52 (1H, m, from CH_2); 1.33 – 1.26 (1H, m, from CH_2); 1.25 (3H, s, quat.C$\underline{CH_3}$); 0.85 (3H, d, *J* = 7 Hz, CH$\underline{CH_3}$); ^{13}C NMR (75 MHz, MeOD) δ_C 215.9 (C=O); 79.0 (quat.C epoxide); 76.1 (epoxide CH); 50.4 (CH_2); 40.2 ($\underline{quat.C}CH_3$); 39.0 (CH_2); 36.3 ($CH_3\underline{CH}$); 35.2 (CH_2); 29.9 (CH_2); 26.8 (CH_2); 16.2 (quat.C$\underline{CH_3}$); 15.1 (CH$\underline{CH_3}$).GCMS (EI) *m/z* 194 [M^+]. IR (film): ν_{max} = 3050 (epoxide CH), 2910, 2860, 1690 (C=O) cm^{-1}.

(±)-(4aR,5S,8R)-8-hydroxy-4a,5-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one 1.3



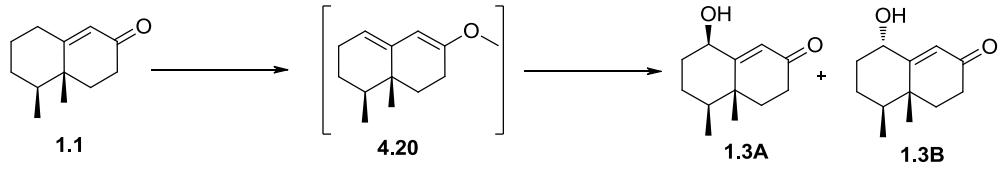
To a solution of compound **4.18** (1.32g, 4.7 mmol, 1.0 equiv.) in freshly distilled anhydrous acetone (20 mL) was added ρ-toluenesulfonic acid (15 mg, 0.08 mmol, 0.02 equiv.). The resulting mixture was stirred at room temperature for 24 hours then concentrated to remove 80% of the acetone. TLC of reaction mixture indicated loss of **4.18** and a new major polar spot corresponding to compound **4.19**. Triethylamine (1 mL) was added to the crude oil and stirred for seven hours at room temperature. The reaction mixture was concentrated to give 1.4 g of a crude orange oil which was purified by column chromatography (gradient 20-50% EtOAc in hex) to afford the title compound (R_f = 0.3, 50% EtOAc in hex) (0.36 g, 40%) as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.83 (1H, s, C=CH); 4.34 (1H, t, *J* = 3 Hz, CHOH); 2.62 – 2.15 (2H, m, CH_2C=O); 2.10 – 1.61 (5H, m, from CH_2's); 1.49 – 1.36 (2H, m, from CH_2 + $CHCH_3$); 1.30 (3H, s, quat.CCH_3); 0.95 (3H, d, *J* = 7 Hz, $CHCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 200.6 (C=O); 168.4 (C=CH); 126.6 (C=CH); 73.4 (CHOH); 43.1 ($CHCH_3$); 38.4 (quat.CCH_3); 36.9 (CH_2); 34.3 (CH_2); 32.8 (CH_2); 24.8 (CH_2); 18.0 (quat.CCH_3); 15.2 ($CHCH_3$). MS: ESI+ 217.2 $[M + Na]^+$.

Data consistent with literature: Bonjoch, J.; Díaz, S.; González, A.; Bradshaw, B.; Cuesta, J.; *J. Org. Chem*. **2005**, *70*, 3749-3752.

(±)-(4aR,5S,8R)-8-hydroxy-4a,5-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one 1.3A

(±)-1α-Hydroxyisoondetianone 1.3B (4aR,5S,8S)-8-hydroxy-4a,5-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one)



To a solution of compound **1.1** (1.4 g, 7.8 mmol, 1.0 equiv.), trimethyl orthoformate (12 mL), methanol (2.8 mL) in DMF (15 mL) was added ρ-toluenesulfonic acid (30 mg, 0.16 mmol, 0.02 equiv.) and the resulting mixture was stirred for 24 hours at room temperature in the dark. Triethylamine (0.87 mL) was added, and the reaction mixture diluted with Et_2O (100 mL), washed with aqueous saturated $NaHCO_3$ (3 x 50 mL), brine (50 mL), dried over $MgSO_4$ and concentrated to give 1.63 g of the dienol ether intermediate **4.20** as a yellow oil which was used immediately in the following reaction. ^{1}H NMR of crude dienol ether **4.20** (300 MHz, $CDCl_3$) δ 5.27 (1H, t, *J* = 4 Hz, C=CH); 5.16 (1H, d, *J* = 1 Hz, C=CH); 3.58 (3H, s, OCH_3); 0.94 – 0.90 (3H, m, $CH\underline{CH_3}$); 0.89 (3H, s, quat.$C\underline{CH_3}$).

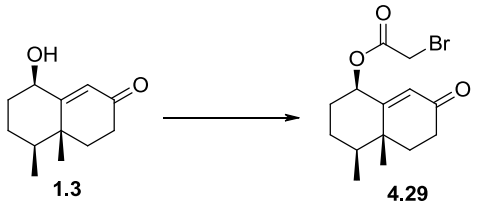
To a rapidly stirring biphasic mixture of the crude dienol ether (7.8 mmol), sodium bicarbonate (3.3 g, 39.2 mmol, 5.0 equiv.) in EtOAc (30 mL), acetone (10 mL) and water (30 mL) at 0 °C, was added a solution of Oxone® (4.8 g, 7.8 mmol, 1.0 equiv.) in H_2O (28 mL) over 30 minutes. The mixture was stirred at 0 °C for one hour. The reaction mixture was allowed to separate and the aqueous layer extracted with EtOAc (3 x 20 mL) and washed with brine. The combined organic layers were dried over $MgSO_4$ and concentrated to give 1.5 g of a crude yellow oil which was purified by column chromatography (gradient 0-30% EtOAc in hex) to afford the title compound **1.3A** (R_f = 0.3, 50% EtOAc in hex) (0.62 g, 41%) as a pale yellow oil followed by the *trans* epimer compound **1.3B** (R_f = 0.25, 50% EtOAc in hex) (0.20 g, 13%) as a pale yellow oil.

^{1}H NMR for *cis* isomer **1.3A** (300 MHz, $CDCl_3$) δ_H 5.80 (1H, s, C=CH); 4.32 (1H, t, *J* = 3 Hz, CHOH); 2.61 – 2.28 (2H, m, $COCH_2$); 2.13 – 1.94 (3H, m, OH + CH_2); 1.92 – 1.58 (3H, m, CH_2's); 1.52 – 1.33 (2H, m, $CHCH_3$ + from CH_2); 1.29 (3H, s, quat.CCH_3); 0.94 (3H, d, *J* = 7 Hz, $CHCH_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 200.7 (C=O); 168.6 (C=CH); 126.5 (C=CH); 73.4 (CHOH); 43.0 ($CHCH_3$); 38.4 (CCH_3); 36.9 (CH_2); 34.3 (CH_2); 32.8 (CH_2); 24.8 (CH_2); 18.0 (CCH_3); 15.2 ($CHCH_3$). MS: ESI+ 195.3 $[M + H]^+$.

^{1}H NMR for *trans* isomer **1.3B** (300 MHz, $CDCl_3$) δ_H 6.17 (1H, d, *J* = 2 Hz, C=CH); 4.33 - 4.25 (1H, m, CHOH); 2.49 – 2.28 (3H, m, OH + CH_2); 2.21 – 2.14 (1H, m, from CH_2); 2.04 – 1.96 (1H, m, from CH_2); 1.82 – 1.70 (1H, m, from CH_2); 1.66 – 1.36 (5H, m, from CH_2's); 1.09 (3H, s, quat.CCH_3); 0.91 (3H, d, *J* = 6 Hz, $CHCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 199.7 (C=O); 171.8 (C=CH); 119.9 (C=CH); 69.0 (CHOH); 42.8 ($CHCH_3$); 39.3 (quat.CCH_3); 36.1 (CH_2); 35.9 (CH_2); 33.7 (CH_2); 28.7 (CH_2); 16.9 (quat.CCH_3); 14.8 ($CHCH_3$). MS: ESI+ 195.3 $[M + H]^+$.

Data consistent with literature: Bonjoch, J.; Díaz, S.; González, A.; Bradshaw, B.; Cuesta, J.; *J. Org. Chem*. **2005**, *70*, 3749-3752.

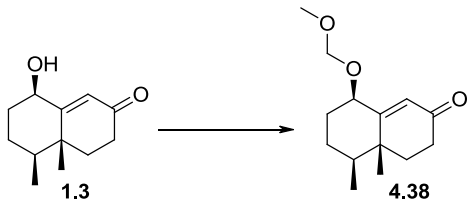
(±)-(1R,4S,4aR)-4,4a-dimethyl-7-oxo-1,2,3,4,4a,5,6,7-octahydronaphthalen-1-yl 2-bromoacetate 4.29



To a stirring solution of compound **1.3** (200 mg, 1.03 mmol, 1 equiv.) in anhydrous CH_2Cl_2 (4 mL) at 0 °C was added anhydrous pyridine (90 µL, 1.13 mmol, 1.1 equiv.) followed by the dropwise addition of bromoacetyl bromide (98 µL, 1.13 mmol, 1.1 equiv.) in anhydrous CH_2Cl_2 (3 mL) over five minutes. The clear yellow solution turned cloudy white. The resulting reaction mixture was stirred at room temperature for one hour, then quenched with the addition of H_2O (10 mL) and extracted with CH_2Cl_2 (2 x 5 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated to give 420 mg of a crude yellow oil which was purified by column chromatography (gradient 5-10% EtOAc in hex) to afford the title compound (R_f = 0.35, 30% EtOAc in hex) (217 mg, 68%) as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.97 (1H, s, C=CH); 5.49-5.42 (1H, m, CHOC=O); 3.84 (1H, d, *J*=12 Hz, from CH_2Br); 3.80 (1H, d, *J*=12 Hz, from CH_2Br); 2.61 - 2.47 (1H, m, from CH_2); 2.46 - 2.36 (1H, m, from CH_2); 2.14 - 2.02 (2H, m, $CHCH_3$ + from CH_2); 1.88 - 1.64 (3H, m, from CH_2's); 1.55 - 1.42 (2H, m, CH_2); 1.25 (3H, s, quat.CCH_3); 0.97 (3H, d, *J* = 7 Hz, CHCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 200.0 (C=O); 165.8 (OC=O); 161.5 (C=CH); 129.4 (C=CH); 76.6 (CHOC=O); 42.6 ($CHCH_3$); 38.4 (quat.CCH_3); 36.8 (CH_2); 34.2 (CH_2); 30.8 (CH_2); 25.9 (CH_2Br); 25.2 (CH_2); 17.4 (quat.CCH_3); 15.1 (CHCH_3); MS: ESI+ 339.0 [^{81}Br M+Na]$^+$; 337.0 [^{79}Br M+Na]$^+$; IR (film) ν_{max} = 2949 (CH_3, CH_2), 2366, 1735 (α-Br ketone), 1682 (C=O), 1262 cm^{-1}.

(±)-(4aR,5S,8R)-8-(methoxymethoxy)-4a,5-dimethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one 4.38

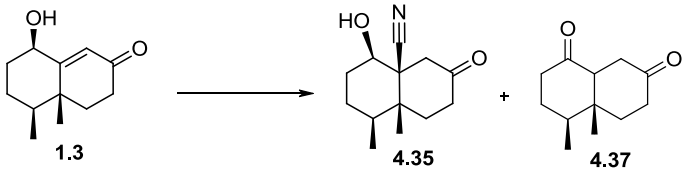


To a stirring solution of compound **1.3** (100 mg, 0.52 mmol, 1 equiv.) in CH_2Cl_2 (2 mL) at 0 °C was added disopropylethylamine (100 µL, 0.57 mmol, 1.1 equiv.) dropwise, followed by the addition of methylchloromethyl ether (50 µL, 0.62 mmol, 1.2 equiv.). The resulting reaction mixture was stirred at 0 °C for one hour and at room temperature overnight. The reaction mixture was quenched with aqueous saturated NH_4Cl (1 mL), extracted with CH_2Cl_2 (2 mL) and the organic fractions combined, washed with H_2O, brine, dried over $MgSO_4$ and concentrated to give 145 mg of a crude yellow oil which was purified by column chromatography (10% EtOAc in hex) to afford the title compound (R_f = 0.58, 50% EtOAc in hex) (100 mg, 85%) as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.80 (1H, s, C=CH); 4.58 (1H, d, *J* = 7 Hz, from $\underline{CH_2}OCH_3$); 4.49 (1H, d, *J* = 7 Hz, from $\underline{CH_2}OCH_3$); 4.15 (1H, t, *J* = 3 Hz, $\underline{CH}$OMOM); 3.34 (3H, s, OCH_3); 2.60 - 2.47 (1H, m, from CH_2); 2.43 - 2.33 (1H, m, from CH_2); 2.03 (2H, ddt, *J* = 13, 5, 2 Hz, CH_2); 1.91 – 1.59 (3H, m, from CH_2's); 1.50 – 1.36 (2H, m, CH_2); 1.19 (3H, s, quat.C$\underline{CH_3}$); 0.94 (3H, d, *J* = 7 Hz, CH$\underline{CH_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 200.1 (C=O); 164.3 ($\underline{C}$=CH); 128.1 (C=$\underline{CH}$); 93.1 (O$\underline{CH_2}OCH_3$); 75.5 ($\underline{CH}OCH_2$); 55.3 (OCH_3); 43.1 ($\underline{CH}CH_3$); 38.4 ($\underline{quat.C}CH_3$); 36.9 (CH_2); 34.3 (CH_2); 31.9 (CH_2); 25.4 (CH_2); 17.1 (quat.C$\underline{CH_3}$); 15.2 (CH$\underline{CH_3}$); MS: ESI+ 216.2 $[M+Na]^+$; 499.4 $[2M+Na]^+$; IR (film) ν_{max} = 2933 (CH_2), 2884, 2824 (OCH_3), 1678, 1444 cm^{-1}.

(±)-(1S,4R,4aR,8aR)-4-hydroxy-1,8a-dimethyl-6-oxodecahydronaphthalene-4a-carbonitrile 4.35

(±)-(4S,4aR)-4,4a-dimethyloctahydronaphthalene-1,7-dione 4.37



A solution of potassium cyanide (64 mg, 1.0 mmol, 2.0 equiv.) and ammonium chloride (46 mg, 0.9 mmol, 1.8 equiv.) in water (1.0 mL) was added to a solution of compound **1.3** (100 mg, 0.5 mmol, 1.0 equiv.) in EtOH (2.0 mL) and the resulting mixture was stirred at reflux for six hours. The reaction mixture was cooled to room temperature and concentrated to remove EtOH. The yellow residue was taken up in EtOAc (2.0 mL) and washed with H_2O, brine, dried over $MgSO_4$ and concentrated to give 83 mg of a pale yellow oil which was purified by column chromatography (15% EtOAc in hex) to afford side product **4.37** (R_f = 0.52, 50% EtOAc in hex) (31 mg, 16%) as a yellow oil, followed by the title compound **4.35** in a mixture with starting material **1.3** (85 mg) as a yellow amorphous solid. A second purification of this mixture by recrystallisation from Et_2O afforded the title compound **4.35** (R_f = 0.25, 50% EtOAc in hex) (37 mg, 34%) as a colourless amorphous solid. The resulting crystallisation liquor was concentrated to afford recovered starting material **1.3** (R_f = 0.3, 50% EtOAc in hex) (35 mg, 35%) as a yellow oil.

Compound 4.37

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.65 – 2.53 (2H, m, CH_2's); 2.47 – 2.28 (5H, m, CH_2's); 2.11 – 1.57 (5H, m, CH2's); 0.99 (3H, d, *J* = 7 Hz, CH$\underline{CH_3}$); 0.89 (3H, s, quat.C$\underline{CH_3}$). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 211.1 (C=O); 209.5 (C=O); 56.7 (quat.C); 41.9 ($\underline{CH}CH_3$); 41.2 (CH_2); 41.0 (quat.C); 38.4 (CH_2); 37.3 (CH_2); 37.0 (CH_2); 31.2 (CH_2); 14.8 (quat.C$\underline{CH_3}$); 10.8 (CH$\underline{CH_3}$). MS: ESI+ 217.2 $[M+Na]^+$. IR (film) ν_{max} = 2933 (CH_2), 2884, 2824, 1680, 1444 cm^{-1}.

Compound 4.35

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.73 (1H, t, *J* = 4.7 Hz, CHOH); 2.88 (1H, d, *J* = 15 Hz, (CN)CCH$_2$C=O); 2.55 (1H, d, *J* = 15 Hz, (CN)CCH$_2$C=O); 2.49 – 2.30 (2H, m, CH$_2$); 2.22 – 2.04 (2H, m, CH$_2$); 1.92 – 1.83 (3H, m, CH$_2$ + OH); 1.78 – 1.66 (3H, m, CH$_2$, CHCH$_3$); 1.41 (3H, s, quat. CCH$_3$); 1.12 (3H, d, *J* = 7.0 Hz, CHCH$_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 206.2 (C=O); 120.9 (CN); 71.0 (CHOH); 51.1 (quat.CCN); 43.7 ((CN)CCH$_2$C=O); 38.0 (quat.CCH$_3$); 36.5 (CH_2); 34.3 (CH_2); 33.0 (CHCH$_3$); 27.8 (CH_2); 25.3(CH_2); 20.6 (quat.CCH$_3$); 15.7 (CHCH$_3$). GCMS (CI) *m/z* 221 $[M]^+$; 239 $[M+NH_4]^+$. IR (film) ν_{max} = 3459 (OH), 2945 (CH_2), 2227 (C≡N), 2140, 1977, 1712 (C=O), 1467 cm^{-1}.