Total Synthesis of the Putative Structure of Tridachiahydropyrone

A thesis submitted for fulfilment of the degree of

Doctor of Philosophy

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For Ella Paige

Tridachia crispata

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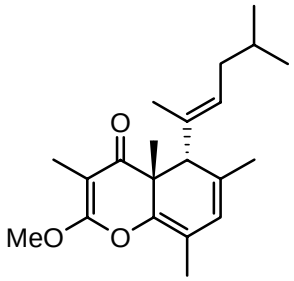
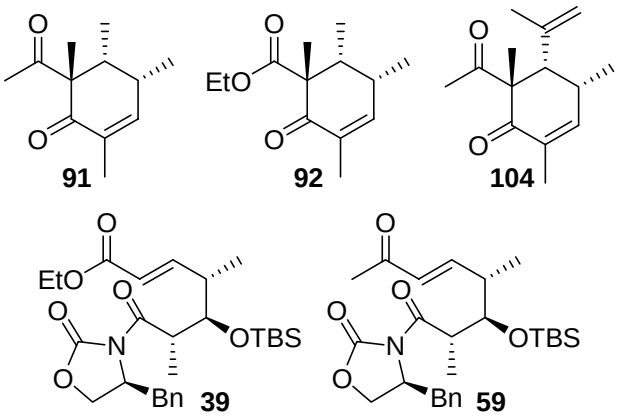
Abstract

Polypropionate marine natural products have emerged as a class of compounds that display a high degree of structural diversity. Specifically, metabolites such as that reported as tridachiahydropyrone (**7**), isolated from sacoglossan molluscs, display novel ring systems. The introductory chapter gives some background on tridachione marine natural products and outlines the isolation of metabolites from several species of sacoglossan mollusc. Chapter One also gives examples of the utility of the tandem conjugate addition-Dieckmann condensation approach being applied to the synthesis of these compounds.

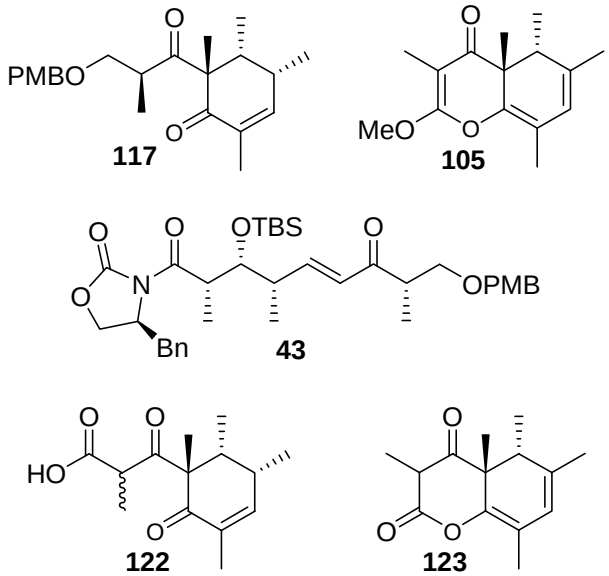


Tridachiahydropyrone (7)

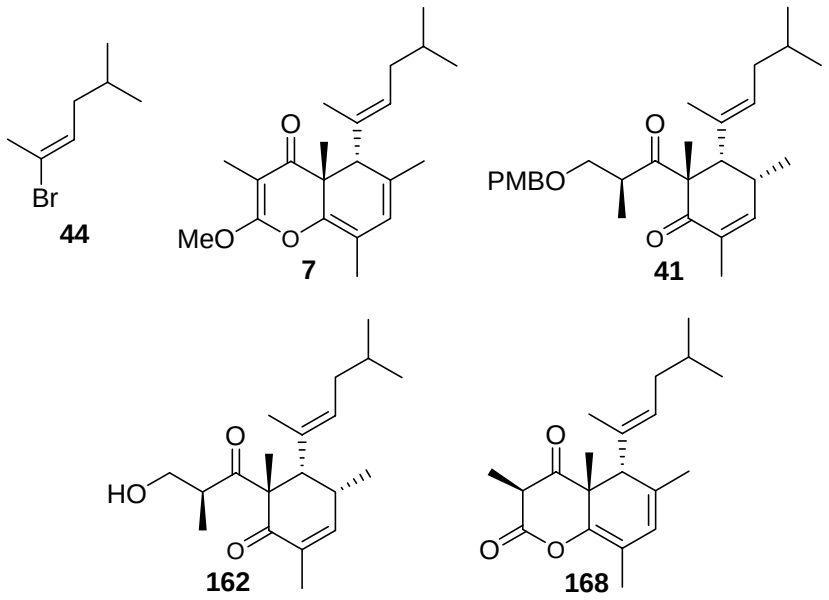
Chapter Two describes the development of the tandem conjugate addition-Dieckmann condensation and subsequent *trans* methylation approach to cyclohexenone rings. The synthetic strategy utilised chiral, functionalised cyclohexenone rings as synthons in the formation of bicyclic ring systems, so development of the carbocyclic ring formation was of vital importance to the overall strategy. Examples are given which confirm the viability of the proposed synthetic route to cyclohexenones such as **91**, **92** and **104** from the reaction of α,β-unsaturated carbonyl compounds **39** and **59** with dialkyl and dialkenyl Gilman cuprates.



Chapter Three describes the incorporation of chiral cyclohexenone **117** into the bicyclic framework of model compound **105**, analogous to the marine natural product reported as tridachiahydropyrone (**7**). The chapter explores the use of cyclohexenone precursor **43** that contained the total carbon framework of the bicyclic core of the desired pyrone. Once again, a tandem conjugate addition-cyclisation reaction was employed using a dialkyl Gilman cuprate, followed by *trans* methylation to give the requisite cyclohexenone synthon **117**. A novel Eaton's reagent-promoted intramolecular cyclisation of acid **122** to pyrone **123** was then effected. Subsequent *O*-methylation afforded α-methoxy-β-methyl-γ-pyrone **105** as a single enantiomer, which had the identical core structure to the natural product. The structure, including relative stereochemistry of **105**, was confirmed by single crystal X-ray analysis.



Chapter Four builds on the previous two chapters and describes the conjugate addition-cyclisation with a higher order Gilman cuprate derived from vinyl bromide **44**, which would deliver the vinyl side-chain required for the synthesis of reported natural product **7**. The same acyclic precursor **43** as used in Chapter Three was cyclised and methylated to yield yet another cyclohexenone synthon **41**. A single crystal X-ray analysis of related alcohol **162** confirmed the relative stereochemistry and structure. Another novel P_2O_5-mediated intramolecular cyclisation was achieved to give pyrone **168** and *O*-methylation provided a compound with the reported structure of natural product **7** as a single enantiomer. The structure of synthetic **7** was established unequivocally through extensive NMR studies. Comparisons of spectral data confirmed that natural tridachiahydropyrone was not the same as synthetic compound **7**, so revision of the assigned natural product structure is warranted. Several other analogues were also synthesised using this methodology, highlighting the versatility of the method under development.



Declaration

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

David W. Jeffery

18 March 2005

Acknowledgments

I would like to thank my supervisor, Dr. Michael Perkins, for his guidance and wisdom during my years of research. Dr. Perkins was always willing to listen and offer suggestions about my research project. He showed enthusiasm towards my research and encouraged and supported my endeavours. I also appreciated Dr. Perkins' good sense of humour and enjoyed the lunches and leisure activities that he organised.

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Publications and Presentations

The following is a list of publications that have resulted from research outlined in this thesis and presentations that were delivered at various symposia.

Publications[🕮]

1. Formation of Highly Substituted Chiral Cyclohexanone Derivatives Using a Tandem Conjugate Addition/Cyclisation
   Jeffery, D.W.; Perkins, M.V. *Tetrahedron Lett.* **2004**, *45*, 8667-8671.

2. Synthesis of an Analogue of the Marine Polypropionate Tridachiahydropyrone
   Jeffery, D.W.; Perkins, M.V.; White, J.M. *Org. Lett.* **2005**, *7*, 407-409.

3. Synthesis of the Putative Structure of Tridachiahydropyrone
   Jeffery, D.W.; Perkins, M.V.; White, J.M. *Org. Lett.* **2005**, accepted.

Presentations

Synthetic Studies Directed Toward the Tridachione Family of Marine Natural Products. Poster presentation delivered at the 19th RACI Organic Conference, Lorne, VIC, July 2003.

Synthetic Studies Directed Toward the Tridachione Family of Marine Natural Products. Oral presentation delivered at the Adelaide Organic Synthesis Symposium, Adelaide, SA, December 2003.

Towards the Total Synthesis of the Marine Natural Product Tridachiahydropyrone. Oral presentation delivered at the 15th Southern Highlands Conference on Heterocyclic Chemistry, Moss Vale, NSW, September 2004.

[🕮] Reprints (and/or preprints) are contained within Appendix A.

Chapter One

Introduction

Polypropionate marine natural products are a class of compounds with a wide range of structural diversity, with many possessing biological activity. Strategies developed for the synthesis of such compounds enhance methodology, confirm structure and stereochemistry and open avenues for the formation of potentially bioactive compounds.

1.1 Synthesis of Marine Natural Products

Terrestrial natural products have long been the focus of the synthetic organic chemist and more recently marine natural products have gained attention. This may be due in part to the abundance and variety of natural products that have been isolated from a diverse range of marine organisms, from molluscs to sponges and bacteria. For instance, in the year 2000 alone the structures of over 800 new marine natural products were published in the literature.[1]

Many marine-derived compounds are reported to possess biological activity, and this, combined with the challenge of the synthesis and necessity for confirmation of structure, has led to many attempts to synthesise such compounds. A motivating factor is that isolation from the natural source generally yields very small amounts (usually milligram quantities) of the compound, which makes harvesting bioactive compounds from marine organisms a rather unattractive option.

Marine metabolites are interesting synthetic targets because many are rather complex molecules, often containing a variety of functional groups, many stereocentres and elaborate ring systems. Adding to the challenge and complexity, there is no single way to carry out these syntheses, rather a myriad of plausible strategies. Once complete, however, such natural product syntheses allow for biological testing of compounds, and the possibility of scale-up for commercial preparation. Furthermore, the methodology developed for the synthesis is invaluable in expanding the synthetic arsenal available to the organic chemist.

1.2 Biological Activity

Significant biological activity has been associated with many marine natural products, such as the toxic marine compounds which have life-threatening paralytic[2] or diarrhetic[3] properties. It is of considerable importance to understand the nature of these toxic compounds obtained from marine organisms. This information may help prevent poisonings and death, which stem from incidences such as people consuming fish or shellfish that have fed on toxic organisms. Then there are the poisonous organisms that use toxins as defence mechanisms (eg. cone fish, blue-ringed octopus) which also pose a hazard.

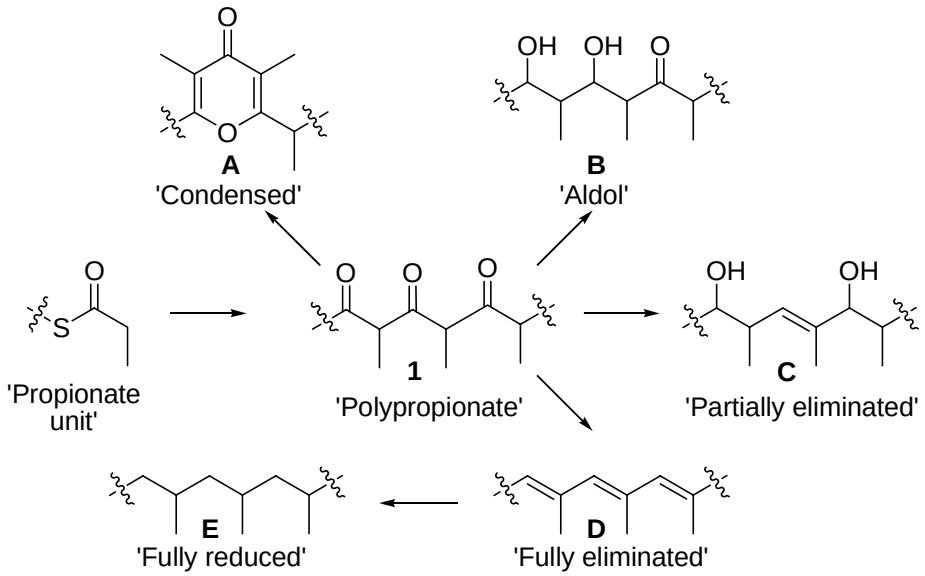
In contrast, an increasing number of these marine-derived natural products have potential beneficial applications in medicine, possessing desirable attributes such as antimicrobial and antifungal,[4-9] cytotoxic [5,10-14] or antiviral[11,13] properties. The discovery of new medicines is always a necessity and could have a positive impact on people's lives. There is virtually an untapped ocean of compounds with possible medicinal properties just waiting to be discovered or synthesised, and one such group of compounds is the polypropionates.

1.3 Polypropionate Marine Natural Products

Over the past few decades, marine-derived polypropionate metabolites have emerged as a class of structurally unique natural products. Polypropionates obtained from terrestrial bacteria are already considered an important class of compounds for their biological activity and the same may be true for marine polypropionates. Marine molluscs appear to offer a wealth of polypropionate metabolites, with some compounds isolated having beneficial bioactivity for humans, but in the main they impart some influence or advantage to the organism in which they are produced.

The polypropionate skeleton, seen for example in the generic polypropionate, tricarbonyl **1** in Scheme 1.1 below, is a common motif found in molluscan metabolites, and arises from the enzymatic condensation of propionate units. This leads to a linear carbon chain consisting of alternating oxygenated and methylated carbon centres, which may undergo a variety of transformations. For example, direct condensation leads to pyrone **A**. Reduction of carbonyl groups in **1** leads to the commonly encountered aldol **B**. This in turn gives rise to partially eliminated **C** or fully eliminated **D**, after

elimination of secondary hydroxyl groups. The double bonds of fully eliminated **D** can be further reduced to afford fully reduced **E**.



Scheme 1.1: *Generic polypropionate **1** and commonly encountered derivatives.*

Common structural motifs arising from polypropionate derivative **1** and **A-E** are shown in Figure 1.1 and include the following: spiroacetal and pyrone rings as in auripyrones A (**2**) and B (**3**), hemiacetal rings as in denticulatins A (**4**) and B (**5**) and alkyl/alkenyl chains as in siphonarienfuranone (**6**). The rings are all made possible because of the high level of oxygenation and enolisability of the typical polypropionate backbone, where appropriately situated carbonyl oxygens or hydroxyls may nucleophilically attack carbonyl carbons further along the chain. Furanone rings, such as found in siphonarienfuranone (**6**), cyclise similarly but do not arise from a typical polypropionate skeleton.

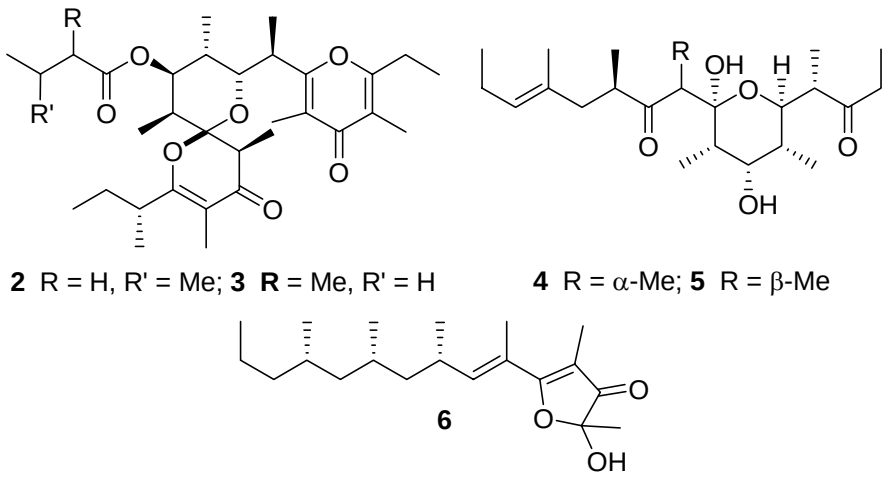
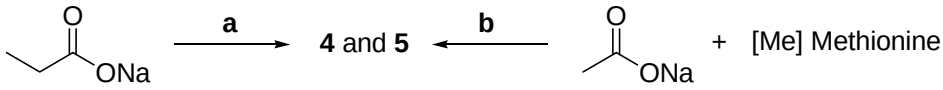


Figure 1.1: *A selection of polypropionates showing structural diversity.*

1.4 Polypropionate Biosynthesis

Studies of polypropionate biosynthesis have been carried out by incorporating radioisotopes such as ^{14}C into compounds to which the molluscs are then exposed. Some of the earlier work by Ireland and Scheuer involved placing molluscs in seawater that contained ^{14}C-labelled sodium hydrogen carbonate and subsequently isolating ^{14}C-labelled polypropionate metabolites.[15] In other experiments by Cimino and coworkers, molluscs were exposed to ^{14}C-containing propionate salts in seawater and left for several days. The subsequent isolation and analysis of polypropionate metabolites showed they contained the radioactive label.[16,17] Experiments performed by Garson *et al*. sort to probe whether the biosynthetic pathway incorporated propionate units (Path a) or acetate units (Path b, Scheme 1.2). The study, involving the formation of denticulatins A (**4**) and B (**5**), confirmed the source of the polypropionate backbone as propionate units (Path a), as opposed to acetate units followed by enzymatic methylation, with the use of ^{14}C-radiosotopes.[18]



Scheme 1.2: *Polypropionate and acetate plus methylation pathways to denticulatins (**4**) and (**5**).*[18]

1.5 Tridachione Family of Polypropionates

1.5.1 Sacoglossan Molluscs: A Source of Novel Polypropionates

A structurally novel family of marine polypropionates is the tridachiones (Figures 1.2 and 1.3), such as tridachiahydropyrone (**7**), 9,10-deoxytridachione (**10**), tridachiapyrones A (**14**) to I (**23**) and crispatone (**29**), isolated from sacoglossan molluscs.[9,14,15,19-25] The molluscs that yield these metabolites tend to lack a protective shell and most have the peculiar ability of sequestering and utilising organelles from other marine organisms.[23,25]

The order Sacoglossa is divided into two major classes; shelled (suborder Oxynoacea) and shell-less (suborder Plakobranchacea). The molluscs discussed in the following paragraphs are shell-less and are contained in the superfamily Plakobranchoidea (= Placobranchoidea; = Elysioidea) and family Plakobranchidae (= Elysiidae). The molluscs are further classified by genus and those discussed below are described as *Elysia, Placobranchus, Tridachia* and *Tridachiella*.[26]

Molluscs of the family Plakobranchidae (= Elysiidae) are classified according to anatomical features and similarities. Comparison of parapodia, colour, frill appearance and even branching of hepatic portal vessels are some of the indicators used in the classification process.[27] The field of taxonomy is such that classifications are continually being revised, and it was often found that *Tridachia* was also referred to as *Elysia* in the literature, due to the dynamic nature of this field.

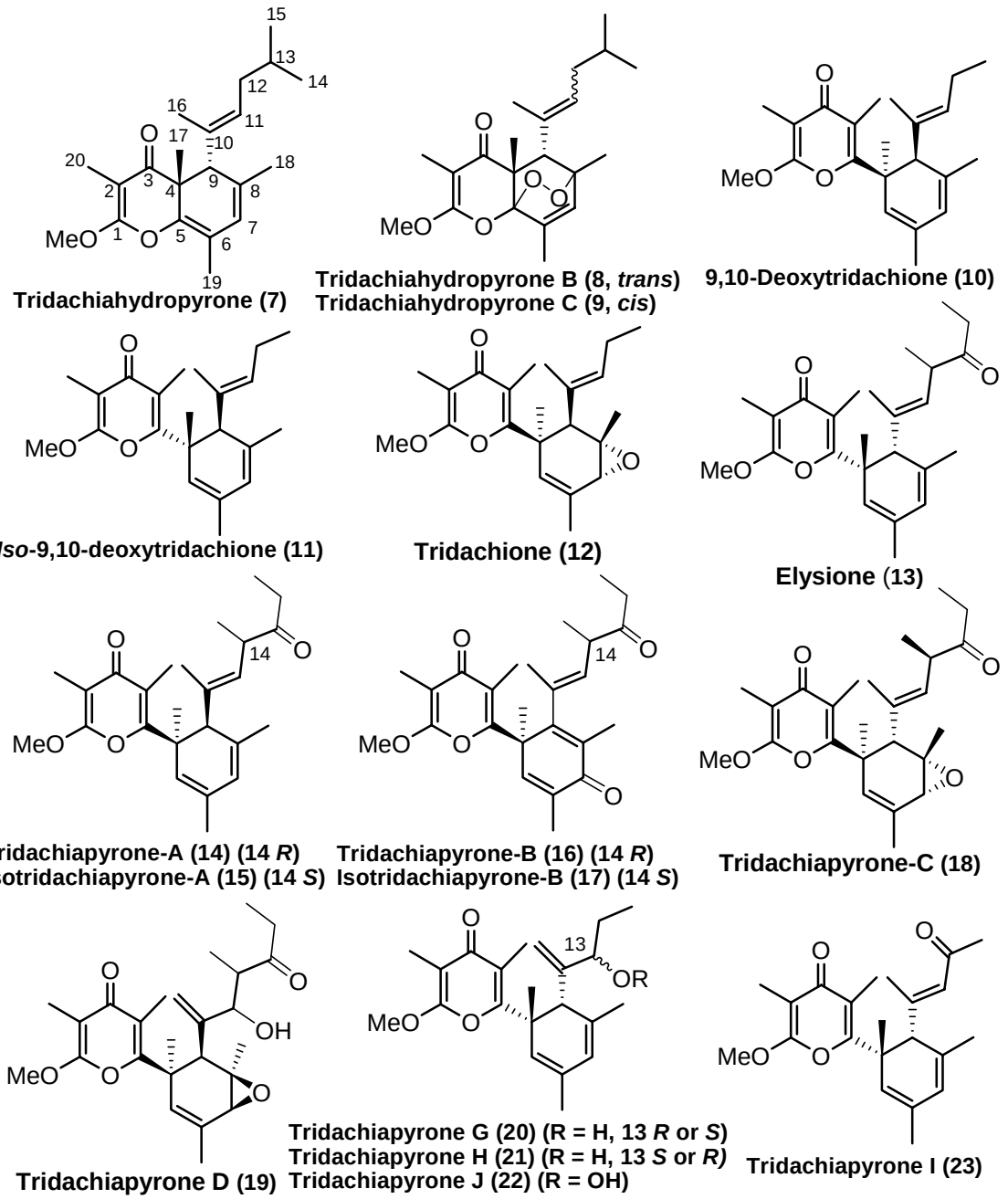


Figure 1.2: *Tridachione marine natural products displaying both pyrone ring and hexadiene ring (at various levels of oxidation).*

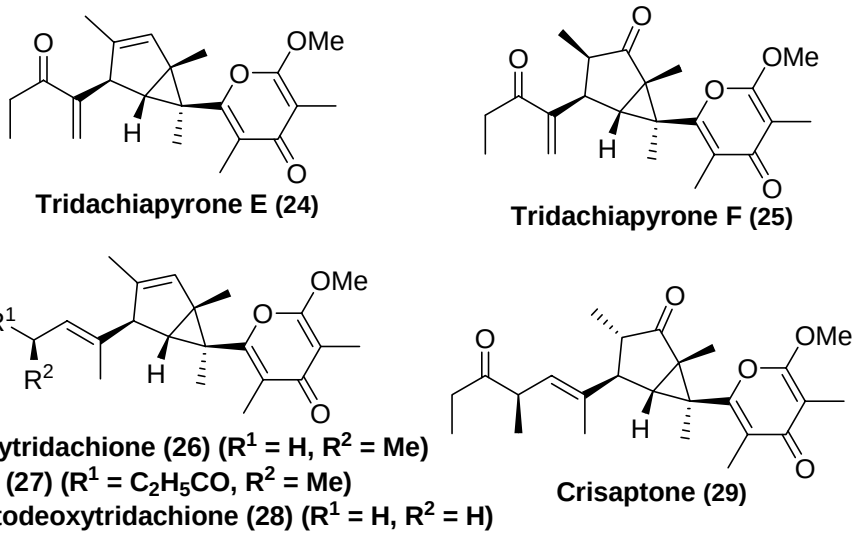
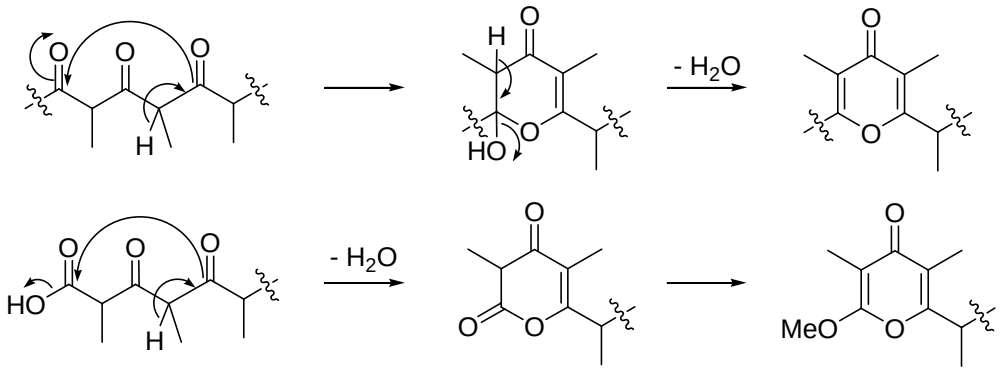


Figure 1.3: *Other tridachione marine natural products showing both pyrone and bicyclohexene ring (at various levels of oxidation).*

The purpose of these tridachione polypropionate metabolites is unclear but they may act as a chemical defence mechanism against predation[28,29] or even as a defence against exposure to sun rays.[23] A common feature of many of these particular non-linear polypropionates is the presence of both a γ-pyrone ring, and a cyclohexadiene ring at various levels of oxidation (Figure 1.2). Notably, the γ-pyrone moiety bears an α-methoxy group, meaning the pyrone has a higher oxidation state than other pyrone-containing polypropionates. This indicates cyclisation may occur onto an acid/ester carbonyl to form the pyrone, rather than a ketone carbonyl, as is the norm (Scheme 1.3).

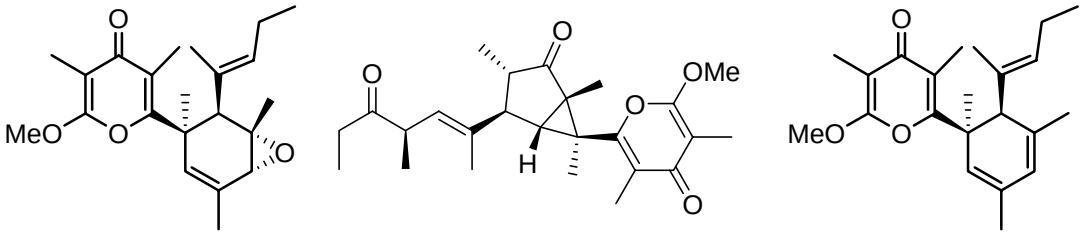
In fact, in tridachiahydropyrone (**7**) both rings are contained in a bicyclic system, with the pyrone existing as a γ-dihydropyrone ring, which is rare in marine organisms.[23] Tridachiahydropyrone (**7**) is also peculiar in that it seems to contradict the normal polypropionate rule, with a shift of a methyl to C-13. This may indicate that an alternative unit is incorporated during the biosynthesis. Irrespective of this, development of methodology to access unusual bicyclic pyrones of this type will aid in the advancement of synthetic organic chemistry.



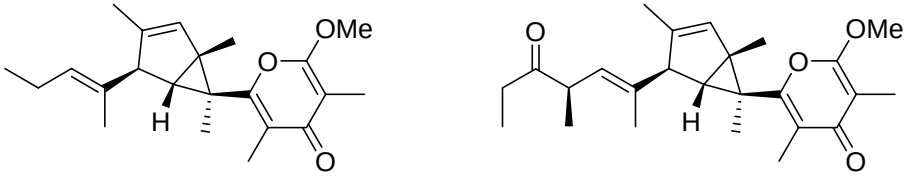
Scheme 1.3: *Cyclisation modes leading to α-alkyl- and α-methoxy-γ-pyrones.*

1.5.2 Isolation and Structure Determination

The first tridachione type marine natural product was described in 1978 when tridachione (**12**) was isolated by Ireland *et al*.[19] from *Tridachiella diomedea* specimens collected in the Gulf of California. In 1979 Ireland *et al*.[20] isolated crispatone (**29**) from *Tridachia crispata* collected at Glover Reef, Belize and from samples obtained from Panama. This was followed by the work of Ireland and Faulkner[21] in 1981, who isolated the (–) enantiomer of 9,10-deoxytridachione (**10**) [also isolated from *Placobranchus ocellatus*,[15] and converted into photodeoxytridachione (**26**)[15,21] (Section 1.5.4)] as another metabolite from *T. diomedea*, along with tridachione (**12**). This time samples were collected in the Gulf of California and on the Pacific coast of Panama and El Salvador. In the same report, samples of *T. crispata* were collected from Glover Reef, Belize and on the Caribbean coast of Panama. This species of mollusc yielded metabolites crispatone (**29**) and crispatene (**27**), with the bicyclo[3.1.0]hex-2-ene ring in the latter being photochemically related to 9,10-deoxytridachione (**10**).

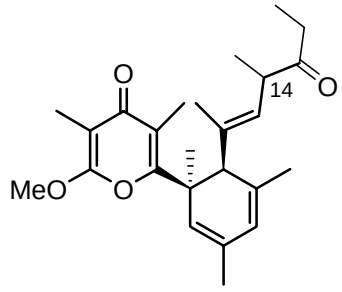


Tridachione (12) **Crisaptone (29)** **9,10-Deoxytridachione (10)**

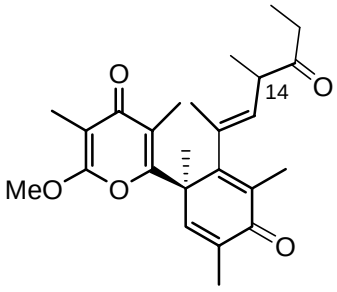


Photodeoxytridachione (26) **Crispatene (27)**

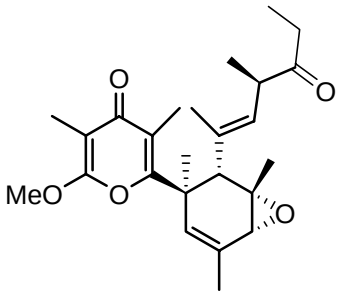
In 1985 Ksebati and Schmitz[14] compared metabolites from *T. crispata* gathered on the coast of Jamaica with those already reported by Ireland and Faulkner. Once again, crispatone (**29**) and crispatene (**27**) were isolated, but Ksebati and Schmitz also discovered eight new γ-pyrone-containing metabolites. These new metabolites included tridachiapyrone-A (**14**) and isotridachiapyrone-A (**15**), which were almost identical to 9,10-deoxytridachione (**10**), except for the addition of a propionyl group in the side-chain. Tridachiapyrone-B (**16**), isotridachiapyrone-B (**17**), tridachiapyrone-C (**18**) and tridachiapyrone-D (**19**) are similarly related, but possess higher degrees of oxygenation, bearing epoxide, alcohol and ketone moieties. Tridachiapyrone-E (**24**) appeared to be related to crispatene (**27**), having the same cyclic structure, while tridachiapyrone-F (**25**) contains one more oxygen than **24** but the same cyclic skeleton. During the Ksebati and Schmitz study, crispatene (**27**), crispatone (**29**) and all tridachiapyrones except E (**24**) and F (**25**) were tested for cytotoxicity *in vitro* against lymphocytic leukemia cells, with **14**, **16**, **19**, **27** and **29** proving active.[14]



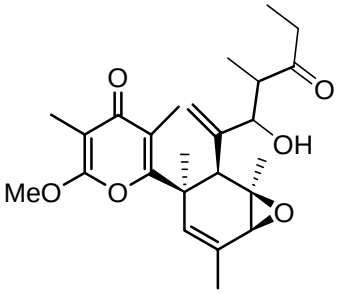
Tridachiapyrone-A (14) (14 *R*)
Isotridachiapyrone-A (15) (14 *S*)



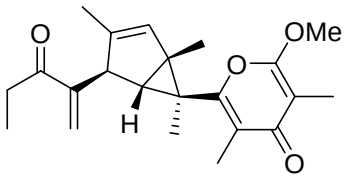
Tridachiapyrone-B (16) (14 *R*)
Isotridachiapyrone-B (17) (14 *S*)



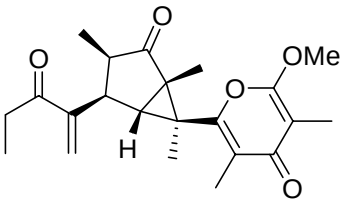
Tridachiapyrone-C (18)



Tridachiapyrone D (19)



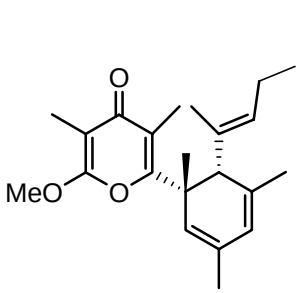
Tridachiapyrone E (24)



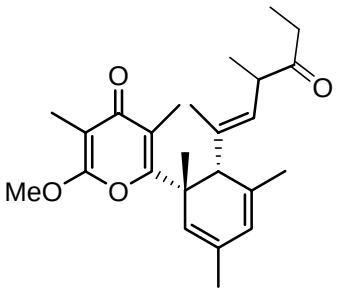
Tridachiapyrone F (25)

Subsequently, in 1986 Dawe and Wright[9] determined the structures of metabolites from *Elysia chlorotica* specimens collected around the Bay of Fundy, Nova Scotia. They identified the (+) enantiomer of 9,10-deoxytridachione (***ent*-10**), the enantiomer of **10** found in *T. diomedea*, and elysione (**13**) (also isolated from *Elysia viridis*[16]), which appeared to be the enantiomer of one of the metabolites isolated from *T. crispata*. Both

metabolites inhibited the growth of Gram (+) bacterium, *Micrococcus luteus*, but only ***ent*-10** was active against Gram (+) *Bacillus subtilis*.

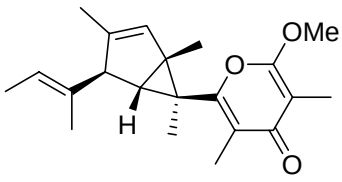


***ent*-10**

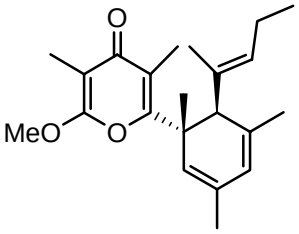


Elysione (13)

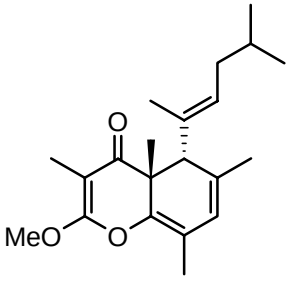
Gavagnin *et al.*[22] reported several new metabolites in 1994 from the mollusc *Elysia timida*, collected off the Italian and Spanish coasts, along with the known (–) enantiomer of 9,10-deoxytridachione (**10**) and related photodeoxytridachione (**26**). The new isolates were 15-norphotodeoxytridachione (**28**), closely related to photodeoxytridachione (**26**) and crispatene (**27**), and *iso*-9,10-deoxytridachione (**11**), which is related to 9,10-deoxytridachione (**10**) but has *cis* relative stereochemistry. Further work by Gavagnin *et al.*[23] in 1996 identified tridachiahydropyrone (**7**) as a metabolite of *T. crispata*, collected off the coast of Venezuela. As mentioned above, this compound displayed an unusual, fused, bicyclic carbon skeleton and was the first of its type to contain this fused ring system. Another study by Gavagnin *et al.*[24] in 1997 identified known metabolites crispatene (**27**) and photodeoxytridachione (**26**) from populations of *T. crispata* collected from the Venezuelan coast and crispatene (**27**) and crispatone (**29**) from specimens collected off the Mexican coast.



15-Norphotodeoxytridachione (28)



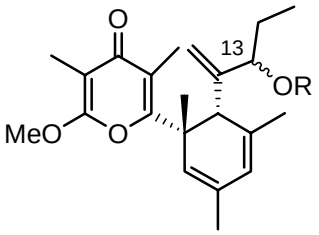
***Iso*-9,10-Deoxytridachione (11)**



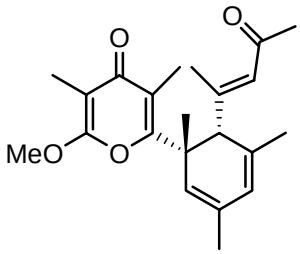
Tridachiahydropyrone (7)

In 2000, Fu *et al*.[25] identified six new metabolites from *P. ocellatus*, collected from the Philippines, along with the (+) enantiomer of 9,10-deoxytridachione (**10**). The new compounds were designated tridachiapyrones G (**20**)-J (**23**), because of their structural similarity to 9,10-deoxytridachione (**10**), and tridachiahydropyrones B (**8**) and C (**9**), which appear to be photooxygenation products of tridachiahydropyrone (**7**).

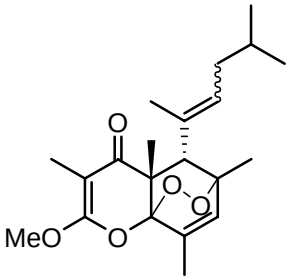
It became apparent from the preceding isolations that geographical differences in populations of molluscs had only a marginal effect on the metabolites produced. This indicated, therefore, that the metabolites are synthesised *de novo* rather than simply coming from dietary sources, and the biosynthesis of such metabolites is relatively conserved between the various mollusc species.



Tridachiapyrone G (20) (R = H, 13 *R* or *S*)
Tridachiapyrone H (21) (R = H, 13 *S* or *R)*
Tridachiapyrone J (22) (R = OH)



Tridachiapyrone I (23)



Tridachiahydropyrone B (8)
Tridachiahydropyrone C (9)

The isolation techniques reported in the literature involved extracting and purifying the metabolites of the various molluscan samples. Generally, the ether soluble fraction from an acetone extraction of the homogenised mollusc was chromatographed on silica and further purified by preparative TLC. Alternatively, extraction was accomplished with methanol/dichloromethane, giving hexane and dichloromethane soluble propionates which were separated on silica or by HPLC. Standard spectroscopic methods were then used to determine the structure of the metabolites and these techniques included: HRMS, ^{1}H and ^{13}C NMR, and COSY, HETCOR, HMBC and NOE NMR experiments. These experiments provided some knowledge of the stereochemistry present in the metabolites.

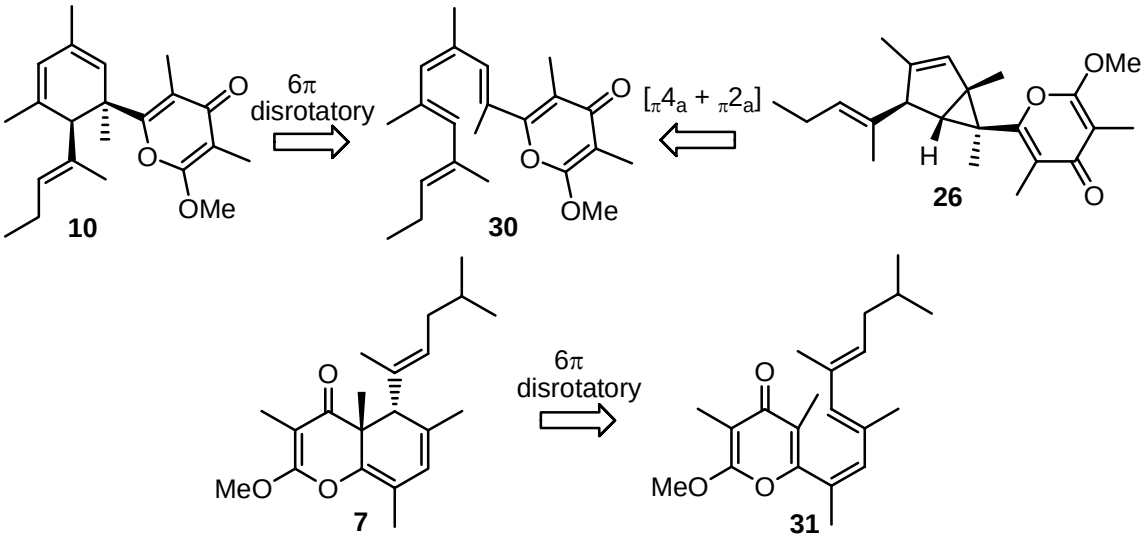
1.5.3 Stereochemistry

At present, the absolute stereochemistry of the tridachiones discussed above has yet to be established. It has been determined that certain groups are *cis* or *trans* to each other, but the absolute configuration of the stereocentres has not been assigned. The total synthesis of these tridachione natural products as single enantiomers will thus allow for the assignment of absolute stereochemistry. Upon completion of a synthesis, the optical rotation data can be compared with that of the authentic natural product to determine the absolute configuration of the natural product. If it transpires that the opposite enantiomer was synthesised, valuable information can still be gained. The methodology will exist and the synthesis can be repeated with the appropriate chiral starting materials.

1.5.4 Possible Biosynthetic Relationships

Previous work by Ireland and Scheuer has demonstrated that 9,10-deoxytridachione (**10**) can be photochemically converted *in vivo* into photodeoxytridachione (**26**).[15] The transformation may proceed *via* a $[_{\pi}4_a + {}_{\pi}2_s]$ cycloaddition but since no racemisation occurs, Ireland and Faulkner have postulated that the reaction occurs photochemically through the more direct $[_{\sigma}2_a + {}_{\pi}2_a]$ mechanism.[21] Further to this, Ireland and Faulkner have demonstrated the *in vitro* conversion of **10** into **26** by photolysis in benzene.[21] These results suggest that biosynthetically, **26** is derived from **10**, but theoretically, at least, it may be possible that both **10** and **26** come from a common acyclic precursor **30**.[30] Thus, 9,10-deoxytridachione (**10**) may arise through thermal, disrotatory 6π electrocyclisation and photodeoxytridachione (**26**) may come from the thermal $[_{\pi}4_a + {}_{\pi}2_a]$ cycloaddition (Scheme 1.4).[30]

Extension of these theories may be applied to the biosynthesis of tridachiahydropyrone (**7**), whereby 6π electrocyclisation of achiral tetraene **31** (Scheme 1.4) affords the bicyclic ring system and stereochemistry as seen in tridachiahydropyrone (**7**). Contrasting this, the approach described in the coming chapters was not designed to be biomimetic and as such does not rely on electrocyclic reactions for ring formation and control of stereochemistry. However, the concept of using a precursor that contains the necessary carbon framework of the bicyclic ring system was a common link.



Scheme 1.4: *Possible biosynthetic origins of some tridachione natural products.*

1.5.5 Tridachiones as Synthetic Targets

The tridachiones are interesting synthetic targets for a number of reasons. Firstly, they possess a γ-pyrone ring, as mentioned above, which is similar to the dihydropyrone found in the cytotoxic auripyrones[12] A (**2**) and B (**3**) and in the membrenones[31] A (**32**)-C (**34**) (Figure 1.4), which are thought to impart chemical defensive properties[32]. Tridachiapyrone-A (**14**) has already shown activity against lymphocytic leukemia cell lines,[14] so by analogy tridachiahydropyrone (**7**) and other related tridachiones may also possess beneficial biological activity, and their synthesis could allow for biological testing. Secondly, this challenging synthesis will aid in further extending the synthetic methodology available to chemists. Highlighting this, tridachiahydropyrone (**7**) contains a novel bicyclic structure not attainable with current synthetic chemistry. Devising a new synthetic methodology, therefore, will enhance the capabilities of synthetic organic chemists. Finally, synthesis of such natural products confirms their structure and allows for the assignment of absolute stereochemistry.

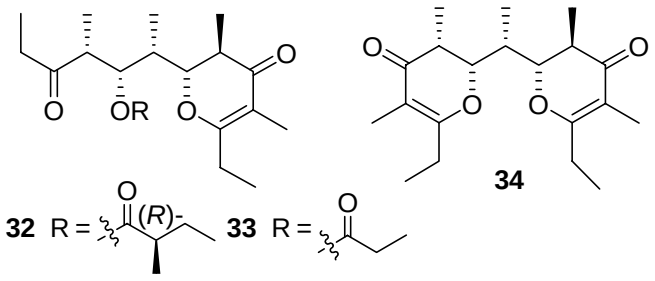
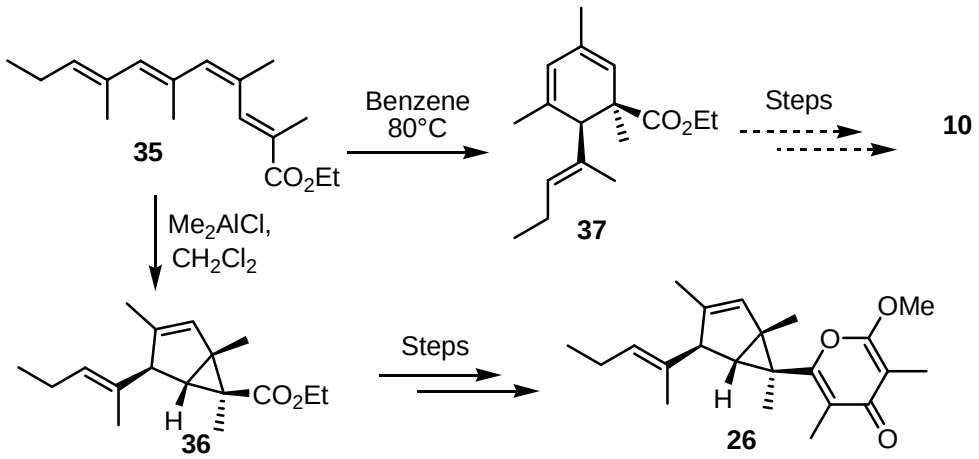


Figure 1.4: *γ-dihydropyrone containing membrenones A (**32**)-C (**34**).*

1.5.6 Previously Reported Synthetic Approaches

Tridachiones have largely escaped the attention of synthetic organic chemists. Recently, however, Miller and Trauner[30] have reported an elegant approach to (±)-photodeoxytridachione (**26**) using a Lewis acid catalysed cyclisation of tetraene intermediate **35** (Scheme 1.5). The bicyclo[3.1.0]hexene core **36** of the natural product, with its two adjacent quaternary stereocentres, was formed in one step (73%) from acyclic precursor **35** by treatment with a catalytic amount of dimethylaluminium chloride in CH_2Cl_2. In addition, thermal cyclisation of tetraene **35** yielded cyclohexadiene **37**, which could serve as an intermediate in the total synthesis of 9,10-deoxytridachione (**10**). Although this was a racemic approach to a natural product, the authors also discussed the possibility of asymmetric synthesis using a chiral Lewis acid, and they are investigating this further.



Scheme 1.5: *Miller and Trauner's approach to (±)-photodeoxytridachione (**26**).*

In contrast to Miller and Trauner's racemic approach, the methodology developed and described in the following chapters has the ability to deliver enantiomerically pure natural products. The choice of chiral starting material dictates which enantiomer results, so there is total control of the synthesis from the beginning. The methodology required to undertake this work led to the formulation of several clear aims for the direction of the research.

1.6 Aims of Research Work Described

The overall aims of the research described in this thesis were the development of a synthetic methodology for the total synthesis of tridachione marine natural products as single enantiomers and to complete a synthesis of the reported structure of

tridachiahydropyrone (**7**). Incorporated into these themes are several key objectives which are discussed in the following three chapters.

One necessary objective was the development of the tandem conjugate addition-Dieckmann condensation (also referred to herein as addition-condensation) and subsequent *trans* methylation approach to cyclohexenone rings. The planned synthetic strategy utilised chiral, functionalised cyclohexenone rings as synthons in the formation of bicyclic ring systems, so development of the addition-cyclisation aspect was of vital importance to the overall success of the project. Another important objective was the incorporation of a chiral cyclohexenone into the bicyclic framework of a model compound analogous to the marine natural product tridachiahydropyrone (**7**). Therefore, a novel intramolecular cyclisation, required to form the core bicyclic framework of these types of molecules, had to be developed.

Ultimately, an objective was to effect a conjugate addition-cyclisation with the requisite vinyl side-chain of natural product **7**. An acyclic precursor common to the model study was envisaged to be cyclised and methylated to yield the desired cyclohexenone synthon. The novel intramolecular cyclisation developed for the model pyrone would again be employed to form the bicyclic core of natural product **7**. It was planned that other analogues could also be synthesised by this method, highlighting the versatility of the approach.

Thus, the overall development of methodology for the synthesis of tridachione natural products would incorporate the following novel aspects: formation of chiral, highly substituted cyclohexenones using a tandem conjugate addition-cyclisation approach; utilisation of cyclohexenone derivatives as synthons to install the carbocyclic ring of the bicyclic natural product; intramolecular cyclisation of the cyclohexenone carbonyl oxygen onto a carboxylic acid moiety to afford the desired bicyclic core of natural product **7**. These novel aspects can be seen in the retrosynthetic analysis which follows.

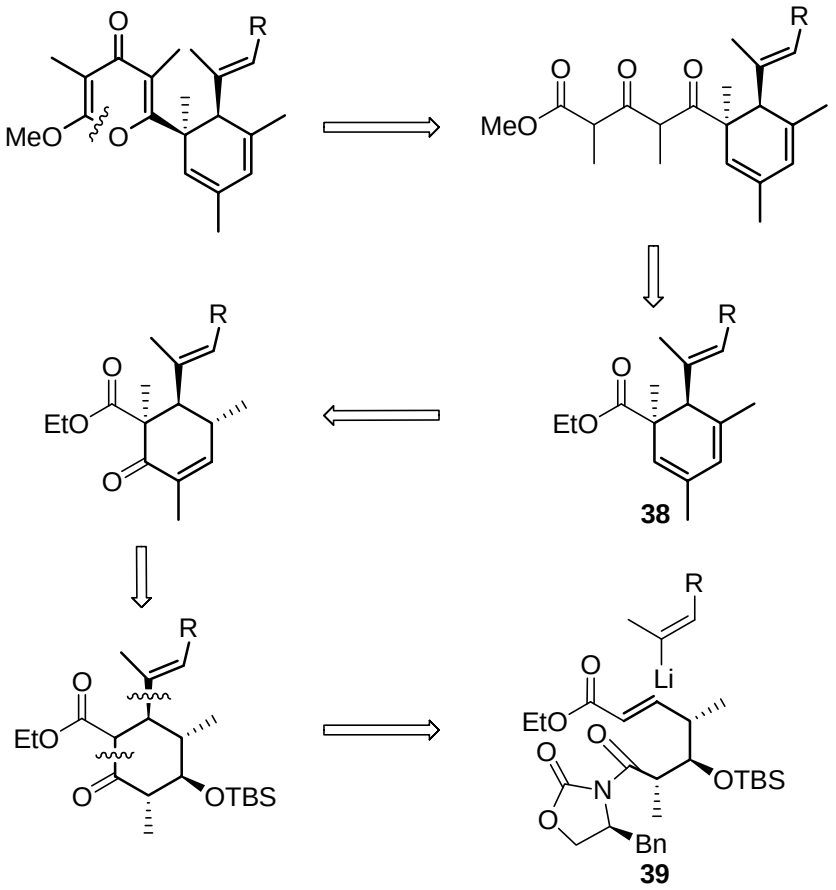
1.7 Retrosynthetic Analysis

1.7.1 General Tridachione Retrosynthetic Strategy

The retrosynthetic analysis for tridachione natural products is shown in Scheme 1.6 for the tethered analogues and Scheme 1.7 for tridachiahydropyrone (**7**) itself. Either way,

the synthetic strategy hinged upon the formation of chiral, highly substituted cyclohexenone derivatives as synthons to install the cyclohexadiene moiety found in many tridachione marine natural products. Tethered, bicyclic tridachiones such as **10** and **11** should prove simpler to synthesise than tridachiahydropyrone (**7**) using this methodology, because suitable reactions already exist for pyrone ring formation.

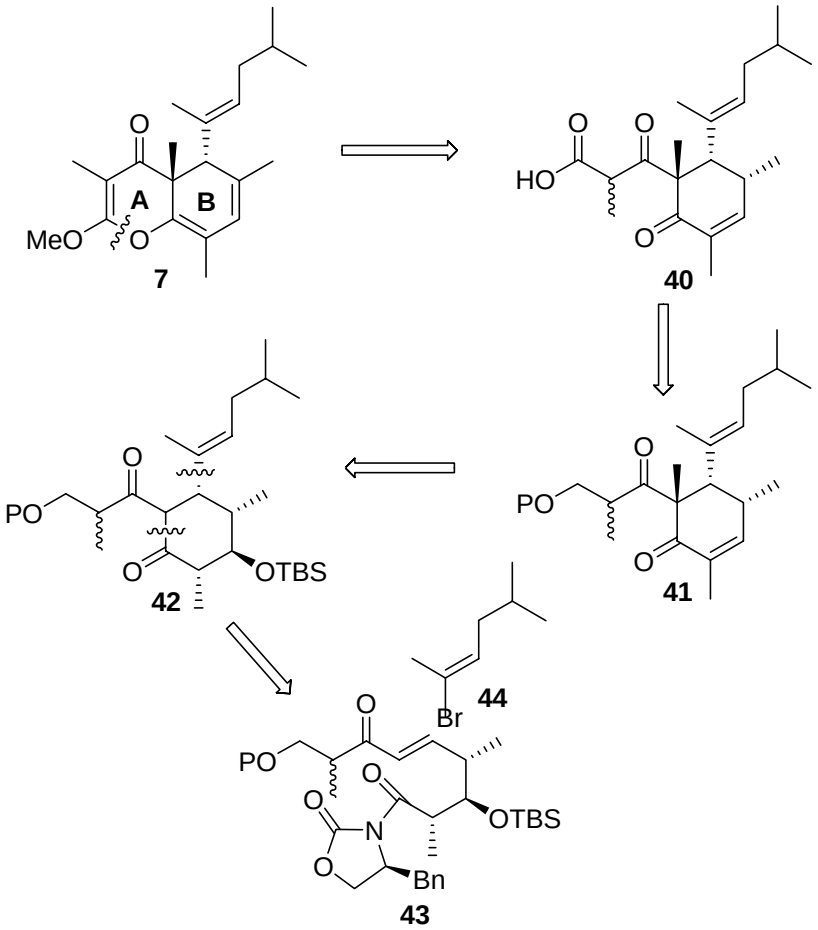
The retrosynthesis of the tethered analogues was planned such that the pyrone ring would be formed in the appropriate manner in the final step, but the synthesis incorporated a simpler acyclic precursor **38** (Scheme 1.6), rather than having the carbon skeleton for both rings already present (as in Scheme 1.7). Subsequently, the backbone for the pyrone ring would be built-up, rather than being incorporated into the initial acyclic precursor (see Chapter Five). Regardless, the strategy for tethered analogues utilised cyclohexenone derivatives formed from a tandem conjugate addition-Dieckmann condensation with enoate **39**. This approach displayed versatility in that various side-chains can be added depending on the target under investigation.



Scheme 1.6: *General retrosynthesis of tridachione natural products to an α,β-unsaturated ester **39** and vinyl lithium species, where R contains various functionalities.*

1.7.2 Tridachiahydropyrone: Pyrone Formation and Acyclic Precursor

The starting point for the retrosynthetic analysis for tridachiahydropyrone (**7**) was the opening of the pyrone ring to give the monocyclic adduct **40** (Scheme 1.7). While there was literature precedent for pyrone formation with enolisable tricarbonyl compounds,[33-36] as opposed to the ketoacid postulated here, the products do not contain a fused, bicyclic moiety (Section 3.5). Adduct **40** could be derived from monocyclic, protected alcohol **41,** which can be seen with appropriate manipulations to arise, *via* cyclohexenone **42,** from acyclic precursor **43.** It was considered that the cyclisation of **43** to **42** was the most crucial and bold step of the synthesis. This novel step involves formation of the **B** ring *via* a tandem 1,4 conjugate addition-Dieckmann condensation.[37-43] Subsequent *trans* methylation[44-47] of **42** (derived from acyclic precursor **43** and vinyl side-chain **44)** should give **41**. Further retrosynthesis of **43** and **44** will be discussed in the appropriate sections.



Scheme 1.7: *Retrosynthesis of tridachiahydropyrone (7) to enone **43** and vinyl bromide **44**.*

1.7.3 Novel Cyclisation

The conjugate addition-cyclisation step is crucial to the proposed synthetic strategy for the **B** ring formation as it accomplishes several objectives in a minimal number of steps. The first step is the addition of the vinyl side-chain and concerted formation of the six-membered ring. The second step is *trans* methylation, which completes the installation of the two stereocentres as required for the natural product. While there are alternative synthetic strategies, that proposed in Scheme 1.7 had the potential to be highly efficient. This cyclisation offers a novel approach to the formation of tridachione polypropionates and utilises an Evans chiral auxiliary as a leaving group[48-52] in the tandem addition-cyclisation. The stereochemistry present in **43** should facilitate cyclisation due to all the groups adopting the preferred equatorial position in the product (Section 2.2).

1.7.4 Inherent Stereochemistry

The usefulness of the stereochemistry in the stereotriad of enone **43** may not be limited to the cyclisation. It was anticipated it would direct the facial attack of the vinyl side-chain nucleophile in the conjugate addition, improving the diastereoselectivity of the reaction and overall yield of the synthesis. Only two stereocentres remain in the target **7** so most of the stereochemistry is simply used to induce the desired cyclisation and stereoselectivity of reactions. The *trans* stereochemistry required for the natural product, therefore, will be relayed through stereochemistry that does not appear in the final product.

The stereochemistry depicted throughout was drawn as a particular absolute configuration, giving enantiomer **7** of the natural product. This particular stereochemistry was adopted arbitrarily, as the natural product absolute stereochemistry was unknown. The important point is that the relative stereochemistry of acyclic precursor **43** should be as depicted to make the cyclisation thermodynamically favourable. The stereochemistry shown in the retrosynthesis results from employing an (*S*)-chiral auxiliary in conjunction with the aldehyde obtained from an (*S*)-chiral ester (Section 2.4).

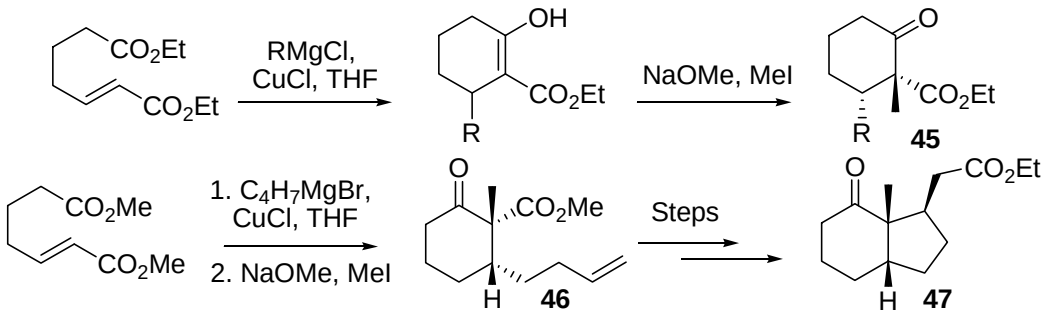
1.8 Conjugate Addition-Dieckmann Condensation

Formation of the cyclohexenones relies entirely on the success of the tandem conjugate addition-Dieckmann condensation (addition-cyclisation) approach. While this was an untested strategy for the synthesis of tridachiones, developing a versatile, viable method

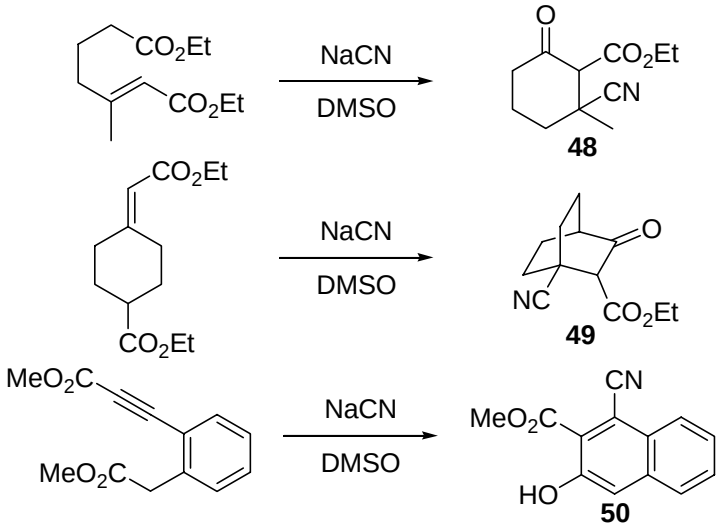
would mean a whole range of tridachione natural products could conceivably be accessed. The use of such a conjugate addition-Dieckmann condensation to form six-membered rings has been reported several times in the literature in simpler systems, but its application to polypropionate marine natural product synthesis was novel. Some examples of the utility of addition-cyclisation reactions in the formation of six-membered rings are shown below.

1.8.1 Versatility of the Addition-Cyclisation Approach

An addition-cyclisation approach was used to form simple β-ketoesters such as **45**[39] and **46**,[40] the latter being converted to an octahydro-7-oxo-1*H*-indene derivative **47** (Scheme 1.8). Cyanide salts were also chosen as the source of the nucleophile in several addition-cyclisation reactions such as for the formation of the cyano-bearing cyclohexanone derivative **48**,[37] the bicyclic ketone **49**[38] and naphthalene **50**[41] (Scheme 1.9).



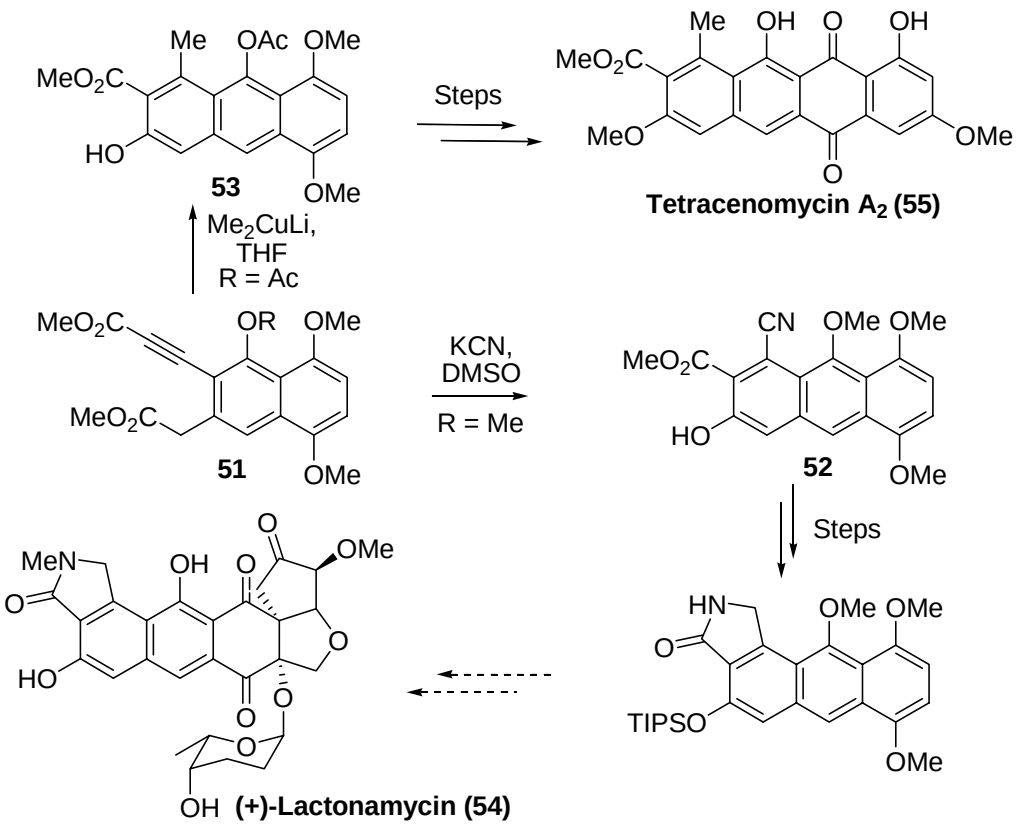
Scheme 1.8: *Tandem conjugate addition-Dieckmann condensation of cuprates with simple α,β-unsaturated esters.*



Scheme 1.9: *Tandem conjugate addition-Dieckmann condensation of cyanide salts with α,β-unsaturated esters.*

Both cyanide salts and dimethylcopper lithium have been successfully added to alkynyl ester **51** to form highly substituted anthracenes such as **52**[41] and **53**,[43] which may be

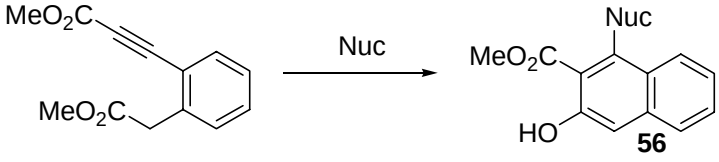
incorporated into bioactive molecules such as lactonamycin (**54**) and tetracenomycin A_2 (**55**) (Scheme 1.10).



Scheme 1.10: *Tandem conjugate addition-Dieckmann condensation approach to polyketide metabolites lactonamycin (**54**) and tetracenomycin A_2 (**55**).*

1.8.2 The Use of Different Nucleophiles

The scope of such an addition-cyclisation reaction was studied in the formation of substituted naphthalenes **56**,[42] with a wide variety of nucleophiles, such as phenoxides, cuprates and malonate anions proving viable (Scheme 1.11). These reactions show that this is a versatile approach to the formation of six-membered rings from different substrates with a number of different, generally soft nucleophiles.



Nuc = Me_2CuLi, Bu_2CuLi, $NaCH(CO_2Me)_2$, $NaCH_2NO_2$, NaOPh, *p*-MeOPhONa, *p*-ClPhONa, $HCCCH_2ONa$, NaN_3, PhSNa, $(CuH{\cdot}Ph_3P)_6$

Scheme 1.11: *Tandem conjugate addition-Dieckmann condensation of various nucleophiles with an alkynyl ester to form substituted naphthalenes **56**.*

Chapter Two

Conjugate Addition-Cyclisation Approach: A Model Study

In order to utilise cyclohexenones as synthons in natural product synthesis, the proposed addition-cyclisation methodology must be developed. This chapter details preliminary work undertaken on the addition-cyclisation and subsequent trans methylation approach to several highly substituted, chiral cyclohexenone derivatives.

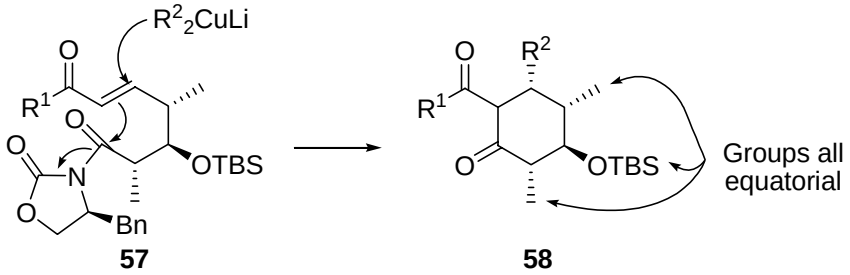
2.1 Chiral Cyclohexenones as Synthons

As outlined in the retrosynthesis (Section 1.7.2), the approach to tridachiahydropyrone (**7**) and other tridachiones relies upon the use of chiral, cyclohexenone derivatives as synthons for the formation of the cyclohexadiene ring. While the use of cyclohexenone rings as scaffolds for natural product synthesis is reported in the literature,[53-58] stereoselective synthesis of the cyclohexenone ring itself is uncommon. Utilisation of the cyclohexenone ring as a synthon in the formation of tridachione natural products is novel in its approach and should provide a general route to the installation of the cyclohexadiene ring found in these natural products. It was envisaged that this method would cater for the addition of different side-chains to a common α,β-unsaturated carbonyl compound, and thus allow formation of a variety of tridachione natural products as single enantiomers.

2.2 Synthetic Considerations for Successful Cyclisation

Consideration was given to how best to facilitate cyclisation of a suitable acyclic precursor as well as the various approaches that might be taken to form such a precursor. The chosen strategy uses Evans' aldol chemistry to install stereocentres into precursor **57,** where in the cyclic product **58**, substituents adopt the more favourable equatorial positions (Scheme 2.1). Therefore, the intrinsic ability to form a thermodynamically favourable product should facilitate cyclisation. This, along with the relay of stereochemistry to the remaining stereocentres, justifies the reason for using stereochemistry that is eventually lost at a later stage. The stereochemistry may also

play a part in the selectivity of the conjugate addition-cyclisation reaction by restricting the approach of the cuprate nucleophile.

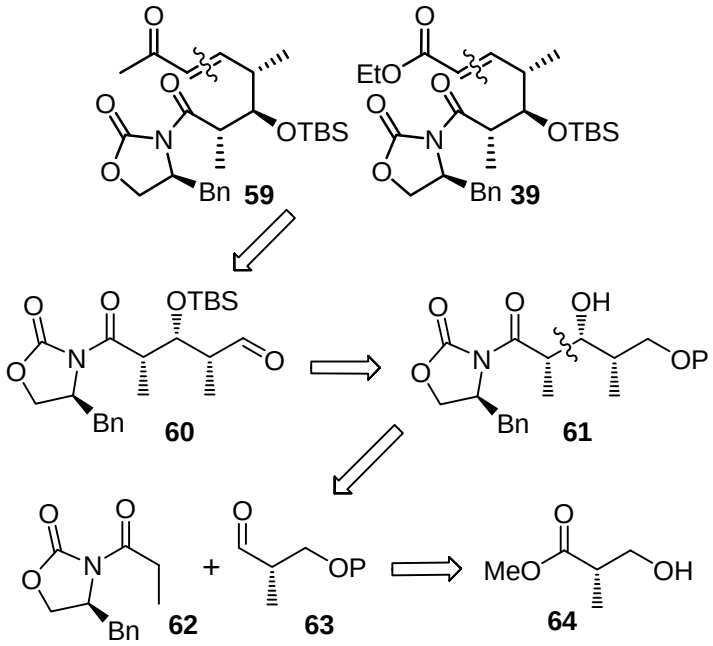


Scheme 2.1: *Cyclisation to **58** facilitated by stereochemistry of acyclic precursor **57**.*

For the above route to be viable it was necessary to investigate whether the chiral auxiliary used in the stereoselective aldol could act as a leaving group in such a condensation. Only a few examples of displacement of an Evans auxiliary by carbon based nucleophiles in cyclisation reactions have been reported.[48-52] Uncertainty also surrounded the versatility of such an approach to tridachione marine natural products and whether different cuprates could be tolerated.

2.3 Formation of Some Chiral Cyclohexenones

To answer these questions, a model study was undertaken to determine the viability of the addition-cyclisation approach to the formation of highly substituted, chiral cyclohexenones. For this purpose, α,β-unsaturated ketones or esters were required and to this end, enone **59** and enoate **39** were thought to arise from the Wittig reaction of aldehyde **60** and commercially available ylides (Scheme 2.2). Aldehyde **60** was the common precursor to all the cyclohexenone synthons that would be required for syntheses in this project. As such, a reliable, stereoselective route amenable to multi-gram scale synthesis was necessary. In an attempt to maximise selectivity for a single diastereomer, *syn* aldol chemistry[59-61] using an Evans chiral auxiliary[61] was employed in the acquisition of aldehyde **60**.



Scheme 2.2: *Retrosynthetic analysis of α,β-unsaturated carbonyl compounds **39** and **59** showing common aldehyde **60**.*

2.3.1 Retrosynthetic Analysis of Aldehyde Fragment

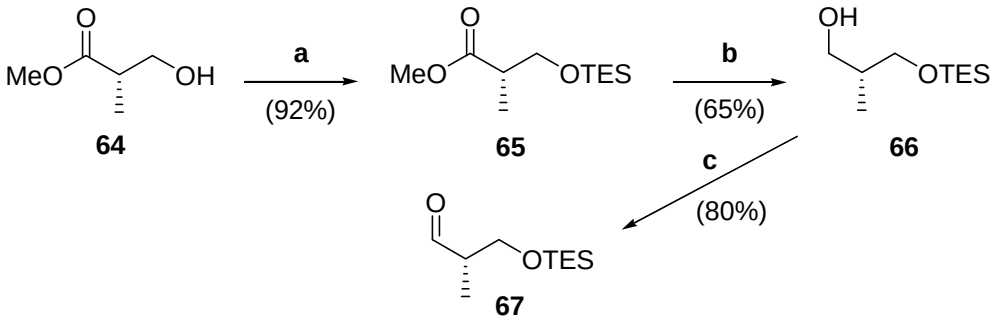
Continuing with the retrosynthetic pathway outline in Scheme 2.2, aldehyde **60** was envisaged to arise from manipulation of aldol product **61** obtained from the stereoselective, boron-mediated, *syn* aldol coupling[59,60] of precursors **62** and **63**. Acylated oxazolidinone **62**, known as an Evans chiral auxiliary,[61] is readily available and protected aldehyde **63** comes from commercially available hydroxy ester **64**. Aldol product **61** can be transformed into **60** by first protecting the aldol adduct, and then deprotecting and oxidising the primary alcohol to aldehyde **60**. Thus, the different protecting groups employed should allow for selective removal and therefore control of the synthesis.

2.4 Stereoselective Gram-Scale Synthesis of Aldehyde 60

2.4.1 Acquisition of Chiral Aldehyde 67

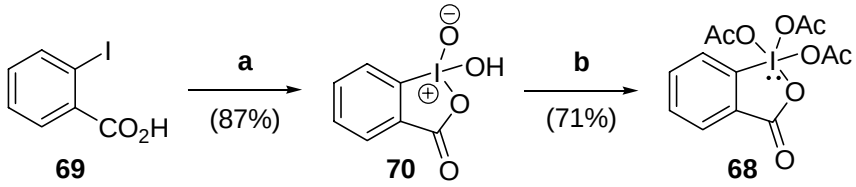
Initially, the primary alcohol of (*S*)-methyl 3-hydroxy-2-methylpropionate (**64**) was protected as the known[62] triethylsilyl (TES) ether **65** (92%) by reaction with triethylsilyl trifluoromethanesulfonate (TESOTf) and pyridine in CH_2Cl_2 at room temperature (Scheme 2.3). Reduction of the ester with diisobutylaluminium hydride[63] (DIBAL) in Et_2O at –78°C required careful thin layer chromatography (tlc) monitoring to ensure complete reduction to known[62] alcohol **66** (65%), otherwise mixtures of **66**, starting

material and known[64] aldehyde **67** were obtained. Careful product isolation (due to the labile TES group) involved quenching the reaction with Rochelle's salt (potassium sodium tartrate)[62] rather than an acidic product isolation. While theoretically it should be possible to stop reduction at aldehyde **67**, in practice it was simpler to allow complete reduction to alcohol **66** and oxidise back to aldehyde **67** (80%) using Dess-Martin periodinane (**68**) in CH_2Cl_2 at room temperature.[65] Interestingly, the TES group did not tolerate Swern[66] or pyridinium chlorochromate (PCC)[67] oxidation. Dess-Martin periodinane (**68)** was synthesised by the established method of Dess and Martin[65] (Scheme 2.4). Firstly, 2-iodobenzoic acid (**69**) was converted into 2-iodoxybenzoic acid (**70**) (87%) by heating with potassium bromate ($KBrO_3$) and H_2SO_4. Acylation of the isolated material with Ac_2O/AcOH afforded over 30 grams of *tris* acylated **68** (71%, Scheme 2.4).



Reagents and conditions: a. i. Pyridine (2 eq), CH_2Cl_2, -78°C; ii. TESOTf (1.2 eq), -78°C, 30 min to rt, 16h; **b.** DIBAL (4 eq), Et_2O, -78°C, 4h; **c.** Dess-Martin periodinane (1.5 eq), CH_2Cl_2, rt, 2h.

Scheme 2.3: *Manipulation of hydroxyester **64** to aldehyde **67**.*



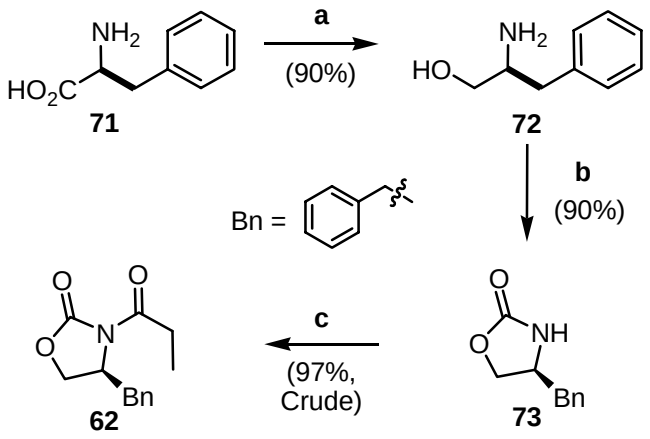
Reagents and conditions: a. $KBrO_3$ (1.3 eq), H_2SO_4 (0.73 M, 1.57 eq), 68°C, 3.6 h; **b.** Ac_2O (9.5 eq), AcOH (13 eq), 85°C, 2h to rt, 17 h.

Scheme 2.4: *Synthesis of Dess-Martin periodinane **68**.*

2.4.2 *Syn* Aldol Coupling of Aldehyde 67 with Chiral Auxiliary 62

In order to undertake the planned aldol reaction, chiral auxiliary **62** was synthesised by the highly reliable procedure of Evans and Gage[61] (Scheme 2.5). (*S*)-Phenylalanine (**71**) was reduced to (*S*)-phenylalanol (**72**) (90%) by treatment with boron trifluoride diethyl etherate (BF_3•OEt_2) under reflux in THF, followed by borane-methyl sulfide complex

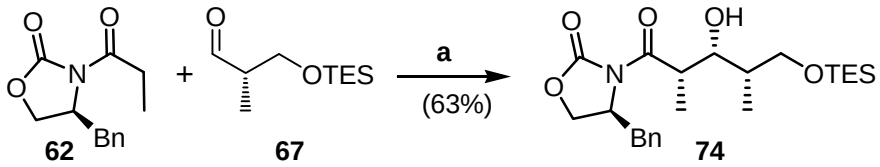
(BH_3•SMe_2). Oxazolidinone **73** was formed by reacting **72** with diethyl carbonate ($(EtO)_2CO$) in the presence of anhydrous K_2CO_3 while distilling off the ethanol by-product. Acylation of **73** was achieved by deprotonation with *n*-butyl lithium (*n*-BuLi) in THF at –78°C, followed by reaction with propionyl chloride (EtCOCl), affording *N*-acyl chiral auxiliary **62** in excellent yield (97% crude, 78% over 3 steps).



Reagents and conditions: a. i. $BF_3{\cdot}OEt_2$ (1 eq), THF, reflux, 2h; ii. $BH_3{\cdot}SMe_2$ (1.15 eq), reflux, 6 h; **b.** $(EtO)_2CO$ (2 eq), K_2CO_3 (0.3 eq), 135°C, 3 h; **c.** i. *n*-BuLi (1.01 eq), THF, -78°C; ii. EtCOCl (1.1 eq), -78°C, 30 min to rt.

Scheme 2.5: *Synthesis of acylated Evans chiral auxiliary **62**.*

Treatment of *N*-acyl auxiliary **62** with dibutylboron trifluoromethanesulfonate (Bu_2BOTf) in CH_2Cl_2 at 0°C, followed by Et_3N[61] afforded the (*Z*)-enolate, which underwent a *syn* aldol coupling with aldehyde **67** (–78°C to 0°C) to afford aldol adduct **74** (63%, >95% ds by ^1H NMR, Scheme 2.6).



Reagents and conditions: a. i. Bu_2BOTf (1.2 eq), CH_2Cl_2, 0°C; ii. Et_3N (1.3 eq), 0°C, 30 min; iii.Aldehyde **67** (0.5 eq), CH_2Cl_2, -78°C, 20 min to 0°C, 4h.

Scheme 2.6: *Aldol between chiral auxiliary **62** and aldehyde **67**.*

The proton nuclear magnetic resonance (^1H NMR) spectrum of aldol adduct **74** displayed the appropriate resonances (Figure 2.1). In particular, the oxymethine proton appears as a doublet of doublets at δ 4.08 (J = 7.0, 3.8 Hz) and couples to both methyl methine protons, which appear as multiplets at δ 3.97 (app. qn, J = 6.9 Hz) and δ 1.80-

1.69. The two diastereotopic TES oxymethylene protons, which appear as doublet of doublets at δ 3.75 (*J* = 9.9, 4.0 Hz) and δ 3.64 (*J* = 9.9, 4.2 Hz), show reciprocal couplings to each other as well as couplings to the methine multiplet at δ 1.80-1.69. The hydroxyl proton appears as a broad singlet at δ 3.37. The two methyl groups appear as doublets at δ 1.34 (*J* = 6.6 Hz) and δ 0.99 (*J* = 6.9 Hz) and couple to the appropriate methine protons. The remaining resonances at δ 7.38-7.17 (m, 5H), δ 4.72-4.61 (m, 1H), δ 4.20-4.16 (m, 2H), δ 3.25 (dd, 1H, *J* = 13.2, 3.0 Hz), 2.77 δ (dd, 1H, *J* = 13.2, 9.4 Hz) and δ 0.96 (t, 9H, *J* = 7.8 Hz) and δ 0.61 (q, 6H, *J* = 7.8 Hz) are attributed to the chiral auxiliary and the TES protecting group, respectively. The infrared spectrum contained a broad absorption band at 3504 cm^{-1}, and absorptions at 1782 and 1697 cm^{-1}, indicative of the alcohol functionality and carbonyl groups, respectively, and an accurate mass measurement confirmed the expected molecular formula of $C_{23}H_{37}NO_5Si$.

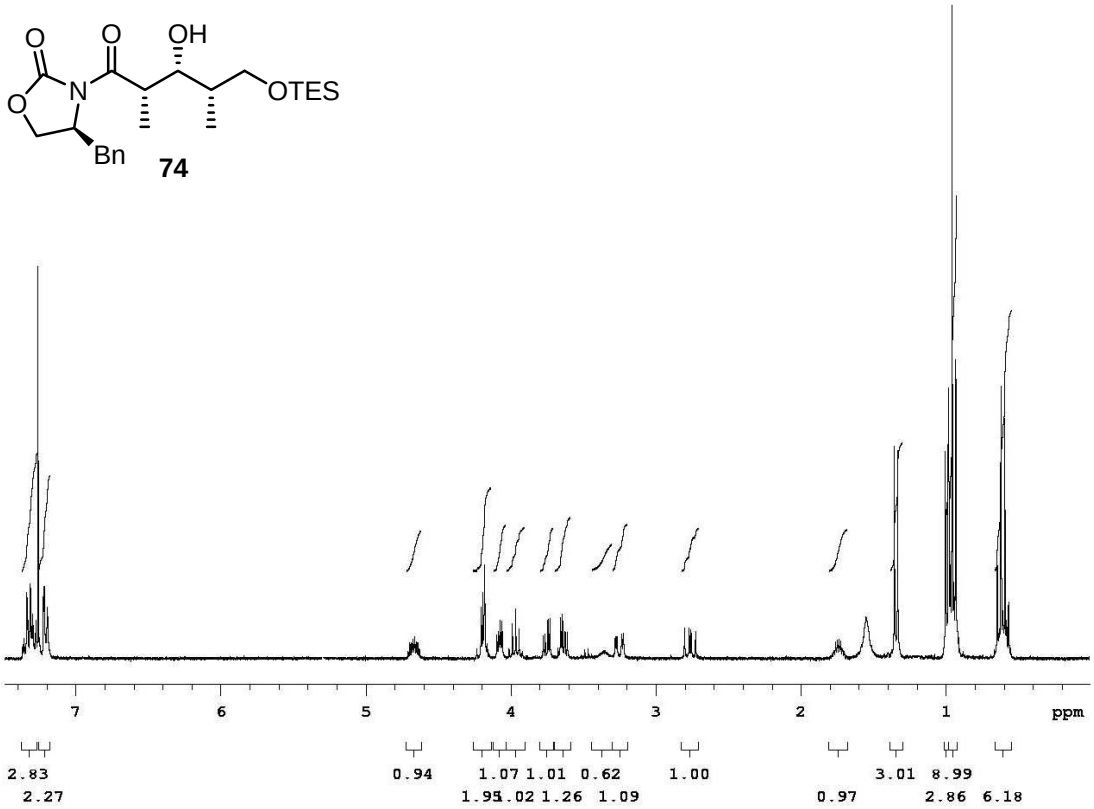
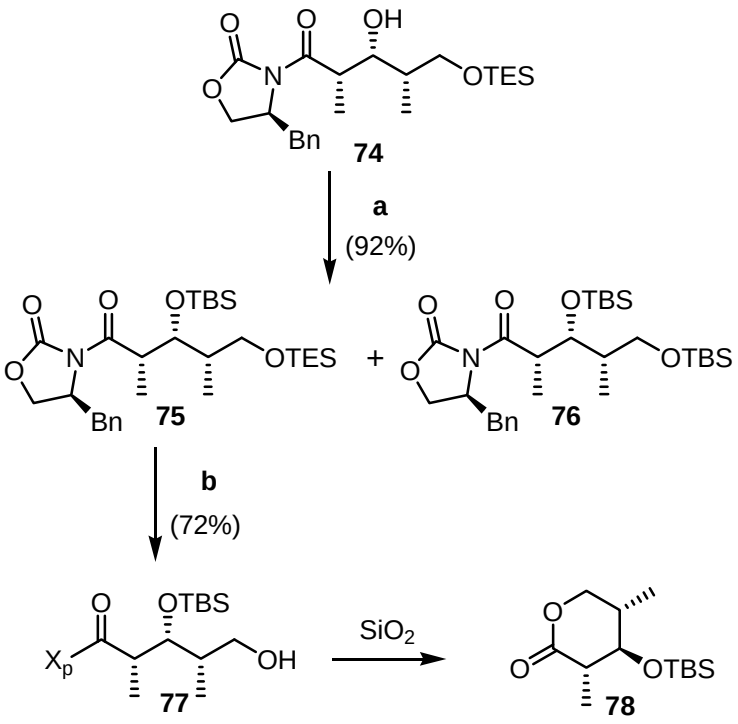


Figure 2.1: *300 MHz ^1H NMR spectrum of aldol adduct **74** in $CDCl_3$.*

2.4.3 Protecting Group Manipulation of Adduct 74

The secondary alcohol of adduct **74** was protected as the *t*-butyldimethylsilyl (TBS) ether **75** (92%) by treatment with 2,6-lutidine and *t*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) in CH_2Cl_2[68]at –78°C (Scheme 2.7). Unfortunately,

there was some replacement of the TES protecting group with a TBS group, giving the di-TBS protected product **76**, which was inseparable from **75** by silica column chromatography. Deprotection, however, of **75** with pyridinium *p*-toluenesulfonate (PPTS) in 1:1 CH_2Cl_2/MeOH at room temperature overnight afforded primary alcohol **77** (72%, based on recovery of **76**), which was readily separable from the di-TBS contaminant **76** (Scheme 2.7).



Reagents and conditions: a. i. 2,6-lutidine (3 eq), CH_2Cl_2, -78°C; ii. TBSOTf (1.5 eq), -78°C, 1 h; **b**. PPTS (cat.), MeOH, CH_2Cl_2, rt, 14 h.

Scheme 2.7: *TBS protection of aldol adduct **74** and subsequent TES deprotection to give primary alcohol **77**.*

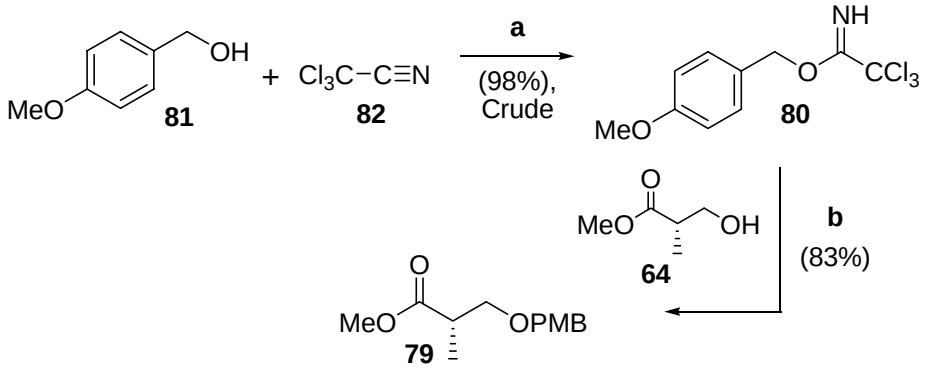
At this point it is worthwhile pointing out that chromatography of **77** on silica led to almost complete conversion to known[69] lactone **78** (Scheme 2.7) due to the acidic nature of the silica and the in-built tendency of **77** to cyclise (due to the equatorial orientation of the substituents, Section 2.2). Although this was an undesirable outcome, it was encouraging that the chiral auxiliary could act as a leaving group in this system. The cyclisation problem was overcome by buffering the silica before use with pH 7

buffer.[#] Careful chromatography with buffered silica allowed for purification of **77** with minimal to no lactonisation.

2.4.4 An Alternative to the TES Protecting Group

It was apparent that the TES protecting group lability would become a problem for large-scale synthesis of **60**, so the use of a *p*-methoxybenzyl (PMB) protecting group was explored. Thus, hydroxyester **64** was protected as the known[70] PMB ether **79** (83%) by reaction with PMB-acetimidate **80** and a catalytic amount of triflic acid (TfOH) in Et_2O[71] at room temperature (Scheme 2.8). Purification was achieved by distillation under reduced pressure,[72] making the procedure suitable for multi-gram synthesis. Acetimidate **80** was readily prepared by the sequence shown in Scheme 2.8 from *p*-methoxybenzyl alcohol (**81**), NaH and trichloroacetonitrile (**82**).[71]

Interestingly, the relative amount of triflic acid used was dependent upon the scale of the reaction. Reactions performed on one gram of **64**, for instance, required up to 6 mole% acid, while a 10-gram reaction required only 0.3 mole%. Indeed, even 3 mole% triflic acid in a 10-gram reaction resulted in immediate boiling of the solvent and decomposition of the acetimidate. These observations were not entirely unexpected, however. Decomposition of acetimidate **80** was also reported by Nakajima *et al.*[71] in the presence of 10 mole% TfOH, although there was no specific discussion regarding the scale of the reaction.



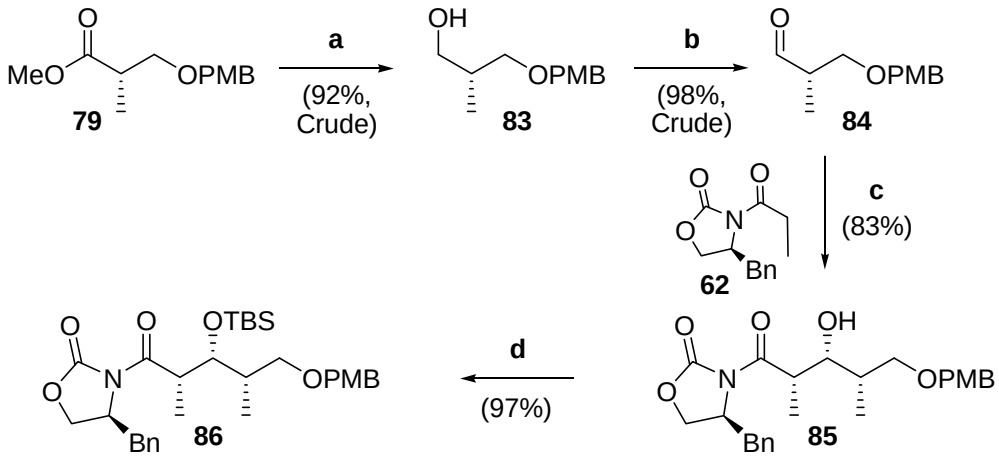
Reagents and conditions: a. i. NaH (0.1 eq), Et_2O, rt; then alcohol **81** (1 eq), rt; ii. Nitrile **82** (1 eq), 0°C to rt, 1.5 h; **b.** Imidate **80** (1.5 eq), ester **64**, TfOH (0.3 mol%), Et_2O, rt, 45 min.

Scheme 2.8: *An alternative protecting group giving PMB ether **79**.*

[#] Buffered silica was prepared by slowly turning a round bottom flask containing 100 g of flash silica and 10 mL pH 7 phosphate buffer on a rotary evaporator without vacuum overnight at room temperature.

2.4.5 An Improved Reduction Procedure

In light of the tendency for DIBAL reduction to be sluggish and give mixed reduction products, known[70] alcohol **83** was subsequently obtained (92%, crude) by reduction of ester **79** with lithium aluminium hydride ($LiAlH_4$) in THF at room temperature (Scheme 2.9). This reaction proved to be very clean and no purification of **83** was required. Swern oxidation ($(COCl)_2$, DMSO, Et_3N)[66] of **83** to known[70] aldehyde **84** was performed, and modified product isolation[73] (simple $NaHSO_4$ and $NaHCO_3$ washings) negated the need for purification. Aldol condensation of aldehyde **84** with chiral auxiliary **62** occurred as previously described to afford aldol adduct **85** (83%, >95% ds by ^{1}H NMR) and subsequent TBS protection as described above yielded differentially protected product **86** in excellent yield (97%, 60% over 5 steps from hydroxyester **64**). These modifications allowed for a smooth transition from hydroxyester **64** to compound **86,** which has been carried out on a 10-gram scale.



Reagents and conditions: a. $LiAlH_4$ (1.1 eq), 0°C to rt, 30 min; **b.** i. DMSO (1.5 eq), CH_2Cl_2, -78°C; ii. $(COCl)_2$ (3 eq), -78°C, 30 min; iii. Alcohol **83**, CH_2Cl_2, -78°C, 45 min; iv. Et_3N (6 eq), -78°C, 30 min to rt; **c.** i. Auxiliary **62**, Bu_2BOTf (1.2 eq), CH_2Cl_2, 0°C, 30 min; ii. Et_3N (1.3 eq), 0°C, 30 min; iii. Aldehyde **84** (0.5 eq), CH_2Cl_2 , -78°C, 30 min to 0°C, 2.5 h; **d.** i. 2,6-lutidine (3 eq), CH_2Cl_2, -78°C; ii. TBSOTf (1.5 eq), -78°C, 4 h.

Scheme 2.9: *Modified strategy for large-scale synthesis of adduct **86**.*

The ^{1}H NMR of TBS protected aldol adduct **86** displays the expected resonances (Figure 2.2). Notably, the TBS oxymethine appears as a complex multiplet at δ 4.17-4.08 (which includes the oxazolidinone methylene protons) and shows couplings to both methyl methine protons at δ 3.98 (app. qn, J = 7.0 Hz) and δ 1.91-1.83. One diastereotopic PMB oxymethylene proton appears as a doublet of doublets at δ 3.45 (J = 9.2, 6.2 Hz), while the other exists as a complex multiplet at δ 3.27-3.22 (along with a

benzylic methylene from the auxiliary). Both oxymethylene protons show the expected couplings to each other and to the methine proton at δ 1.91-1.83. One methyl doublet appears at δ 1.24 (J = 6.9 Hz), while the other methyl is coincident with the TBS group at δ 0.92 (12H). Both methyl groups show couplings with the appropriate methine protons. The remaining protons that appear at δ 7.36-7.18 (m, 7H), δ 6.87 (d, 2H, J = 8.4 Hz), δ 4.66-4.57 (m, 1H), δ 4.42 (s, 2H), δ 3.80 (s, 3H), δ 2.75 (dd, 1H, J = 13.2, 9.9 Hz) and δ 0.057 (s, 3H) and δ 0.041 (s, 3H) are attributed to the chiral auxiliary, PMB protecting group and TBS protecting group. Absorptions in the infrared spectrum at 1783 and 1696 cm^{-1}were indicative of the two carbonyl groups and an accurate mass measurement confirmed the expected molecular formula of $C_{31}H_{45}NO_6Si$.

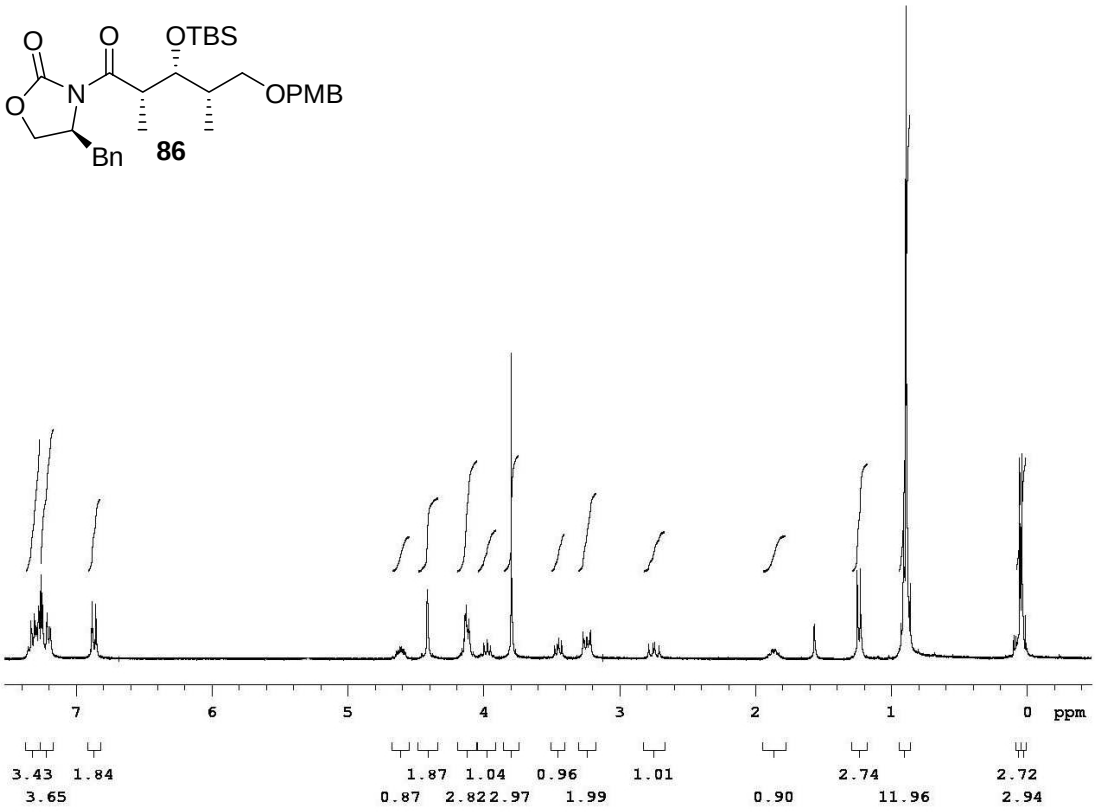
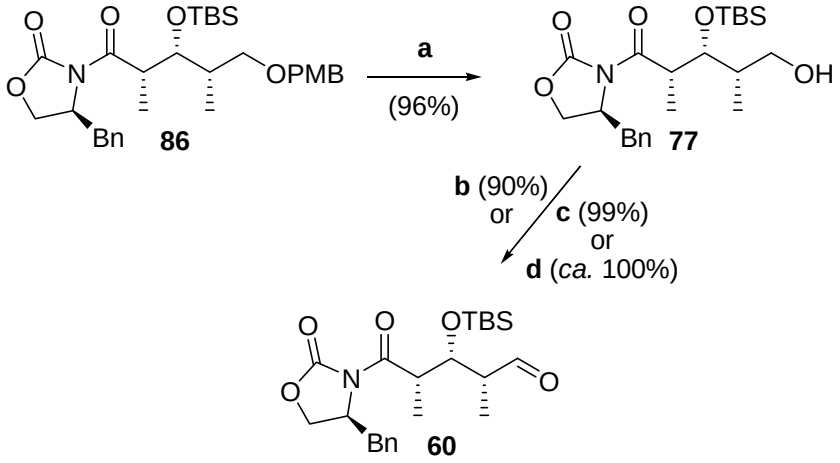


Figure 2.2: *300 MHz ^1H NMR spectrum of TBS protected aldol adduct **86** in $CDCl_3$.*

2.4.6 Selective PMB Removal and Oxidation to 60

Selective deprotection of PMB ether **86** to give alcohol **77** was accomplished (96%) by reaction with 2,3-dichloro-5,6-dicynao-1,4-benzoquinone (DDQ) in CH_2Cl_2 and pH 7 buffer at 0°C[74] (Scheme 2.10). Purification was performed on buffered silica to avoid lactonisation as previously described (Section 2.4.3). Subsequent oxidation to desired aldehyde **60** was achieved either under Swern conditions,[66] with modified product

isolation[73] (99% crude), with PCC in CH_2Cl_2 at room temperature[67] (90%, crude) or with Dess-Martin periodinane[65] in CH_2Cl_2 at room temperature (*ca.* 100%, crude, Scheme 2.10).



Reagents and conditions: a. DDQ (1.3 eq), CH_2Cl_2, pH 7 buffer, 0°C, 4h; **b.** PCC (3 eq), CH_2Cl_2, rt, 3h; **c.** i. DMSO (1.5 eq), CH_2Cl_2, -78°C; ii. $(COCl)_2$ (3 eq), -78°C, 30 min; iii. Alcohol **87**, CH_2Cl_2, -78°C, 45 min; iv. Et_3N (6 eq), -78°C, 30 min to rt; **d.** Dess-Martin periodinane (1.5 eq), CH_2Cl_2, rt, 2 h.

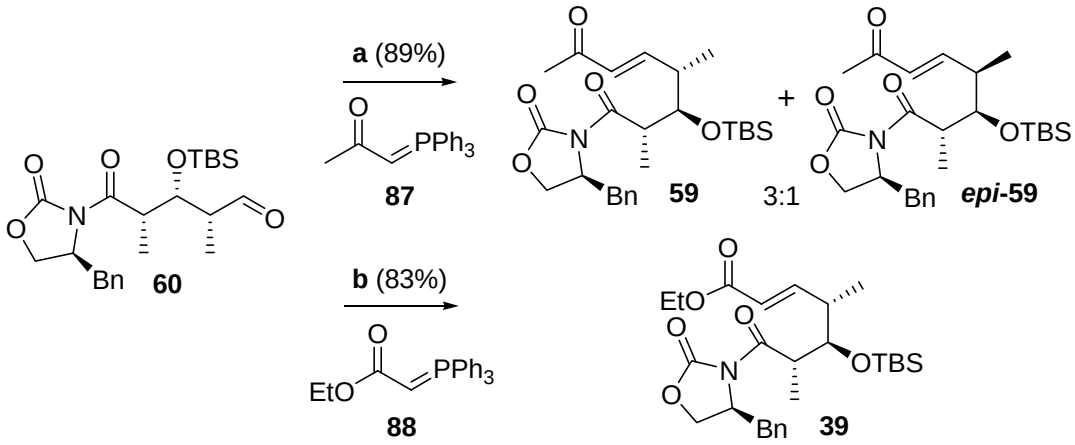
Scheme 2.10: *Deprotection and oxidation sequence to afford aldehyde **60**.*

These three oxidation methods gave comparable results and all have their own advantages and disadvantages. For example, PCC was experimentally simpler and ideal for smaller quantities of alcohol **77** (<0.5 gram), but trituration of the reaction mixture to isolate the product was tedious on a larger scale. Swern conditions were excellent for gram quantities of alcohol **77**, where the reaction was quicker and aldehyde **60** was easier to isolate. The Swern reaction, however, is a bit more experimentally demanding and gives noxious dimethyl sulfide (Me_2S) as a by-product. Finally, Dess-Martin oxidation was the method of choice, with the only disadvantage being the time involved making the reagent. This oxidant was mild and simple to use, the reaction was quick and the product was exceptionally easy to isolate.

2.4.7 Formation of α,β-Unsaturated Compounds 39 and 59

All that remained was to react aldehyde **60** with commercially available, stabilised ylides **87** and **88** to give enone **59** and enoate **39**, respectively. Reaction of aldehyde **60** with (carbethoxymethylene)triphenylphosphorane (**88**) in CH_2Cl_2 occurred over four days at room temperature to afford **39** in high yield (89%) and with excellent (*E*)-selectivity (Scheme 2.11). In contrast, reaction of **60** with 1-triphenylphosphoran-

ylidene-2-propanone (**87**) was more sluggish, taking four days at 80°C in toluene to afford **59** (83%), but again high (*E*)-selectivity was observed. Unfortunately, there was a degree of epimerisation of the aldehyde α-chiral centre such that an inseparable mixture (3:1 at best), containing the minor epimer ***epi*-59**, was obtained (Scheme 2.11). This epimeric mixture was used in the subsequent reactions, but only **59** is shown for simplicity.



Reagents and conditions: a. Ylide **87** (1.5 eq), toluene, 80°C, 4d; **b.** Ylide **88** (1.5 eq), CH_2Cl_2, rt, 4d.

Scheme 2.11: *Wittig reaction between aldehyde **60** and ylides **39** and **59**.*

Evidence for the (*E*)-double bond can be derived from the magnitude of the coupling constants in the ^{1}H NMR spectra of **39** (Figure 2.3). For compound **39**, the vinyl protons appear as doublet of doublets at δ 7.02 (*J* = 15.6, 7.8 Hz) and δ 5.80 (*J* = 15.6, 1.2 Hz). The downfield signal at δ 7.02 is consistent with the β-proton of an α,β-unsaturated carbonyl system, while the large, reciprocal coupling of 15.6 Hz confirms the presence of an (*E*)-double bond. Apart from the diagnostic vinyl protons, the remaining resonances are similar to those found in compound **86**, with the exception of those relating to the PMB and oxymethylene groups. Similarly, the vinyl protons in compound **59** appeared as doublet of doublets at δ 6.88 (*J* = 16.3, 8.3 Hz) and δ 6.03 (*J* = 16.3, 1.2 Hz). Again, the downfield signal at δ 6.88 is consistent with the β-proton of an α,β-unsaturated carbonyl system, while the large, reciprocal coupling of 16.3 Hz confirms the (*E*)-double bond. The infrared spectra of both **39** and **59** contained an absorption at *ca.* 1780 cm^{-1} and two at *ca.* 1700 cm^{-1}, indicating the presence of three carbonyl groups, while accurate mass measurements confirmed the expected molecular formula of **39** to be $C_{27}H_{41}NO_6Si$ and **59** to be $C_{26}H_{39}NO_5Si$.

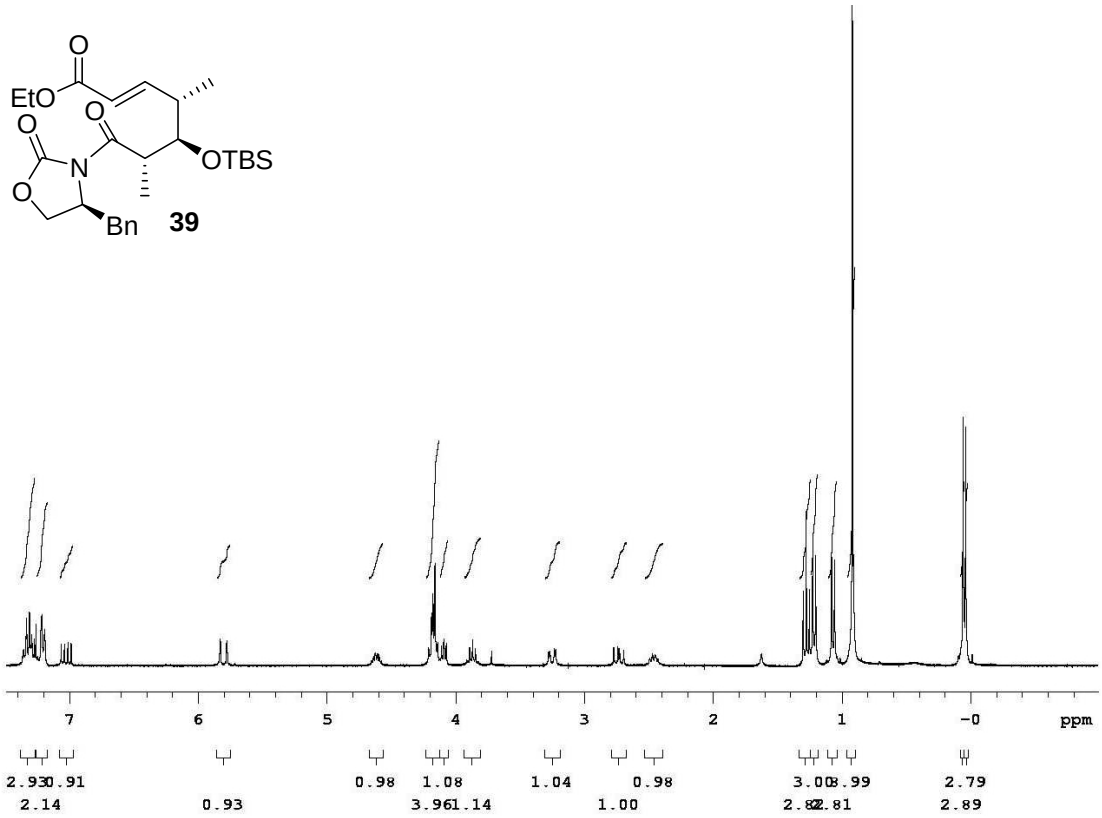


Figure 2.3: *300 MHz ^{1}H NMR spectrum of enoate **39** in $CDCl_3$.*

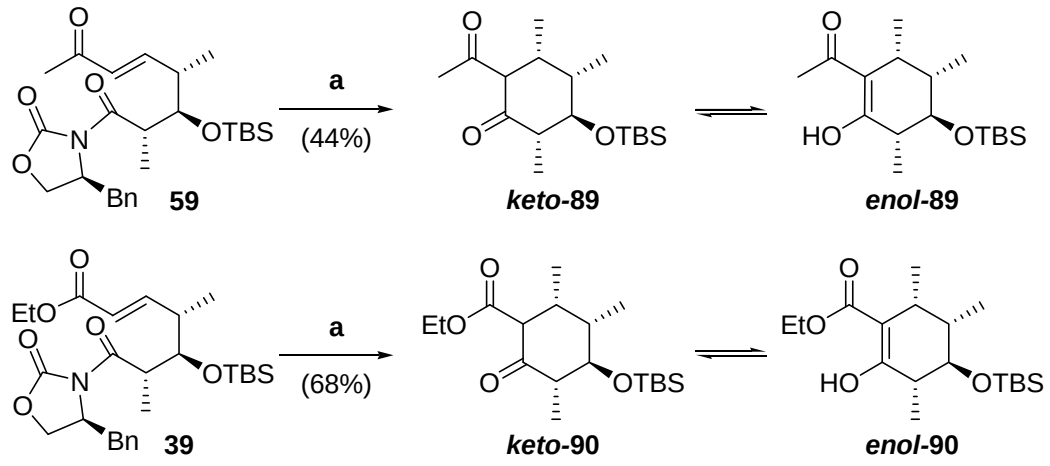
2.5 Accomplishing the Addition-Cyclisation

2.5.1 Addition of Dimethylcopper Lithium

With 500-600 milligrams each of enone **59** and enoate **39** in hand, the next task was to accomplish the addition-cyclisation reactions using a model cuprate. In the first instance, enone **59** and enoate **39** were reacted with a simple cuprate, dimethylcopper lithium (Scheme 2.12). Formation of dimethylcopper lithium involved treating a suspension of copper (I) iodide in 1:1 Et_2O and Me_2S with methyl lithium (MeLi) at room temperature until the initially formed bright yellow precipitate just dissolved.[75] Formation of the cuprate was essentially a titration, such that the exact concentration of the MeLi was not important. The successful formation of the dialkyl cuprate was indicated by the disappearance of the bright yellow precipitate, affording a pale yellow, homogeneous solution.

Addition of either enone **59** or enoate **39** in Et_2O at room temperature resulted in the instantaneous reappearance of the bright yellow precipitate. The reactions were each stirred at room temperature for an hour and quenched by addition of 90% NH_4Cl/10% NH_4OH solution (pH 10) to afford a deep blue aqueous phase (common quench for all

cuprate reactions conducted). This furnished products **89** (44%) and **90** (68%), each of which existed as a mixture of *keto* and *enol* tautomers. Indeed, evidence for successful cyclisation was indicated by the presence of the *enol* protons at δ 16.43 and δ 12.34 for **89** and **90**, respectively, in the ^{1}H NMR spectra of the crude materials. Further evidence for cyclisation was the presence of proton resonances for the free chiral auxiliary **73** in both crude spectra. The low yield of **89** can be accounted for; the diastereomeric product that arose from minor component ***epi*-59** was not isolated.

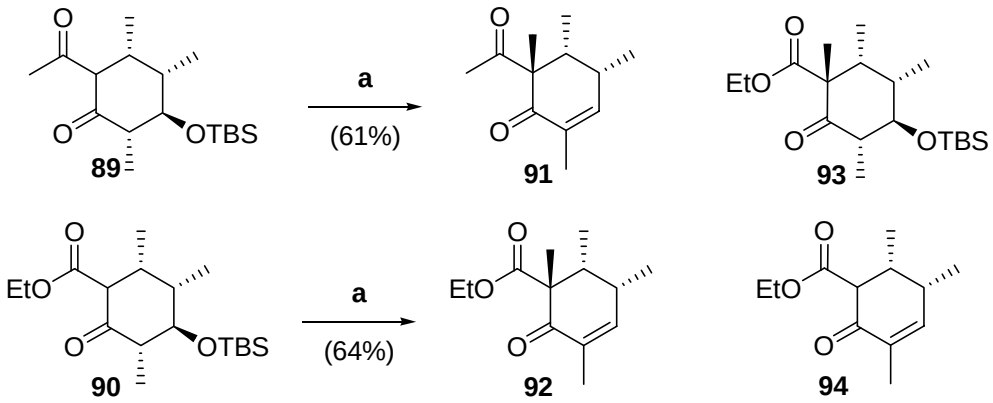


Reagents and conditions: a. i. MeLi (10 eq), CuI (5 eq), Et_2O, Me_2S, rt; ii. Enone **59** (or enoate **39**), Et_2O, rt, 1h.

Scheme 2.12: *Addition of dimethylcopper lithium to enone **59** and enoate **39**.*

2.5.2 *Trans* Methylation to Afford Cyclohexenones

An integral part of the strategy involving chiral cyclohexenone rings as synthons for natural products required forming the quaternary methyl stereocentre *trans* to the side-chain. To this end, cyclohexanones **89** and **90** were *trans* methylated[44-47] by treatment with NaH in THF at room temperature, followed by addition of MeI and stirring; for several hours in the case of **90**, or overnight for **89**. Fortuitously, this procedure occurred with β-elimination of the OTBS group to yield *trans* methylated cyclohexenones **91** (61%) and **92** (64%), as single enantiomers (Scheme 2.13). The elimination negated the need for a separate deprotection/elimination sequence. Sodium ethoxide was also an effective base for the transformation. NaH was deemed to be the base of choice, however, because the stoichiometry could be controlled more precisely, and excess NaH would not react with the methylating agent.



Reagents and conditions: a. i. NaH (2 eq), THF, rt, 10 min; ii. MeI (10 eq), rt, 3-24h.

Scheme 2.13: *Trans methylation of cyclohexanones **89** and **90** with concurrent OTBS elimination.*

The β-elimination was an interesting outcome of the reaction and was found to depend upon the quantity of NaH used and the reaction time employed. In the case of **90**, elimination occurred both prior to and after methylation, as products corresponding to methylated/non-eliminated **93** and unmethylated/eliminated **94** could be isolated, along with **92**, depending on reaction time (Scheme 2.13). Desired cyclohexenones **91** and **92** could be regularly obtained in satisfactory yield by the use of two equivalents of NaH and careful monitoring by tlc, to ensure complete conversion to the methylated/eliminated product.

The ^{1}H NMR spectra of **91** and **92** are quite similar if the ester and methyl ketone resonances are ignored (Figures 2.4 and 2.5, respectively). Of interest are the signals for the enone vinyl protons, which appear as multiplets at δ 6.37-6.34 in **91** and δ 6.50-6.46 in **92**. The two methyl methine protons appear as multiplets at δ 2.90-2.79 and δ 2.21-2.12 in **91** and δ 2.64-2.56 and δ 2.17 (qd, J = 7.0, 5.3 Hz) in **92**. These signals show the appropriate reciprocal couplings to each other and to the corresponding methyl protons in their respective spectra. The vinyl methyl protons appear as multiplets at δ 1.81 (dd, J = 2.6, 1.4 Hz) in **91** and δ 1.82-1.79 in **92** and the quaternary methyl protons appear as singlets at δ 1.35 and δ 1.42 for **91** and **92**, respectively. The remaining resonances are attributed to the ethyl ester or methyl ketone protons and to the protons of the two methyl doublets observed in each spectrum. Infrared absorptions occur at 1703 and 1669 cm^{-1} for **91** and 1730 and 1678 cm^{-1} for **92**, consistent with the presence of two carbonyl groups in each compound. Accurate mass measurements confirmed the expected molecular formula of **91** to be $C_{12}H_{18}O_2$ and that of **92** to be $C_{13}H_{20}O_3$.

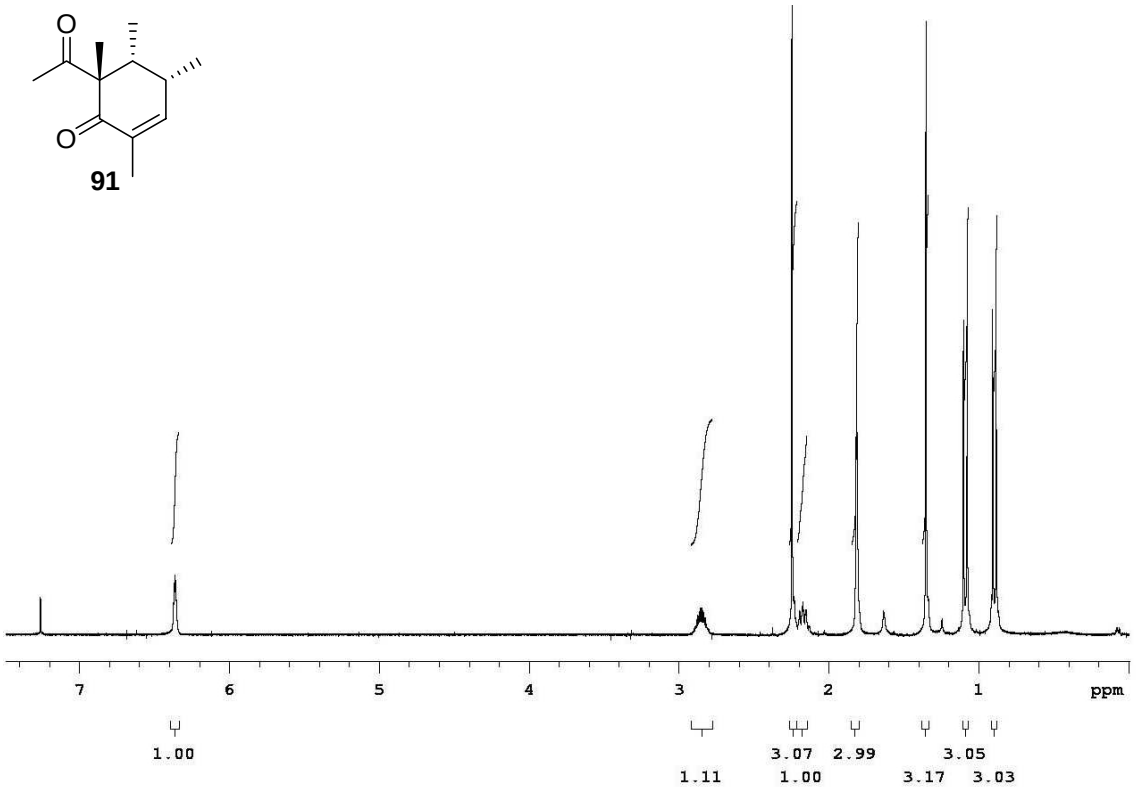


Figure 2.4: *300 MHz ^{1}H NMR spectrum of **91** in $CDCl_3$.*

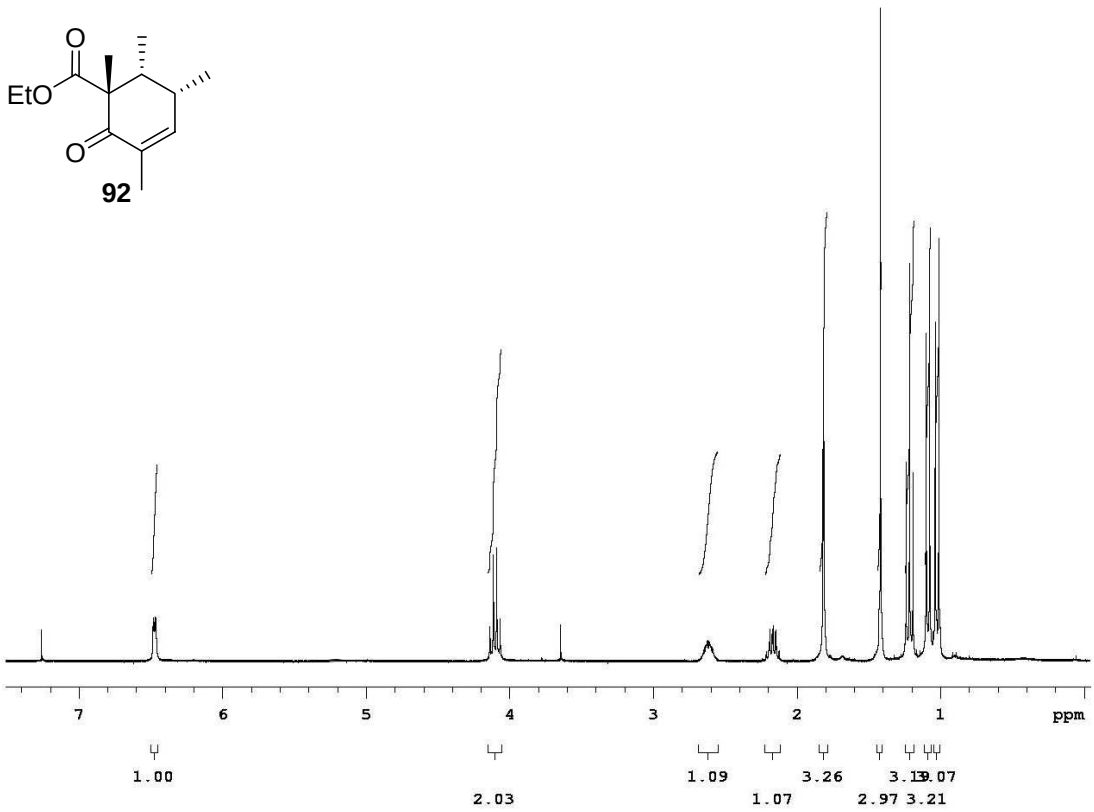
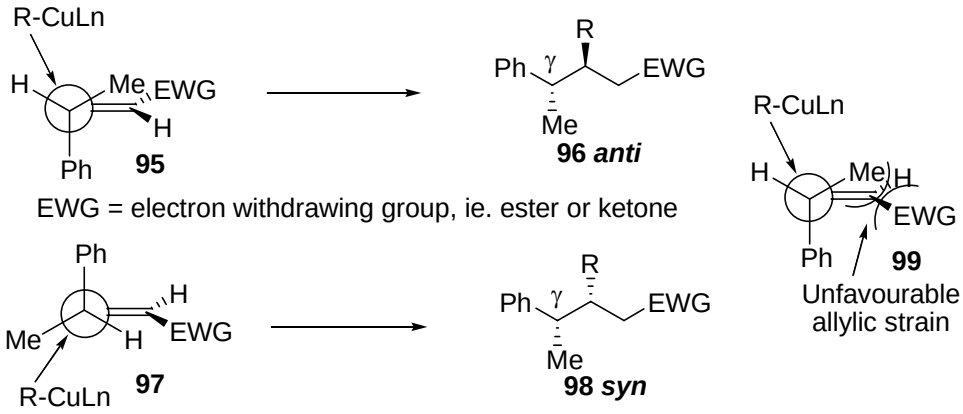


Figure 2.5: *300 MHz ^{1}H NMR spectrum of **92** in $CDCl_3$.*

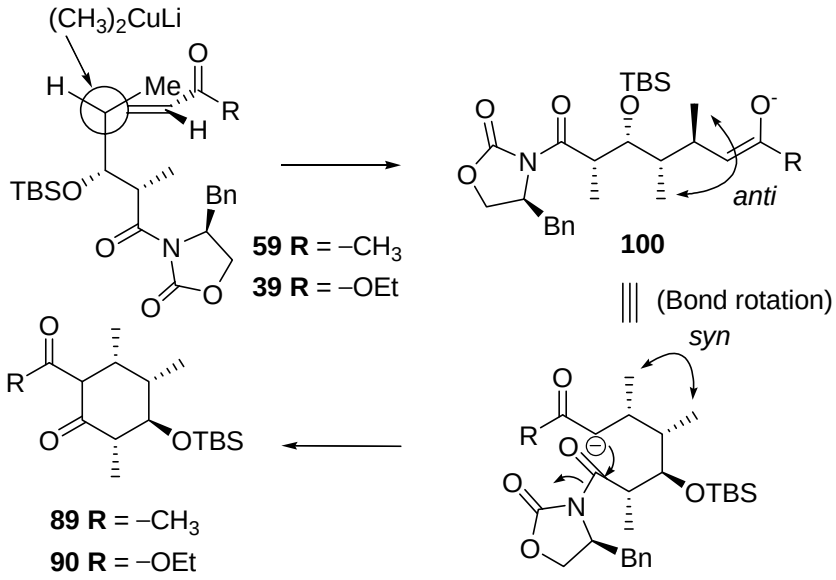
2.5.3 Stereochemistry of the Cyclisation and Methylation

At this point a discussion of the stereochemical outcomes of the addition-cyclisation reaction and subsequent methylation is pertinent. Chounan *et al*. have found that conjugate addition reactions of *trans* α,β-unsaturated monoesters/monoketones occur by a modified Felkin-Anh model.[76] They postulate that Felkin-like attack of a cuprate on a *trans* α,β-unsaturated carbonyl compound **95** affords the Felkin-like product **96**, where the new stereocentre is *anti* to the pre-existing γ-stereocentre (Scheme 2.14). They also found that if the double bond geometry changed from *trans* to *cis* as in **97**, the *syn* isomer **98** was produced. This can be rationalised by considering the two conformations **97** and **99**. Unfavourable, allylic steric interactions exist in **99**, which are alleviated if conformation **97** is adopted.



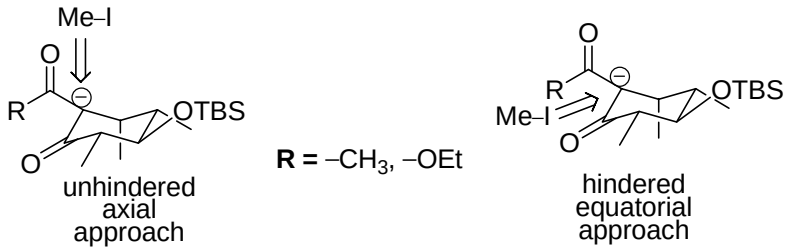
Scheme 2.14: *Modified Felkin-Anh nucleophilic attack on α,β-unsaturated carbonyl compounds.*[76]

Applying these findings to the present work means Felkin-like attack of the cuprate on **39** or **59** affords acyclic intermediate **100** with stereocentres *anti*, but upon cyclisation these stereocentres become *syn*, yielding cyclohexanone **89** or **90** (Scheme 2.15). It is noteworthy that Chounan *et al*. found that the *syn* product was obtained from *cis* α,β-unsaturated monocarbonyl compounds.[76] This could have implications for accessing diastereomeric products of those obtained using a *trans* α,β-unsaturated ketone or ester. Subsequent methylation/elimination could furnish cyclohexenones diastereomeric to those already discussed.



Scheme 2.15: *Felkin-like attack of dimethylcopper lithium on enoate **39** or enone **59**.*

Finally, while there was relevant literature precedent for *trans* methylation, the outcome may also be rationalised due to minimal steric interactions for the incoming methylating agent approaching *axially* (Scheme 2.16). Inference can be drawn that in the event of the OTBS group being eliminated before methylation occurs, subsequent flattening of the ring was not enough to allow an unhindered equatorial approach of the electrophile, which would result in a *cis* methylated product.



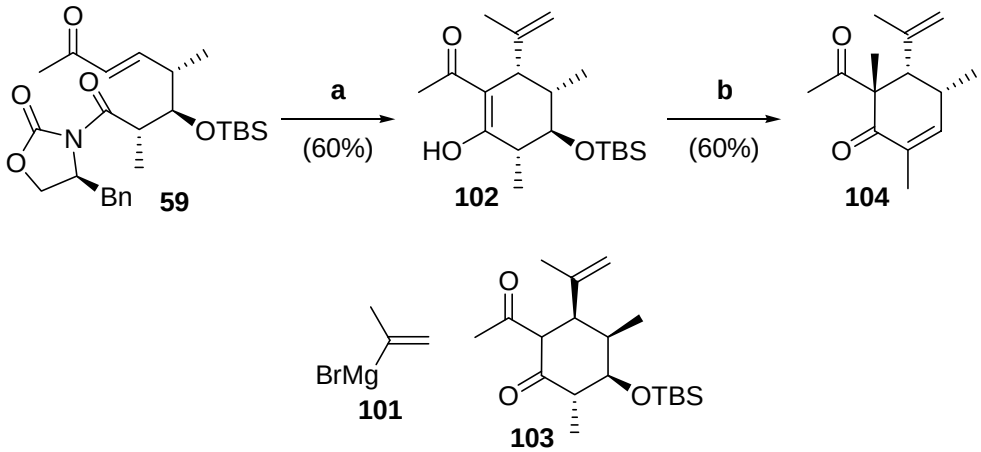
Scheme 2.16: *Axial vs equatorial approach of an electrophile to an enolate.*

2.5.4 Addition of a Vinyl Cuprate

With considerable success in reactions involving simple dimethylcopper lithium, attention was turned to the use of a vinyl cuprate to perform the addition-cyclisation. The use of vinyl cuprates would be paramount in the synthesis of tridachione type natural products. Isopropenylmagnesium bromide (**101**) was chosen as the basis of the cuprate as it was readily available and its use has been well documented in the literature. The nature of cuprates was such, however, that the addition was less straightforward than expected. The problems encountered had more to do with the reactivity of the substrate rather than difficulty in forming the cuprate. As such, success was only observed for the more reactive enone **59**.

The addition-cyclisation was accomplished by employing a similar method to Boring and Sindelar.[77] The cuprate was formed by adding vinyl Grignard **101** to CuI in THF at –78°C. The resulting orange solution was warmed to –20°C and stirred for 20 minutes (Scheme 2.17). Addition of enone **59** at –78°C, followed by warming to room temperature resulted in a black, insoluble mixture. Stirring at room temperature overnight, however, afforded an homogeneous, pale yellow solution, giving the cyclic product **102** in reasonable yield (60%).

The product **102** existed almost exclusively as the *enol* tautomer, as determined from the ^{1}H NMR spectrum. Once again, the *enol* proton at δ 16.36 in the ^{1}H NMR spectrum of the crude product was indicative of successful cyclisation. With careful chromatography, small amounts of the diastereomeric product **103**, which arose from the addition-cyclisation of ***epi*-59**, could be isolated on occasions. Interestingly, **103** existed almost exclusively as the *keto* tautomer, as determined from its ^{1}H NMR spectrum. *Trans* methylation of **102** was carried out by treatment with NaH and MeI in THF as described above, affording cyclohexenone **104** (60%) as a single enantiomer (Scheme 2.17). As before, the stereochemistry of the new stereocentres was assigned based on the findings of Chounan *et al*.[76]



Reagents and conditions: a. i. Grignard **101** (4 eq), CuI (2 eq), THF, -78°C to -20°C, 20 min; ii. Enone **59**, THF, -78°C to rt, 16h; **b.** i. NaH (2 eq), THF, rt, 10 min; ii. MeI (10 eq), rt, 24h.

Scheme 2.17: *Addition of a vinyl cuprate to **59** and subsequent trans methylation to afford **104**.*

The ^{1}H NMR spectrum of **104** displays the expected resonances (Figure 2.6). In particular, the signals for the vinyl protons appear as multiplets at δ 6.41-6.39, δ 4.86-4.84 and δ 4.72-4.70, with the most downfield signal belonging to the enone vinyl

proton. The allylic methine protons appear as multiplets at δ 3.08-2.97 and δ 2.70 (dd, *J* = 5.7, 1.2 Hz) and display the appropriate couplings to each other as well as to their respective methyl protons. The vinyl methyl protons appear as multiplets at δ 1.84-1.82 and δ 1.57-1.56 and the quaternary methyl protons appear as a singlet at δ 1.42. The remaining resonances are attributed to the methyl ketone protons, which appear as a singlet at δ 2.19 and to the protons of the methyl doublet at δ 1.08 (*J* = 7.5 Hz). Infrared absorptions occurred at 1704 and 1666 cm^{-1}, consistent with the presence of two carbonyl groups and an accurate mass measurement confirmed the expected molecular formula to be $C_{14}H_{20}O_2$.

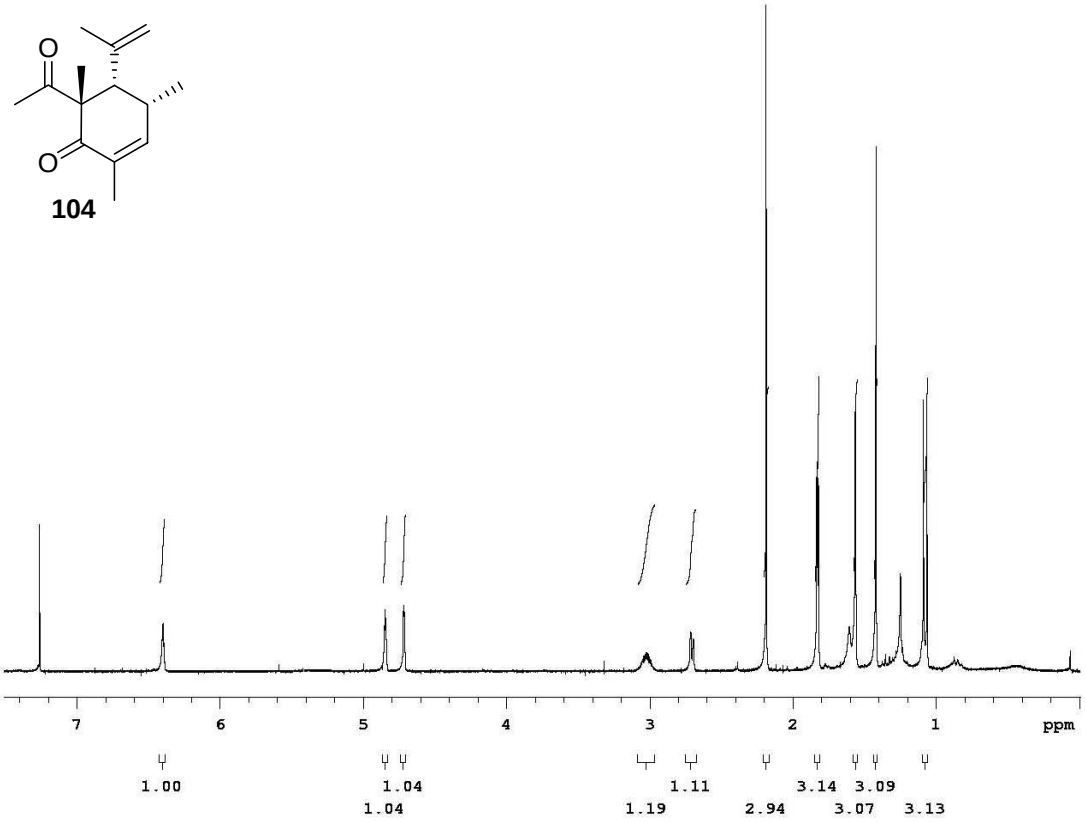


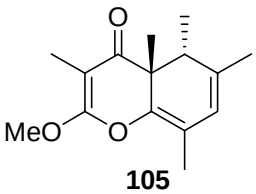
Figure 2.6: *300 MHz ^1H NMR spectrum of **104** in $CDCl_3$.*

The preceding reactions have shown that the tandem conjugate addition-Dieckmann condensation strategy is a viable method for forming the desired six-membered ring systems. Subsequent *trans* methylation, to install the requisite quaternary methyl stereocentre, occurred with concurrent elimination of the OTBS group to afford chiral, highly substituted cyclohexenone derivatives. The next chapter details a model study that investigates the incorporation of a chiral cyclohexenone ring into a fused, bicyclic pyrone containing ring system which is analogous to that found in tridachiahydropyrone (**7**).

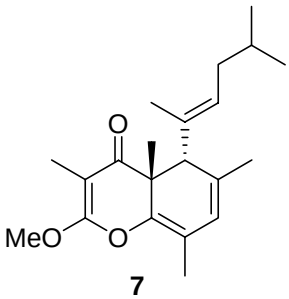
Chapter Three

Fused Bicyclic Pyrone Formation: Model Study 2

*This chapter describes attempts made toward the planned use of a cyclohexenone ring as a synthon in constructing fused, bicyclic pyrone-containing ring systems. A unique, P_2O_5-mediated intramolecular cyclisation of an enone onto an acid moiety is investigated. This leads to bicyclic pyrone **105**, analogous to tridachiahydropyrone (**7**).*



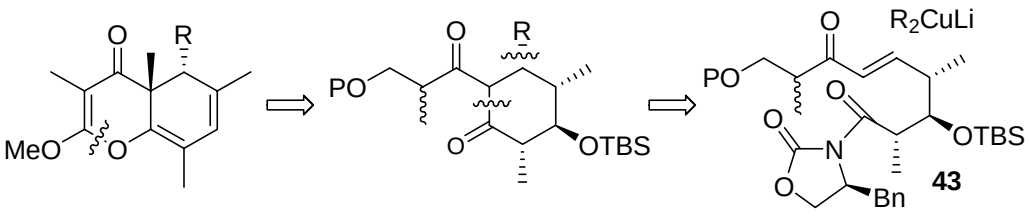
105



7

3.1 Incorporation of a Cyclohexenone Ring into a Bicyclic Ring System

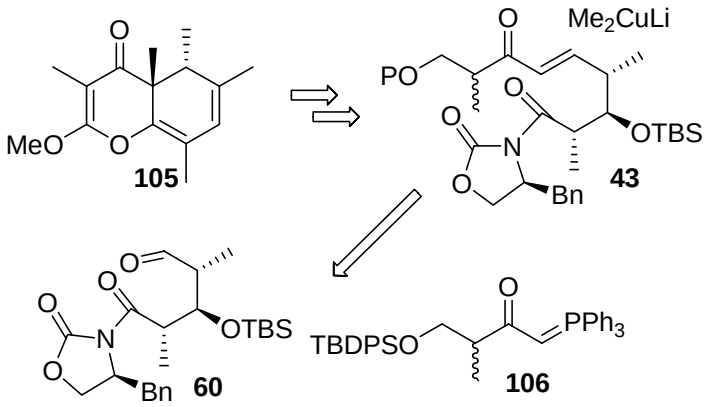
The strategy being developed towards the synthesis of tridachiahydropyrone (**7**) involves incorporating a cyclohexenone ring into a bicyclic system as a cyclohexadiene. Formation of the cyclohexenone would be based on the work described in the previous chapter. Therefore, the intramolecular cyclisation to form the pyrone of the bicyclic ring system required investigation. As depicted in the retrosynthesis (Section 1.7.2), the acyclic precursor **43** to tridachiahydropyrone (**7**) contained almost all of the carbon backbone required, with the remainder coming from the cuprate during the conjugate addition-cyclisation step. This approach makes for a rather convergent synthesis, which may be tolerant of a variety of cuprates (Scheme 3.1).



Scheme 3.1: *Retrosynthetic analysis showing acyclic precursor **43**.*

3.1.1 A Model Bicyclic Pyrone

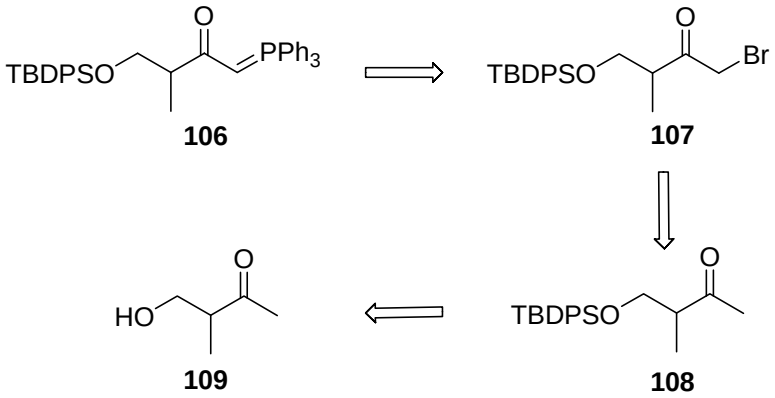
As an alternative to addition of the natural product vinyl side-chain at this point, the use of dimethylcopper lithium was explored on this more complex system involving enone **43**. It was envisaged that the same sequence of reactions as required to form the natural product pyrone could be undertaken in a simpler system. Thus, model pyrone **105** (Scheme 3.2), analogous to tridachiahydropyrone (**7**), could be synthesised, with the only difference being the lack of the vinyl side-chain. This would simplify the procedure, as the goal at this point was to determine whether pyrone formation was achievable using such a cyclohexenone synthon. Aldehyde **60** was common to the model study in the previous chapter so the focus was on accessing the desired ylide **106**.



Scheme 3.2: *Retrosynthetic analysis of model pyrone to aldehyde **60** and ylide **106**.*

3.1.2 Retrosynthetic Analysis of Ylide 106

Stabilised ylide **106** can be seen to come from the reaction of triphenylphoshine with α-bromoketone **107** (followed by treatment with base), which is derived by brominating the suitably protected hydroxyketone **108** (Scheme 3.3). Protected hydroxyketone **108** can be attained by protection of commercially available 4-hydroxy-3-methylbutan-2-one (**109**). At this stage there appeared to be no necessity to use a chiral hydroxyketone and a racemic mixture would suffice, although this would lead to a mixture of diastereomers of **43** (P = TBDPS) which would complicate the synthesis somewhat. An alternative to the use of Wittig chemistry described below involved a Horner-Wadsworth-Emmons (H/W/E) reaction to afford enone **43** (P = PMB) and this will be discussed in due course (Section 3.3).

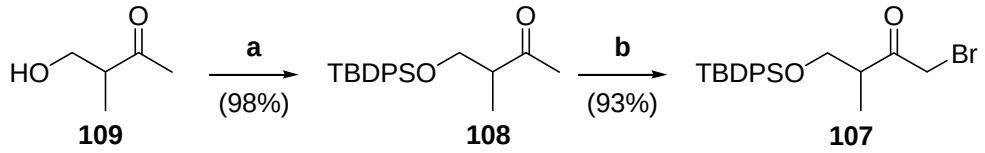


Scheme 3.3: *Retrosynthetic analysis of ylide **106** to hydroxyketone **109**.*

3.2 Acquisition and Reaction of Ylide 106

3.2.1 Kinetic Enolate Monobromination of Ketone 108

Firstly, commercially available hydroxyketone **109** was protected as the *t*-butyldiphenylsilyl (TBDPS) ether. The TBDPS protecting group was chosen because it was deemed robust enough to protect the primary alcohol of **109** through several functional group manipulations. Thus, **109** was treated with 4-(*N*,*N*-dimethylamino)pyridine (DMAP) and Et_3N in CH_2Cl_2 at 0°C, followed by addition of *t*-butyldiphenylsilyl chloride (TBDPSCl). The mixture was stirred at room temperature for 2 days to afford TBDPS protected alcohol (single enantiomer known[78]) **108** in excellent yield (98%, Scheme 3.4).



Reagents and conditions: a. i.DMAP (0.1 eq), Et_3N (2 eq), CH_2Cl_2, 0°C; ii. TBDPSCl (1.2 eq), 0°C to rt, 46 h; **b.** i. LiHMDS (1.5 eq), THF, -78°C, 1 h; ii. TMSCl (3 eq), -78°C to 0°C; iii. Br_2 (2 eq), -78°C, 30 min.

Scheme 3.4: *Transformation of hydroxyketone **109** into bromoketone **107**.*

The next step required monobromination of the α-methyl group of **108** *via* the kinetic enolate to give bromoketone **107**. Attempts using lithium diisopropylamide (LDA) base in THF at –78°C followed by bromine (Br_2) met with limited success. Lithium hexamethyldisilazide (LiHMDS) proved a more fruitful base but the yields were rather poor (40-50%). Finally, the transformation was accomplished by the use of LiHMDS in THF at –78°C followed by trimethylsilyl chloride (TMSCl).[78] Warming the reaction

slowly to 0°C, followed by cooling to –78°C and treating the *in situ* formed TMS enol ether with Br_2[78] and stirring for 30 minutes afforded the desired monobrominated ketone **107** in high yield (93%, Scheme 3.4).

The ^{1}H NMR spectrum of α-bromoketone **107** displays the appropriate resonances (Figure 3.1). Of particular interest are the diastereotopic bromomethylene protons which appear as distorted doublets at δ 4.10 and δ 4.05 which show reciprocal coupling to each other of J = 13.2 Hz. The oxymethylene protons are also diastereotopic and appear as doublet of doublets at δ 3.76 (J = 9.9, 8.2 Hz) and δ 3.68 (J = 9.9, 5.4 Hz) and show reciprocal coupling to each other as well as couplings to the methyl methine multiplet at δ 3.23-3.12. The methyl methine couples with the methyl doublet at δ 1.05 (J = 6.9 Hz) and the remaining resonances are due to the silyl protecting group aromatic protons at δ 7.66-7.59 (4H) and δ 7.45-7.36 (6H) and the *t*-butyl protons at δ 1.03 (9H). The infrared spectrum displayed a dominant absorption at 1718 cm^{-1}, consistent with the presence of a carbonyl group. Accurate mass measurement confirmed the expected molecular formula of $C_{21}H_{27}BrO_2Si$.

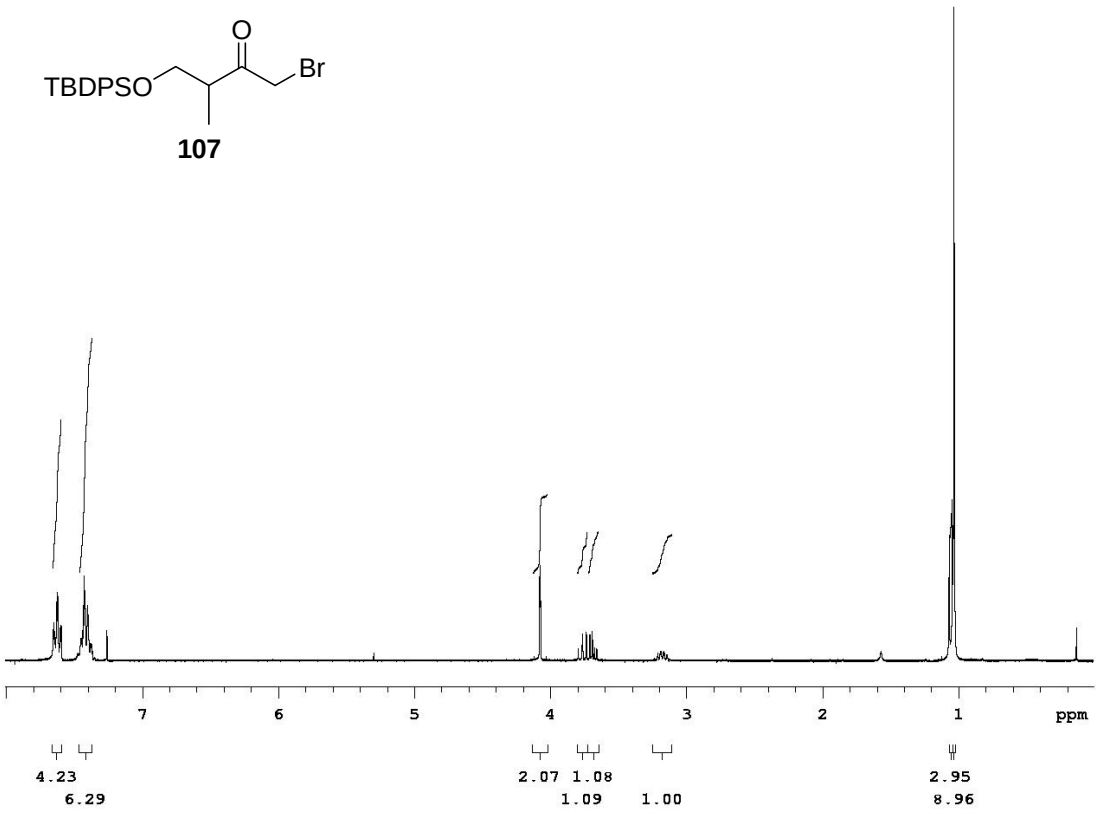
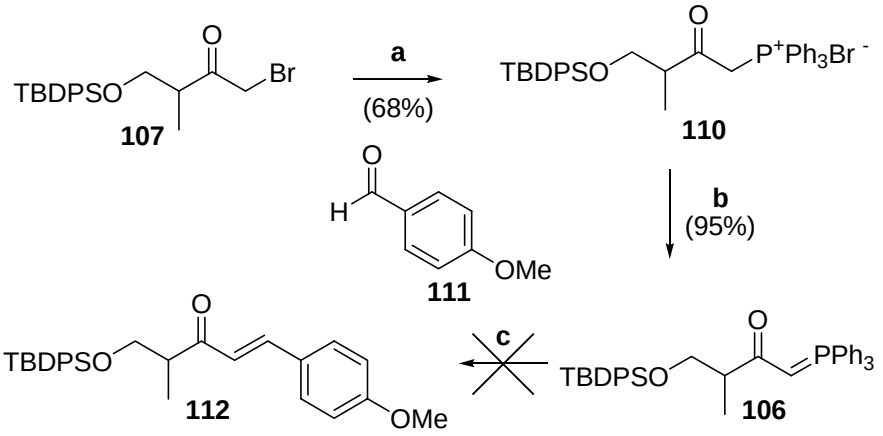


Figure 3.1: *300 MHz ^{1}H NMR spectrum of α- bromoketone **107** in $CDCl_3$.*

3.2.2 An Unsuccessful Wittig Reaction

Bromoketone **107** was converted to phosphonium bromide **110** (68%, crude) by refluxing with triphenyl phosphine (PPh_3) in THF for 2 days (Scheme 3.5). Trituration of the solid produced from the reaction with toluene (to remove unreacted PPh_3) followed by washing with hexanes was sufficient purification of the salt. The ^{13}C NMR displayed several carbon peaks as multiplets due to coupling to phosphorous. Treatment of phosphonium salt **110** with NaOH in THF/H_2O at 0°C in an attempt to form ylide **106** appeared successful, yielding a gummy semi-solid (95%), but attempts to react the ylide with model aldehyde **111** in THF at room temperature failed to afford enone **112** (Scheme 3.5). Without further investigation, attention was turned to the use of a H/W/E type coupling to afford **43** (P = PMB).



Reagents and conditions: a. PPh_3, THF, reflux, 43 h; **b.** NaOH (1.2 eq), THF, H_2O, 0°C, 1h; **c.** Aldehyde **111** (1 eq), THF, rt, 4 days.

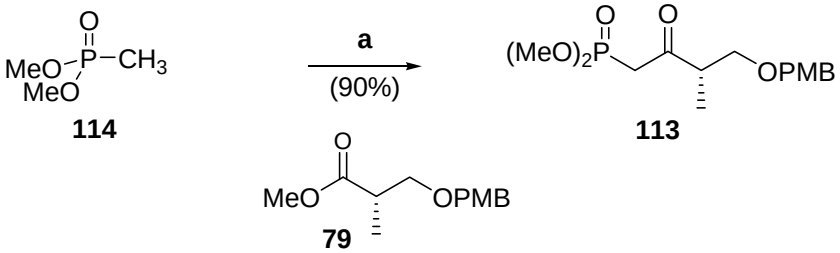
Scheme 3.5: *Formation of phosphonium salt **110**, and reaction of ylide **106** with p-anisaldehyde (**111**).*

3.3 A Horner-Wadsworth-Emmons Type Coupling

3.3.1 β-Ketophosphonate Formation

At the same time that ylide **106** was being synthesised, investigations were under way into using H/W/E chemistry to form the (*E*)-alkene of **43** (P = PMB). While a racemic ketophosphonate would suffice in this case, the temptation to use chiral ester **79**, which was already on hand, to form chiral β-ketophosphonate **113** was enticing. This could afford diastereomerically pure **43** (P = PMB) *via* a H/W/E reaction, which would make the synthesis simpler by not having to separate and characterise diastereomers.

To this end, β-ketophosphonate **113** was formed by reaction of the lithium anion of dimethyl methylphosphonate[79,80] (**114**) with chiral ester **79**. Thus, treating **114** with *n*-BuLi in THF at –78°C for one hour, followed by condensation with ester **79** at –78°C for 15 minutes afforded ketophosphonate **113** in high yield (90%, Scheme 3.6). As was the case previously with observations of carbon coupling to phosphorous, multiplets were observed in the ^{13}C spectrum of **113**. Coupling of β-ketophosphonate **113** and aldehyde **60** was subsequently investigated.



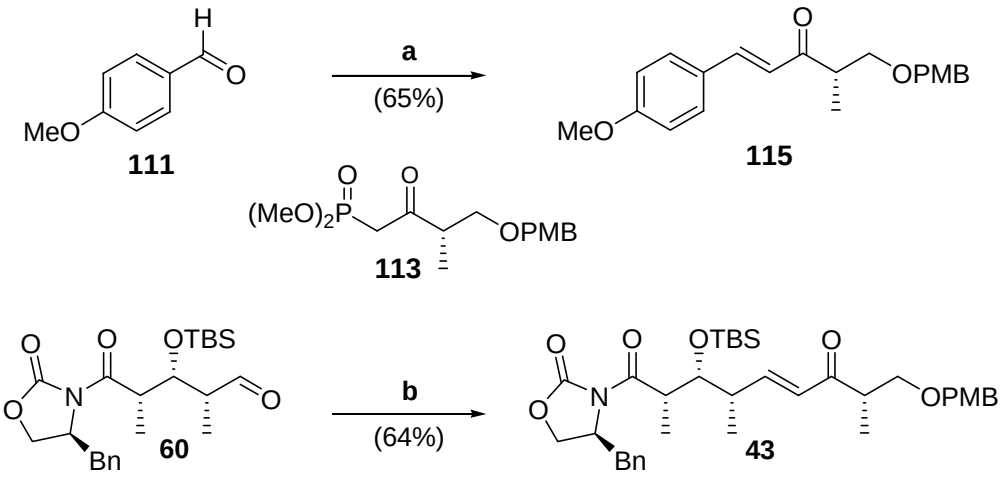
Reagents and conditions: a. i. Phosphonate **114** (4 eq), *n*-BuLi (4 eq), THF, -78°C, 1h; ii. Ester **79**, THF, -78°C, 15 min.

Scheme 3.6: *Formation of chiral β-ketophosphonate **113** from ester **79**.*

3.3.2 Trial of Reaction Conditions for the Coupling

As a starting point, reaction of **113** with *p*-anisaldehyde (**111**) in MeCN in the presence of K_2CO_3[81] at room temperature for 21 hours afforded the expected (*E*)-alkene **115** in moderate yield (65%, based on recovery of **113**, Scheme 3.7). Other approaches were investigated, including using Et_3N in MeCN[82] and NaH in THF in an attempt to couple ketophosphonate **113** with aldehyde **111**, all to no avail.

Eventually, the Masamune-Roush[83] protocol was adopted as a method that could tolerate chiral, base-sensitive substrates. This method involved stirring a solution of ketophosphonate **113**, LiCl and diisoproplyethylamine (DIPEA) in MeCN at room temperature, followed by addition of aldehyde **60** in MeCN and stirring for 4-5 days (Scheme 3.7). While this method was slow in comparison to other reported methods for H/W/E reactions, it did result in formation of **43** (P = PMB) with high (*E*)-selectivity and in reasonable yield (64%). All other coupling attempts using various bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU),[83] $LiOH.H_2O$[84] or activated $Ba(OH)_2.8H_2O$[85] either failed to produce any product **43** (P = PMB), or produced several other products (one resulting from elimination of the OPMB group), with **43** (P = PMB) as a minor component.



Reagents and conditions: a. Ketophosphonate **113** (1eq), K_2CO_3 (1 eq), aldehyde **111**, MeCN, rt, 21 h; **b.** i. Ketophosphonate **113** (1.2 eq), LiCl (1.2 eq), DIPEA (1.05 eq), MeCN, rt; ii. Aldehyde **60**, MeCN, rt, 4.5 d.

Scheme 3.7: *H/W/E reactions of β-ketophosphonate **113** with p-anisaldehyde (**111**) and chiral aldehyde **60**.*

The ^{1}H NMR spectrum of enone **43** (P = PMB) displays the requisite resonances (Figure 3.2) and evidence for the (*E*)-double bond once again comes from the magnitude of the vinyl proton coupling constants. The vinyl protons appear as doublet of doublets at δ 6.94 (*J* = 15.9, 8.1 Hz) and δ 6.16 (*J* = 15.9, 0.9 Hz), with the large coupling constant being consistent with an (*E*)-alkene. The downfield shift of the vinyl proton at δ 6.94 is typical of an α,β-unsaturated carbonyl β-proton. The oxymethine proton appears as an apparent (app) triplet (*J* = 5.7 Hz) and couples to both methyl methine multiplets at δ 3.85 (app qn, *J* = 6.9 Hz) and δ 2.54-2.43. These in turn couple to the corresponding methyl doublets at δ 1.21 (*J* = 6.9 Hz) and δ 1.08 (*J* = 7.2 Hz). The remaining methyl methine proton appears as a multiplet at δ 3.24-3.11 and couples to the methyl doublet at δ 1.10 (*J* = 7.2 Hz) and to both diastereotopic oxymethylene protons. These oxymethylene protons appear as doublet of doublets at δ 3.67 (*J* = 9.2, 7.4 Hz) and δ 3.42 (*J* = 9.2, 5.8 Hz). The remaining resonances are due to the chiral auxiliary and PMB and TBS protecting groups. The infrared spectrum contained absorptions at 1782, 1695 and 1669 cm^{-1} corresponding to the three carbonyl groups. An accurate mass measurement confirmed the expected molecular formula of $C_{36}H_{51}NO_7Si$.

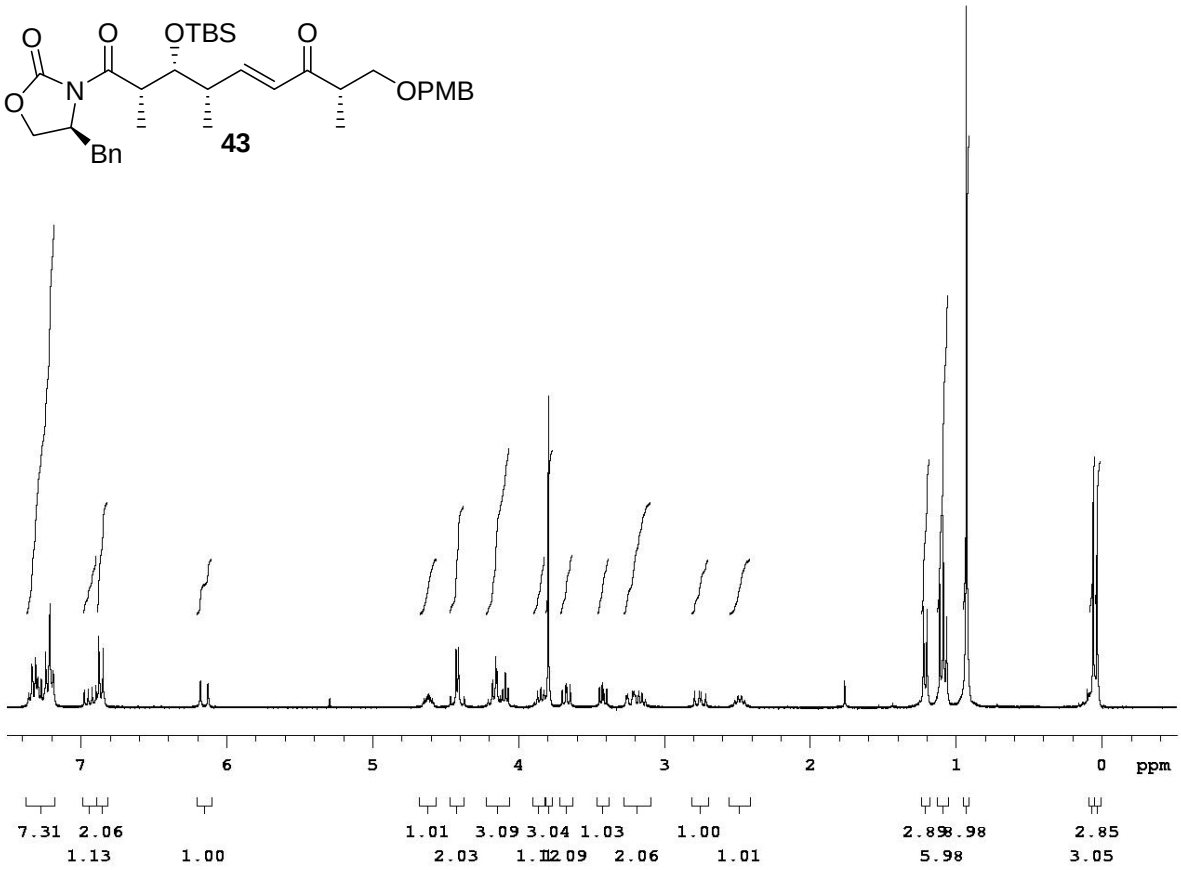
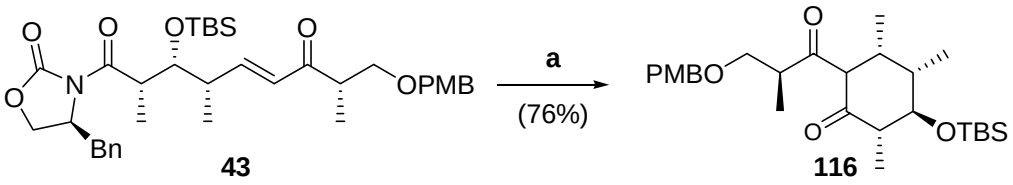


Figure 3.2: *300 MHz ^1H NMR spectrum of enone **43** (P = PMB) in $CDCl_3$.*

3.4 Addition-Cyclisation and *Trans* Methylation

3.4.1 Conjugate Addition of Dimethylcopper Lithium

With over three grams of enone **43** (P = PMB) in hand, a conjugate addition-cyclisation was performed using dimethylcopper lithium. The cuprate was formed in the same, reliable manner as described in Chapter 2, by using MeLi and CuI in Et_2O/Me_2S at room temperature (Scheme 3.8). Approximately 1.5 grams of enone **43** (P = PMB) in Et_2O was added, causing the familiar, bright yellow precipitation. The reaction mixture was stirred at room temperature for one hour to afford cyclohexenone **116** (76%) as a mixture of *keto* and *enol* tautomers. As has been the case, successful cyclisation was evident from the signal in the ^1H NMR spectrum of the crude material at δ 16.82 due to the *enol* proton.

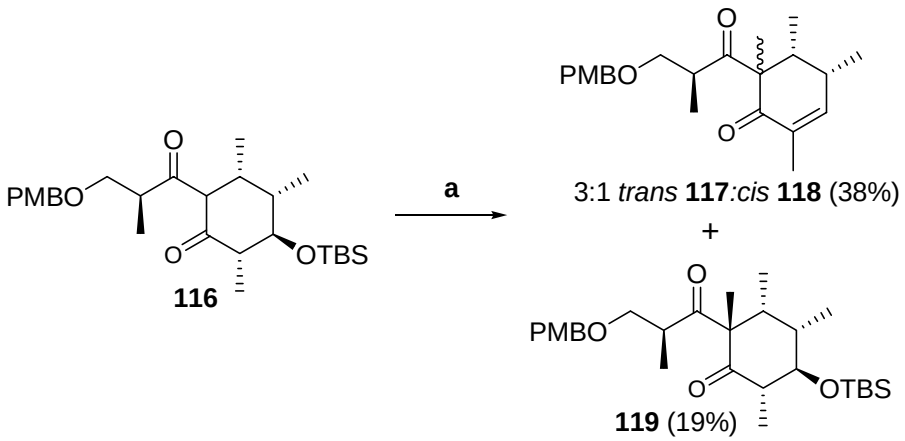


a. i. MeLi (3 eq), CuI (1.5 eq), Et_2O, Me_2S, rt; ii. Enone **43,** Et_2O, rt, 1 h.

Scheme 3.8: *Conjugate addition-cyclisation of enone **43** (P = PMB) with dimethylcopper lithium.*

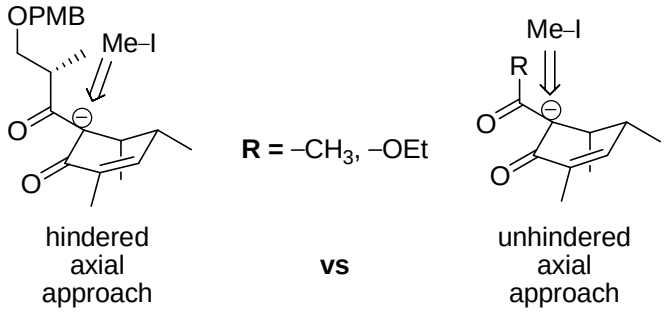
3.4.2 Reduced Selectivity for *Trans* Methylation

Trans methylation of **116** was carried out in the same manner as previously described with NaH and MeI in THF (Scheme 3.9). In this case, however, there was a considerable amount of *cis* methylation, affording *trans*-**117** and *cis*-**118** as an inseparable 3:1 mixture (38%), along with intermediate diketone **119** (19%). This reduced selectivity for the *trans* product was intriguing but can be rationalised by referring to observations made about methylation of cyclohexenone **90** in Chapter 2. From the methylation reaction of **90** (Section 2.5.2) it was found that β-elimination of the OTBS could occur prior to methylation, which would cause a partial flattening of the chair conformation. As opposed to the case where there was a relatively small ester group in **90**, it appears that the extra chain length associated with **116** causes substantial hindrance of the axial approach of the methylating agent in the event that elimination occurs before methylation (Scheme 3.10).



Reagents and conditions: a. i. NaH (2eq), THF, rt, 10 min; ii. MeI (10 eq), rt, 18 h.

Scheme 3.9: *Trans methylation of **116** resulting in loss of selectivity.*

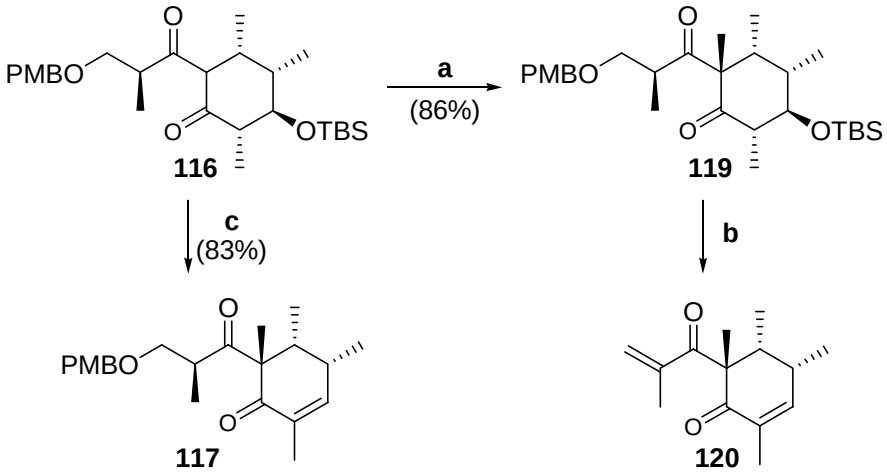


Scheme 3.10: *Reduced selectivity of the methylation due to β-elimination of the OTBS.*

3.4.3 Improving the Selectivity

It was inferred that β-elimination of the OTBS was the cause for reduced selectivity for the *trans* product. As such, the amount of NaH used was kept strictly to one equivalent so it would mainly deprotonate the more acidic proton between the two carbonyl groups. Subsequent trapping of this enolate with methyl iodide afforded the *trans* methylated, non-eliminated cyclohexanone **119**, which could be isolated in good yield (86%, Scheme 3.11). Unfortunately, treatment of purified **119** with one equivalent of NaH in THF to effect OTBS elimination also occurred with elimination of the OPMB group to afford terminal alkene **120** (Scheme 3.11). The use of less base may have overcome this problem, although this was not attempted.

Alternatively, the procedure adopted involved ensuring methylation was complete (by tlc) and then transferring the reaction mixture *via* cannula into 0.5 of an equivalent of NaH in THF to promote elimination. This simple solution was very effective and afforded a more favourable 9:1 mixture of *trans*-**117** and *cis*-**118** (83%, Scheme 3.11). This method did cause a small amount of elimination of the OPMB to afford terminal alkene **120** (<10%). The OTBS elimination appeared to be catalysed by the base, so the use of less base in the elimination step could suppress the formation of **120**. This was not pursued at the time because the yield of **117** was quite acceptable. The mixture of **117**/**118** was used in subsequent reactions but only *trans* isomer **117** is shown for simplicity.



Reagents and conditions: a. NaH (1eq), THF, rt, 10 min; ii. MeI (10 eq), rt, 18 h; **b.** NaH (1eq), THF, rt, 1 h; **c.** i. NaH (1eq), THF, rt, 10 min; ii. MeI (10 eq), rt, 17 h; iii. NaH (0.5 eq), THF, rt, 15 min,

Scheme 3.11: *Improvement to the selectivity of the trans methylation, affording cyclohexenone **117**.*

The ^{1}H NMR spectrum of **117** has a diagnostic resonance for the vinyl proton, which appears as a multiplet at δ 6.36-6.33 (Figure 3.3). There are methyl methine multiplets at δ 3.36 (app. sextet, *J* = 6.6 Hz), δ 2.78-2.69 and δ 2.23-2.19, with the latter two multiplets showing coupling to each other. All three methine protons coupled to their corresponding methyl proton doublets which occur at δ 1.13 (*J* = 6.6 Hz), δ 1.07 (*J* = 7.5 Hz) and δ 0.96 (*J* = 7.2 Hz). The methine proton at δ 3.36 showed coupling to the diastereotopic oxymethylene protons which appear as doublet of doublets at δ 3.66 (*J* = 8.7, 6.6 Hz) and δ 3.28 (*J* = 8.7, 6.3 Hz). The vinyl methyl protons appear as a doublet of doublets at δ 1.77 (*J* = 2.1, 1.5 Hz), while the quaternary methyl protons appear as a singlet a δ 1.40. The remaining signals at δ 7.20 (2H), δ 6.85 (2H), δ 4.41 (1H), δ 4.34 (1H) and δ 3.79 (3H) pertain to the PMB protecting group. The infrared spectrum contained two absorptions at 1699 and 1669 cm^{-1}, consistent with the presence of two carbonyl groups. An accurate mass measurement confirmed the expected molecular formula of $C_{22}H_{30}O_4$. The *cis* isomer had very similar spectral characteristics.

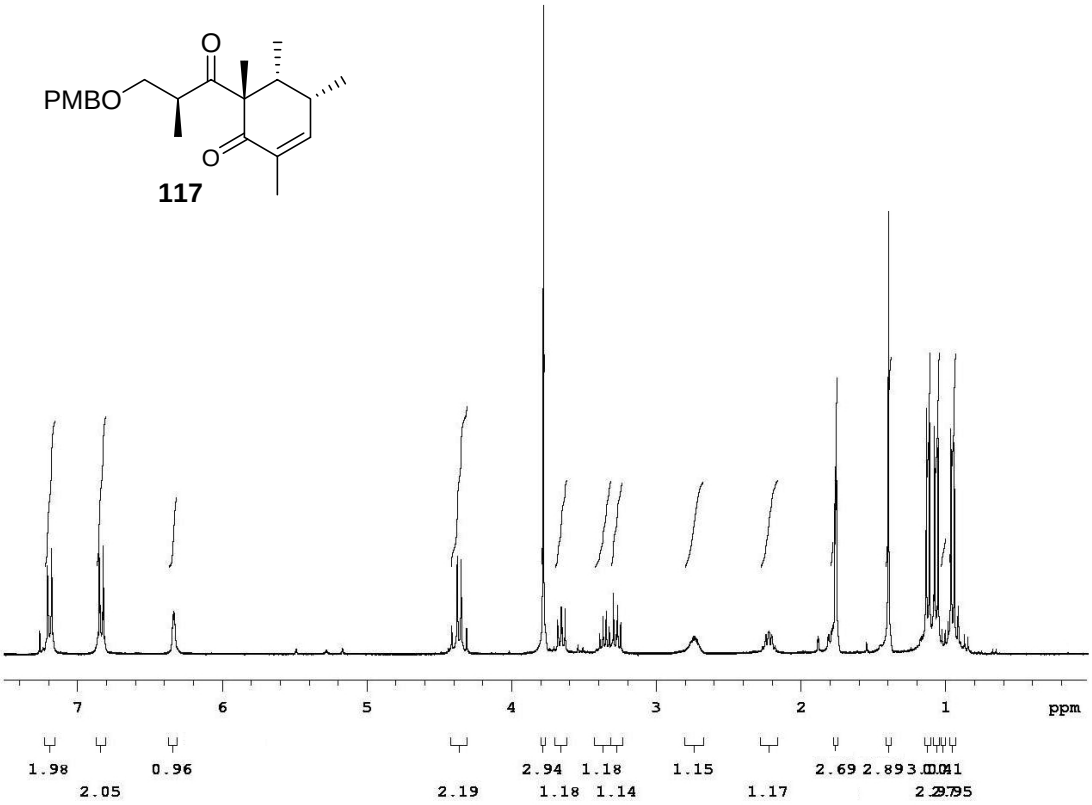


Figure 3.3: *300 MHz ^1H NMR spectrum of cyclohexenone **117** in $CDCl_3$.*

3.4.4 Confirmation of Stereochemistry

The stereochemical assignments of the conjugate addition and methylation have until now been based on literature precedent. It was prudent, therefore, to confirm the stereochemistry of the addition and subsequent methylation by the use of NOE (nuclear Overhauser effect) NMR experiments. NOESY (NOE spectroscopy) experiments were performed on cyclohexenone **117** and cyclohexanone **119**. Figure 3.4 shows the NOE enhancements observed in the NOESY spectra, confirming both the facial selectivity of the addition, which was in accordance with the findings of Chounan *et al.*[76] and that methylation was indeed *trans*.

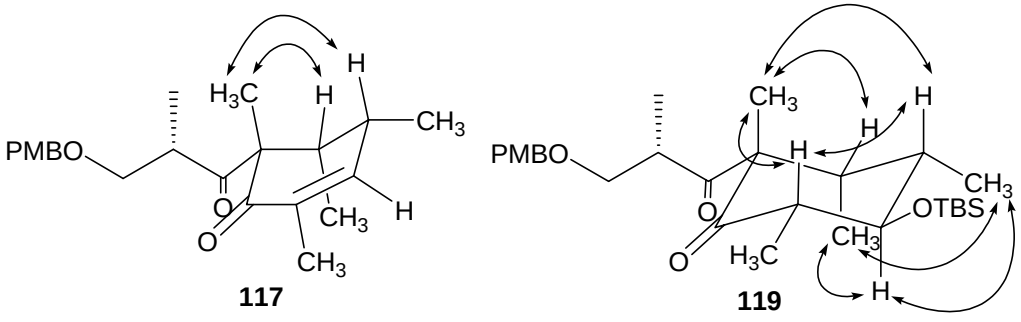


Figure 3.4: *NOE correlations (indicated by arrows) observed for **117** and **119**.*

3.5 A Unique Cyclisation Route

With up to 500 milligrams of cyclohexenone **117** available, the next tasks involved deprotecting the primary alcohol to give **121** and oxidising to the corresponding carboxylic acid **122** (Figure 3.5). At this point it was uncertain how cyclisation of acid **122** to pyrone **123** could be accomplished due to the absence of relevant literature precedent. Precedent existed for cyclising triketones such as **124** with PPh_3/CCl_4 or $(COCl)_2/DMSO$[33,34] and for cyclising diketoesters such as **125** with DBU[35,36] to afford pyrones **126** and **127**, respectively (Scheme 3.12). Clearly, the proposed acid **122** was unlike either of these types of compound, so the most reasonable course of action was to examine cyclisation with something similar, such as methyl ester **128** (Figure 3.5). The transformation from cyclohexenone **117** to acid **122** and methyl ester **128** is described below, followed by work undertaken to achieve the desired cyclisation.

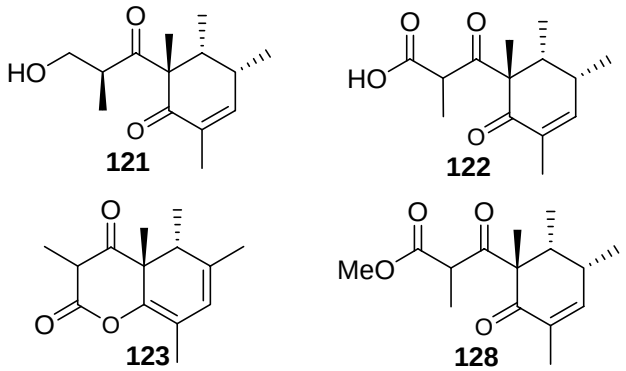
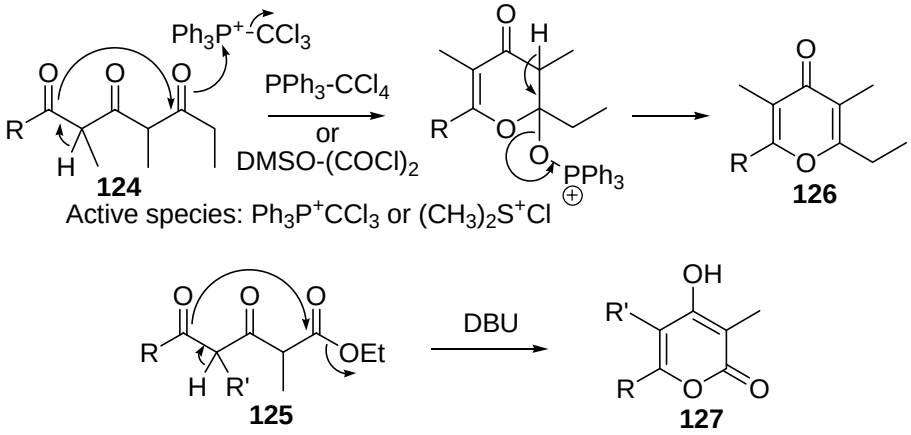


Figure 3.5: *Alcohol **121** and related compounds **122** and **128**, possible precursors to pyrone **123**.*

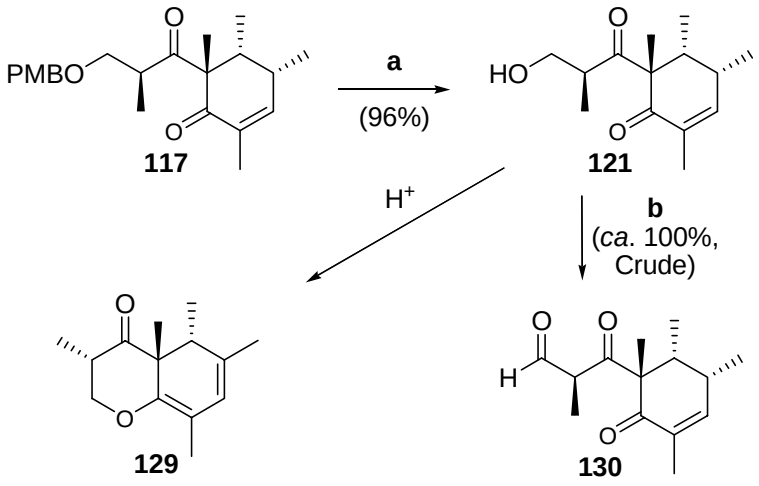


Scheme 3.12: *Pyrone formation from triketone **124** with PPh_3/CCl_4 and diketoester **125** with DBU.*

3.5.1 Conversion of 117 to the Pyrone Precursor

Work began with removal of the PMB protecting group of **117** with DDQ in CH_2Cl_2 and pH 7 buffer at 0°C[74] to afford alcohol **121** in excellent yield (96%, Scheme 3.13). Alcohol **121** was particularly acid-sensitive and cyclised quickly to pyrone **129** (stereochemistry confirmed by NOE experiments) in $CDCl_3$ (due to small amounts of HCl present) or by addition of a small crystal of *p*-TsOH to an NMR tube containing **121**. Subsequently, spectra were recorded in C_6D_6 to alleviate the problem. The ease of cyclisation of alcohol **121** to **129** was interesting, although a pyrone of this type had no synthetic utility for the approach to natural product **7**.

Alcohol **121** was subjected to a two step oxidation procedure in a bid to maintain mild reaction conditions. Firstly, **121** was oxidised with Dess-Martin periodinane[65] in CH_2Cl_2 at room temperature to form aldehyde **130** (*ca.* 100%, crude, Scheme 3.13). The product of the oxidation contained few impurities and showed no epimerisation of the tertiary stereocentre between the two carbonyls. Purification, however, of aldehyde **130** on buffered silica led to epimerisation of this stereocentre.



Reagents and conditions: a. DDQ (1.2 eq), CH_2Cl_2, pH 7 buffer, 0°C, 3 h; **b.** Dess-Martin periodinane (1.5 eq), CH_2Cl_2, rt, 1 h.

Scheme 3.13: *Conversion of PMB ether **117** to aldehyde **130** by deprotection and oxidation.*

The ^{1}H NMR spectrum of aldehyde **130** contained the appropriate resonances (Figure 3.6) with the appearance of a proton doublet at δ 9.68 (J = 2.4 Hz) confirming the presence of the aldehyde. The aldehyde proton showed coupling to the methyl methine

proton which appears as quartet of doublets at δ 4.22 (*J* = 7.0, 2.4 Hz) and this methine proton coupled to protons of the methyl doublet at δ 1.35 (*J* = 7.0 Hz). The other two methyl methine protons appear as multiplets at δ 2.98-2.83 and δ 2.40-2.31 and couple to each other as well as to their respective methyl protons which appear as doublets (*J* = 7.2 Hz) at δ 1.10 and δ 0.83. The vinyl proton appears as a multiplet at δ 6.35-6.30 and the vinyl methyl protons appear as a multiplet at δ 1.80-1.79. The remaining singlet at δ 1.38 is due to the protons of the quaternary methyl group. The infrared spectrum contained absorptions at 1731, 1699 and 1666 cm^{-1}, which were consistent with the presence of three carbonyl groups.

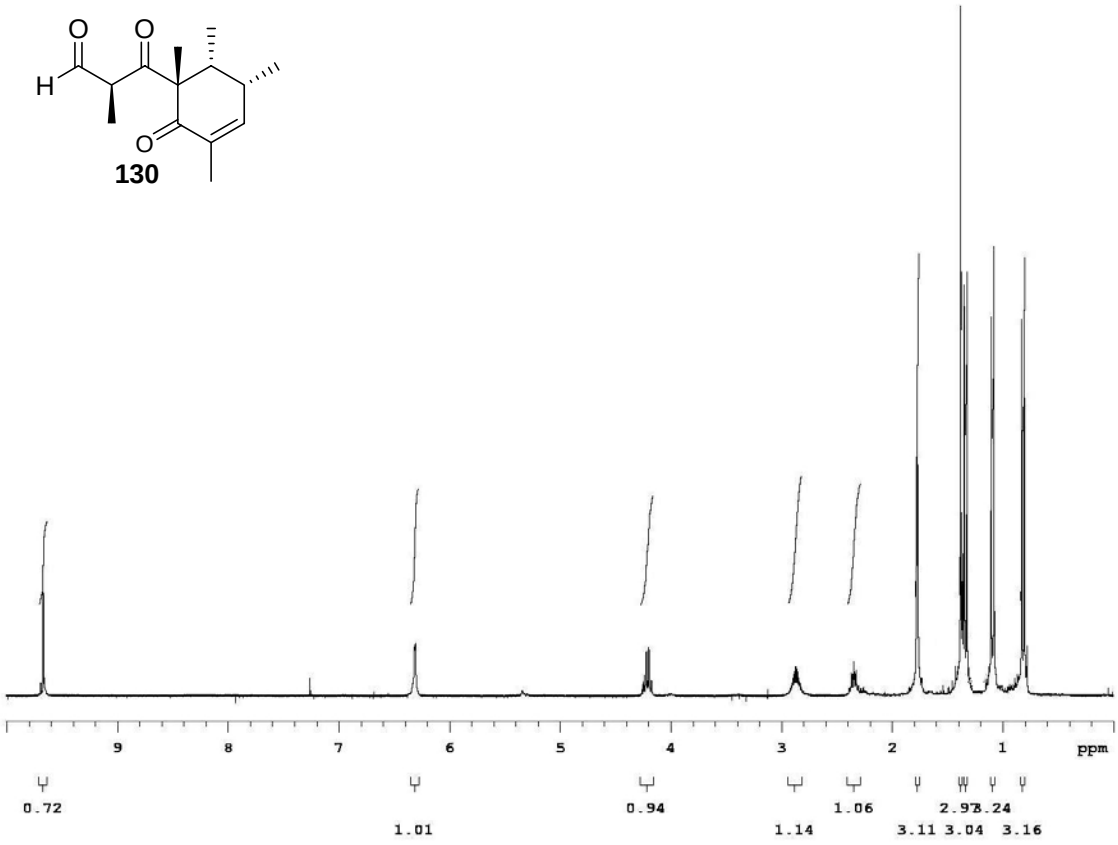
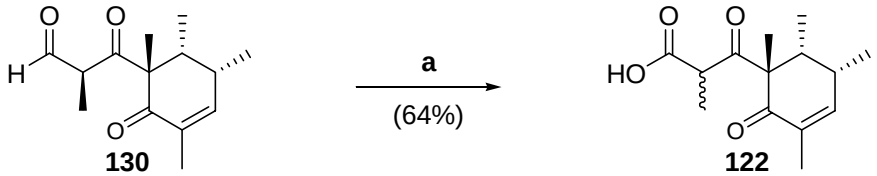


Figure 3.6: *300 MHz ^1H NMR spectrum of aldehyde **130** in $CDCl_3$.*

Aldehyde **130** was further oxidised by treatment with $NaClO_2$ and NaH_2PO_4 in *t*-BuOH and water in the presence of 2-methylbut-2-ene[86] (Me_2C=CHMe) to afford β-ketoacid **122** (64%, Scheme 3.14) as a 1:1 mixture of epimers. Notably, after purification of acid **122** there was no discernible trace of the *cis* isomer (derived from *cis*-**118**) in the ^1H NMR spectrum. The acid was relatively unstable and decarboxylated after several days at room temperature or upon injection into a GC/MS. In any event, synthesis of the proposed precursor to an enantiopure, fused bicyclic pyrone-containing ring system such as found in tridachiahydropyrone (**7**) had been accomplished.

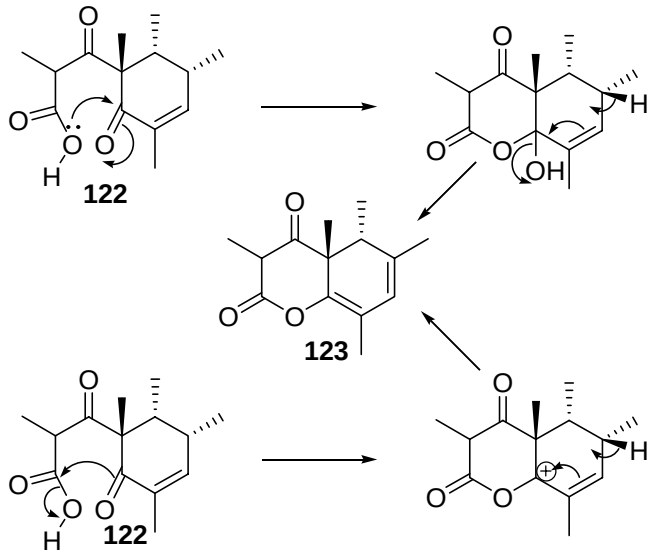


Reagents and conditions: a. $NaClO_2$ (12.5 eq), NaH_2PO_4 (10 eq), *t*-BuOH, H_2O, Me_2C=CHMe, rt, 1h.

Scheme 3.14: *Oxidation of aldehyde **130** to pyrone precursor **122**.*

3.5.2 Examination of Approaches for Cyclisation

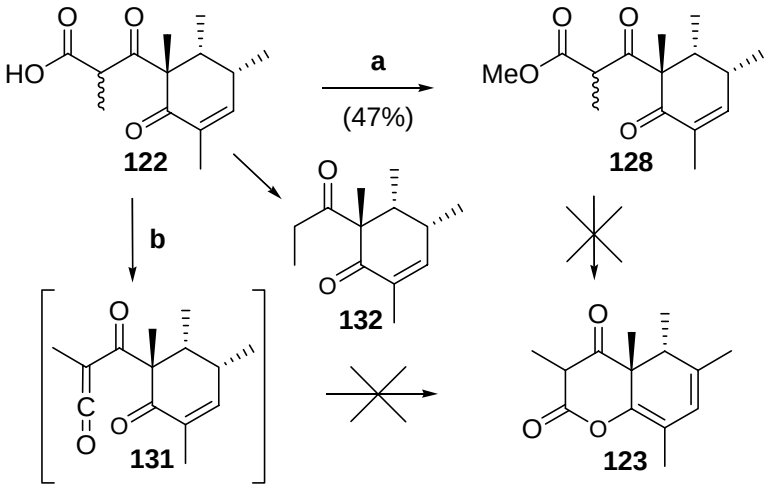
Cyclisation could be envisaged to occur in one of two ways. The hydroxyl of the acid moiety could nucleophilically attack the carbonyl of the cyclohexenone ring, with the subsequent loss off water (Scheme 3.15), similar to the formation of unwanted pyrone **129** (Section 3.5.1). Alternatively, it was more likely that the cyclohexenone oxygen could attack the carbonyl of the acid (or ester) moiety, with the loss off water completing the reaction (Scheme 3.15).



Scheme 3.15: *Possible cyclisation modes for formation of the pyrone ring in **123**.*

At this point some crude acid **122** was transformed into methyl ester **128** by reaction with diazomethane (CH_2N_2, formed from Diazald®) in Et_2O at room temperature. Stirring for ten minutes afforded methyl ester **128** (47%, 2 steps from **130**, Scheme 3.16) as a 3:2 mixture of epimers. Ester **128** resisted any attempts to initiate cyclisation, such as treatment with DBU or PPh_3/CCl_4 in CH_2Cl_2 at room temperature, *p*-TsOH in toluene at 80°C or polyphosphoric acid (PPA) at 100°C. It had become clear that the quaternary methyl group in **128** was eliminating the possibility of forming an enolate at this position. In hindsight, cyclisation modes as depicted in Scheme 3.12 were bound to fail for the present system because of this quaternary methyl group.

Attention was thus turned to effecting cyclisation with acid **122**. Intramolecular coupling using 1,3-dicyclohexylcarbodiimide (DCC) and Et_3N in CH_2Cl_2 or the Yamaguchi method[87,88] failed to afford pyrone **123**. Attempted *in situ* formation of ketene[89] **131** by first forming the corresponding acid chloride,[90] followed by treatment with Et_3N or DBU was also unsuccessful (Scheme 3.16). The latter simply led to decarboxylation to **132** in a matter of hours, as opposed to several days, which was the case for acid **122** alone. Any potential cyclisation procedure had to avoid activating the acid in any way (ie. acid chloride) in the presence of base, or heating the reaction. In light of these results, it was decided that mild, acidic, dehydrating conditions were required.



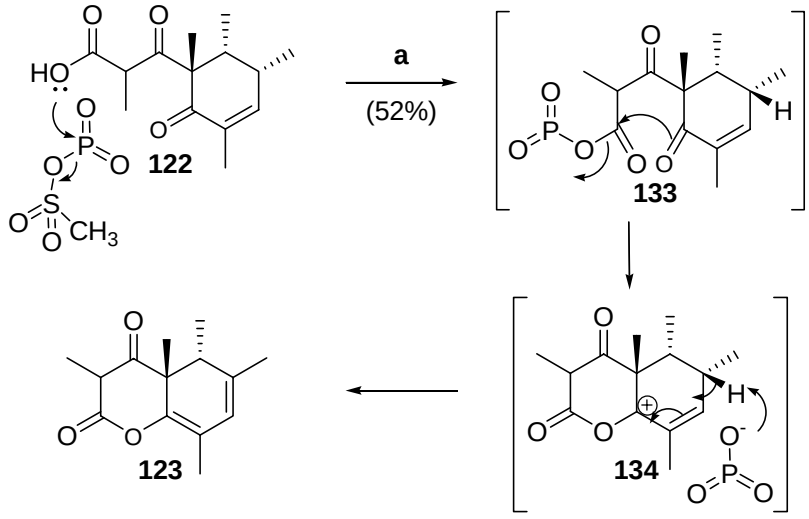
Reagents and conditions: a. CH_2N_2 (excess), Et_2O, rt, 10 min; **b.** i. $SOCl_2$-Benzotriazole (0.1M in CH_2Cl_2, 1.5 eq), rt, 10 min; ii. DBU (2 eq), rt, 3h.

Scheme 3.16: *Attempted cyclisation of ester **128** and acid **122** to pyrone **123**.*

3.5.3 Eaton's Reagent Promoted Cyclisation of Acid 122

Cyclisation was eventually performed with the use of Eaton's reagent (1:10 $P_2O_5/MeSO_3H$)[91] to form pyrone **123** (Scheme 3.17). Eaton's reagent has previously been reported to be used neat as a mild medium for rearrangements.[91-93] The reagent has similar uses to PPA and its effectiveness was thought to be due to formation of a mixed anhydride between P_2O_5 and $MeSO_3H$.[91] Treatment of acid **122** with freshly prepared Eaton's reagent at room temperature for one hour led to several products. Analysis of the crude reaction mixture showed a peak in the GC/MS that had a molecular ion at 234, consistent with desired pyrone **123**. This was the first indication that an effective cyclisation method might have been found.

For the purpose of the current transformation, it appeared that Eaton's reagent could be effective but the reactivity needed to be moderated. To this end, simply using CH_2Cl_2 as the solvent for the reaction between acid **122** and Eaton's reagent and stirring for one hour at room temperature afforded pyrone **123** (52%, Scheme 3.17) predominantly as the *keto* tautomer. This was a unique transformation and the proposed mechanism can be seen in Scheme 3.17. Similar to that proposed by Eaton *et al*.[91] with reference to a mixed anhydride, it is postulated that acid **122** reacts with Eaton's reagent to form mixed anhydride **133**. The anhydride is subsequently attacked by the cyclohexenone carbonyl oxygen to form the bicyclic intermediate **134**. Deprotonation to form the cyclohexadiene of **123** finishes the sequence, which can be seen overall as the intramolecular cyclisation and loss of water from acid **122**.

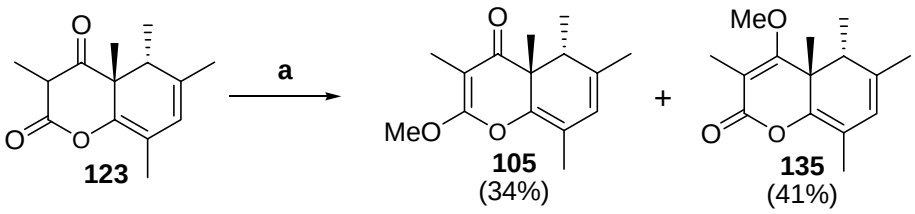


Reagents and conditions: a. 1:10 $P_2O_5/MeSO_3H$ (excess), CH_2Cl_2, rt, 1h.

Scheme 3.17: *Unique intramolecular cyclisation of acid **122** to form pyrone **123**.*

All that remained was to *O*-methylate pyrone **123**, and this was achieved with CH_2N_2 in Et_2O at room temperature (Scheme 3.18). The reaction was complete within 10 minutes, affording α-pyrone **135** (41%) and γ-pyrone **105** (34%), which were readily separable by chromatography on silica. Both isomers were crystalline and a single crystal X-ray

structure determination[ϕ] on each confirmed the structure and relative stereochemistry (Figures 3.7 and 3.8).



Reagents and conditions: a. CH_2N_2 (excess), Et_2O, rt, 10 min.

Scheme 3.18: *O-methylation of **123** provided crystalline pyrones **105** and **135**.*

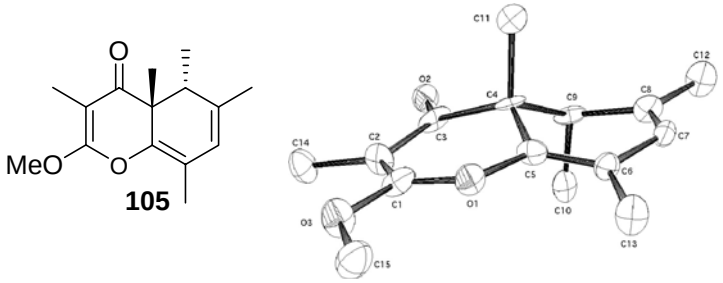


Figure 3.7: *Single crystal X-ray structure of γ-pyrone **105**.*

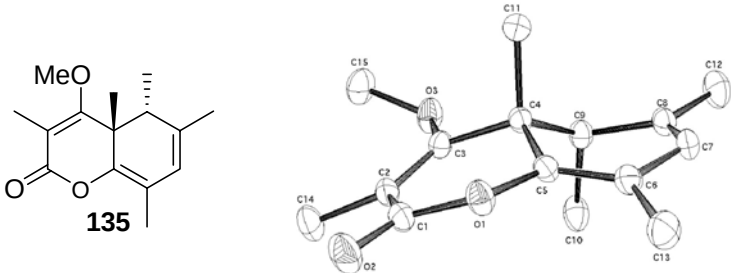
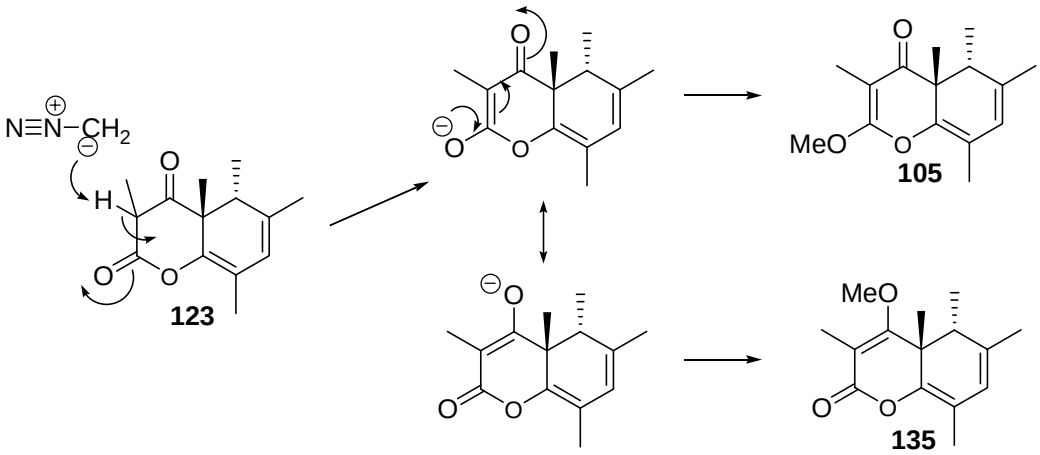


Figure 3.8: *Single crystal X-ray structure of α-pyrone **135**.*

At this point a more regioselective method for the methylation to favour γ-pyrone **105** was contemplated but not attempted (Section 4.6.2). The formation of the two regioisomers can be seen to arise from the ambident nature of the enolate formed by the reaction with CH_2N_2 with pyrone **123** (drawn as the *keto* tautomer, a similar mechanism can be drawn for the *enol* tautomers). This leads to either carbonyl being able to trap the methylating agent, hence the resulting 1.2:1 ratio of the two regioisomers (Scheme 3.19).

[ϕ] CIF files containing X-ray crystallographic data are contained on the compact disc found inside the back cover of this thesis.



Scheme 3.19: *Regioisomers formed due to the ambident nature of the enolate of pyrone **123**.*

The ^{1}H NMR spectra of γ-pyrone **105** and α-pyrone **135** appear similar (Figures 3.9 and 3.10, respectively), with some small differences in chemical shift. Both spectra contain multiplets at *ca.* δ 5.4-5.3 due to the vinyl proton and singlets at *ca.* δ 3.95 from the methoxy protons. The methyl methine proton appears as a quartet at δ 2.38 (J = 6.9 Hz) in **105** and δ 2.17 (J = 6.9 Hz) in **135**. The methine proton couples to the relevant methyl proton doublet apparent in each spectra at δ 0.90 ((J = 6.9 Hz) in **105** and δ 0.86 (J = 6.9 Hz) in **135**. The presence of three vinyl methyl groups can be seen in each spectra with the proton signals at δ 1.78 (d, J = 1.5 Hz), δ 1.75 (s) and δ 1.65 (s) in **105** and δ 1.96 (s), δ 1.76 (d, J = 1.5 Hz) and δ 1.72 (s) in **136**. The quaternary methyl protons appear as a singlet at δ 1.26 in both spectra.

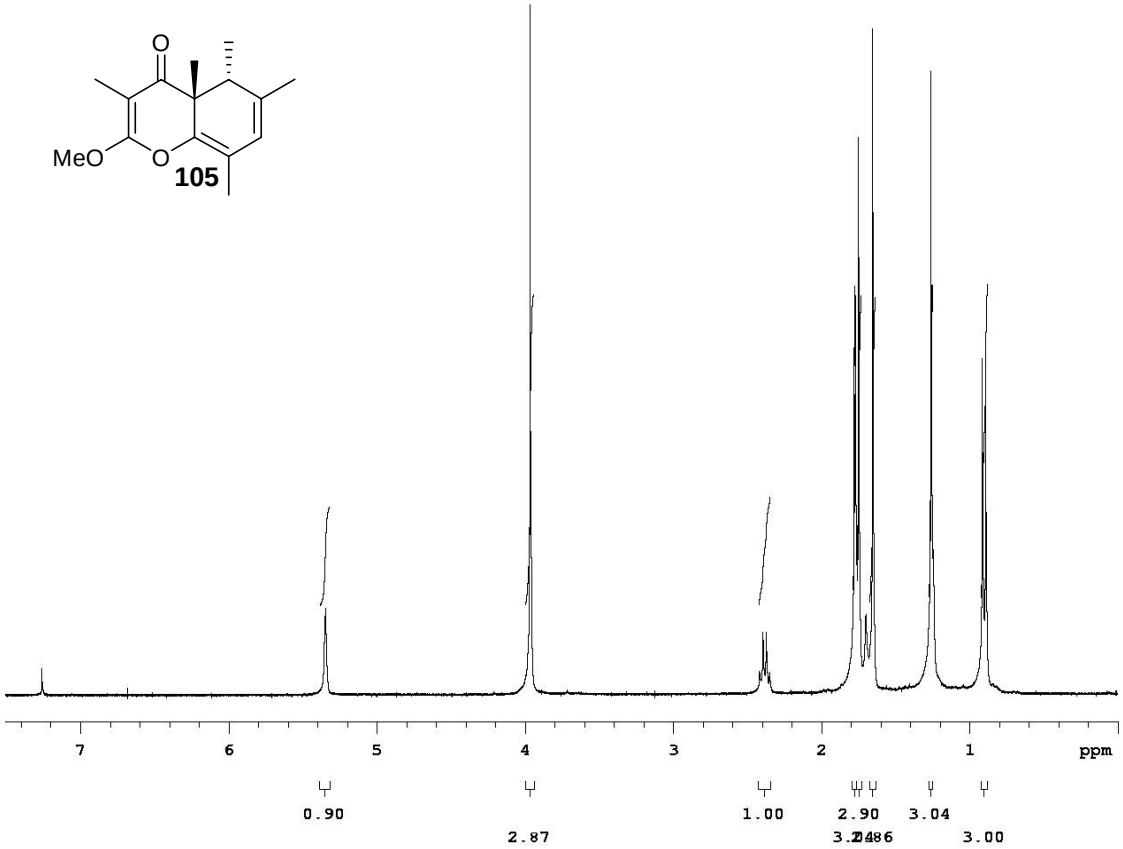


Figure 3.9: *300 MHz ^1H NMR spectrum of* γ-pyrone ***105*** *in $CDCl_3$.*

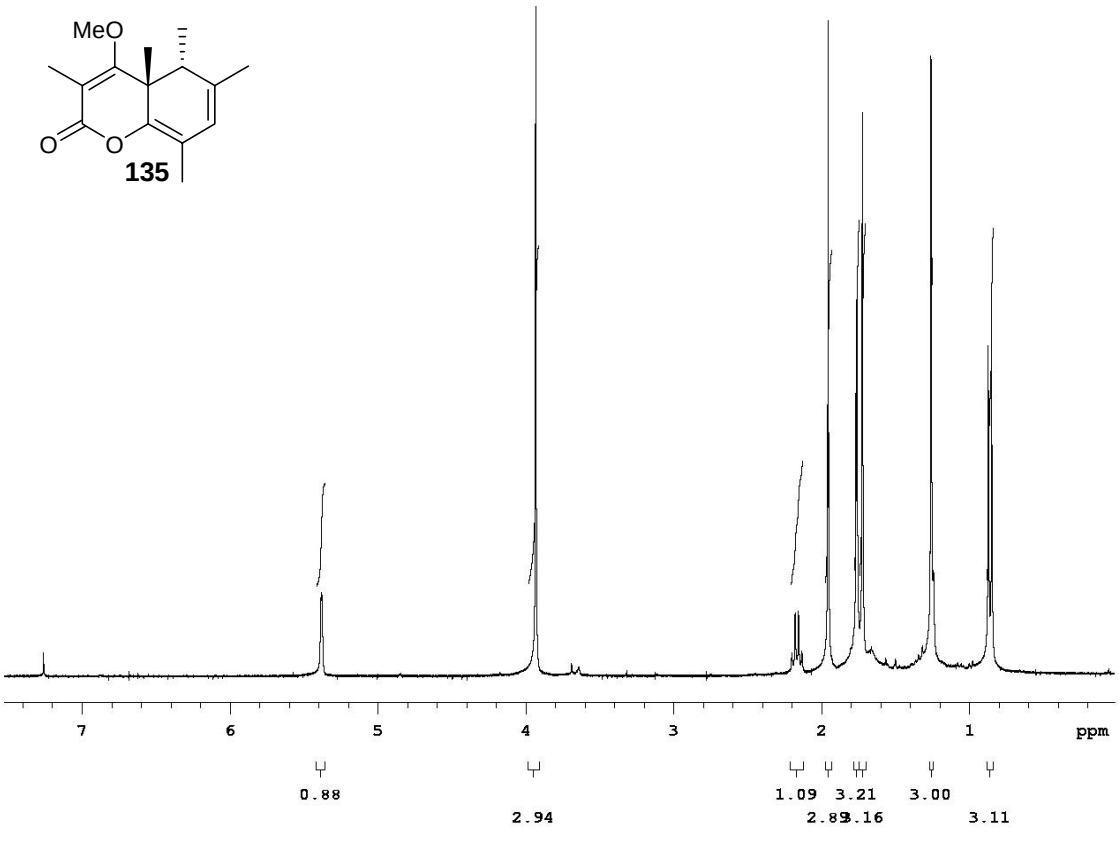


Figure 3.10: *300 MHz ^1H NMR spectrum of α-pyrone* ***135*** *in $CDCl_3$.*

The ^{13}C NMR spectra of γ-pyrone **105** and α-pyrone **135** contain substantial differences but both display the requisite 15 carbon signals (Figures 3.11 and 3.12, respectively). One of the most conspicuous differences is due to the carbonyl carbon. In α-pyrone **135** the carbonyl carbon appears at δ 166, typical of an ester-like carbonyl chemical shift whereas in γ-pyrone **105** the carbonyl carbon appears at δ 194, typical of an enone-like carbonyl chemical shift. The infrared spectra of each pyrone were also markedly different. γ-Pyrone **105** had an absorption at 1642 cm^{-1} corresponding to the carbonyl, while α-pyrone **135** had an absorption at 1724 cm^{-1}. Both had similar electron impact (EI) mass spectra fragmentation patterns, albeit with different intensities, with a molecular ion at *m/z* 248. Accurate mass measurement confirmed the expected molecular formula of $C_{15}H_{20}O_3$ for each isomer.

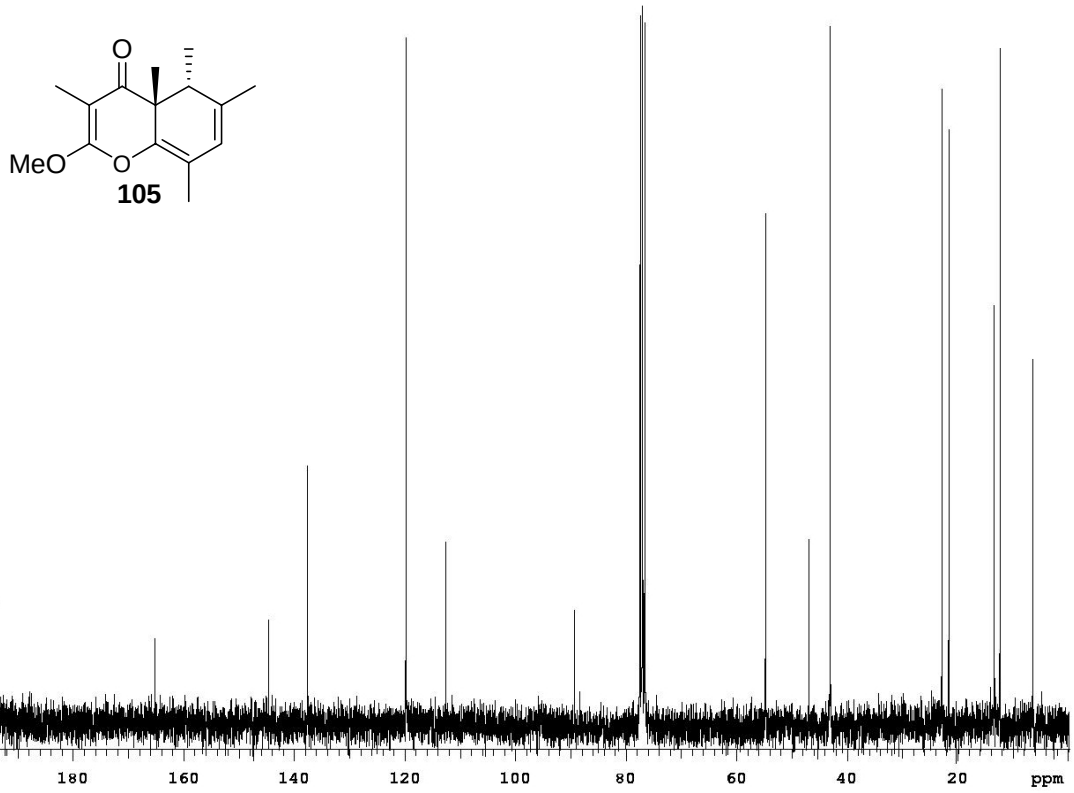


Figure 3.11: *75.5 MHz ^{13}C NMR spectrum of* γ-pyrone ***105*** *in $CDCl_3$.*

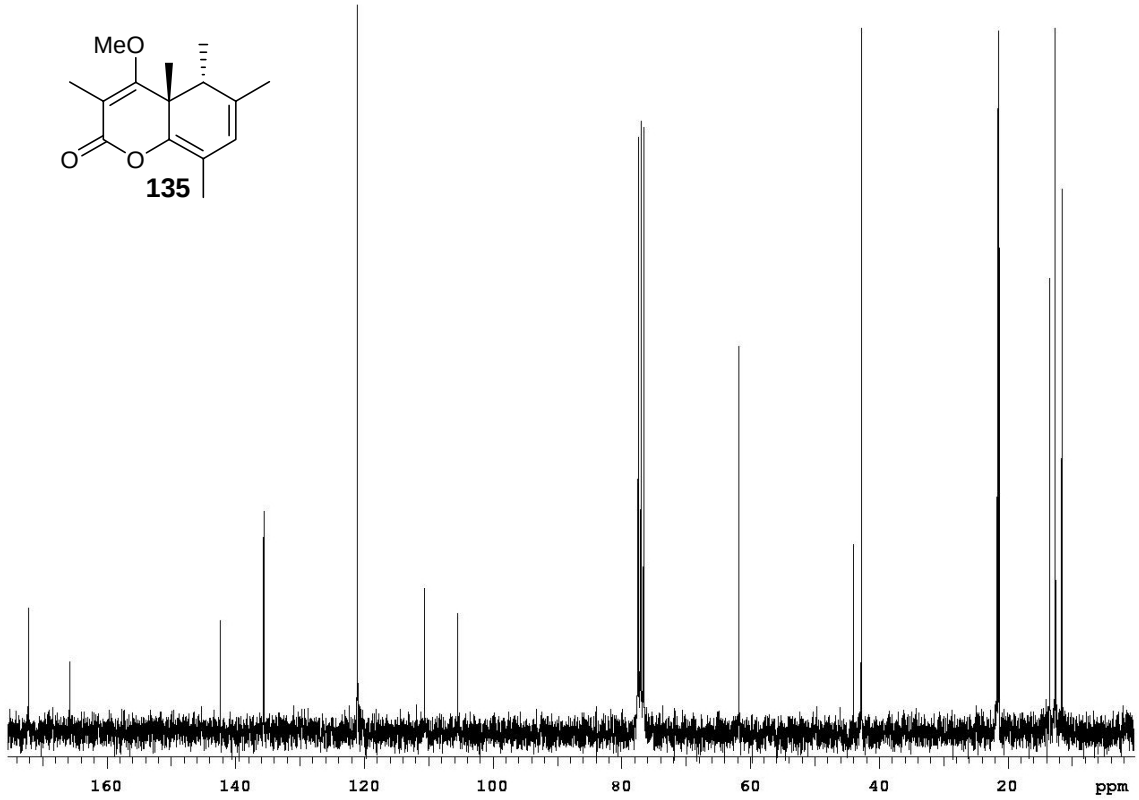


Figure 3.12: *75.5 MHz ^{13}C NMR spectrum of* α-pyrone ***135*** *in* $CDCl_3$.

This chapter has described the development of methodology that allowed for the transformation of acyclic enone **43** (P = PMB) into fused, bicyclic pyrones **105** and **135**. The transformation employed the previously developed novel conjugate addition-cyclisation strategy, utilising a chiral cyclohexenone **117** as a synthon, with the unprecedented pyrone formation being accomplished with Eaton's reagent. The success of the pyrone formation augured well for using such a strategy towards the formation of tridachiahydropyrone (**7**), which is discussed in the next chapter.

Chapter Four

Towards the Total Synthesis of Tridachiahydropyrone

*The synthetic methodology required for the synthesis of the bicyclic ring system found in tridachiahydropyrone (**7**) has been developed and described in the preceding chapters. This chapter outlines the utilisation of this methodology in the synthesis of the structure reported for tridachiahydropyrone (**7**) via an unambiguous route.*

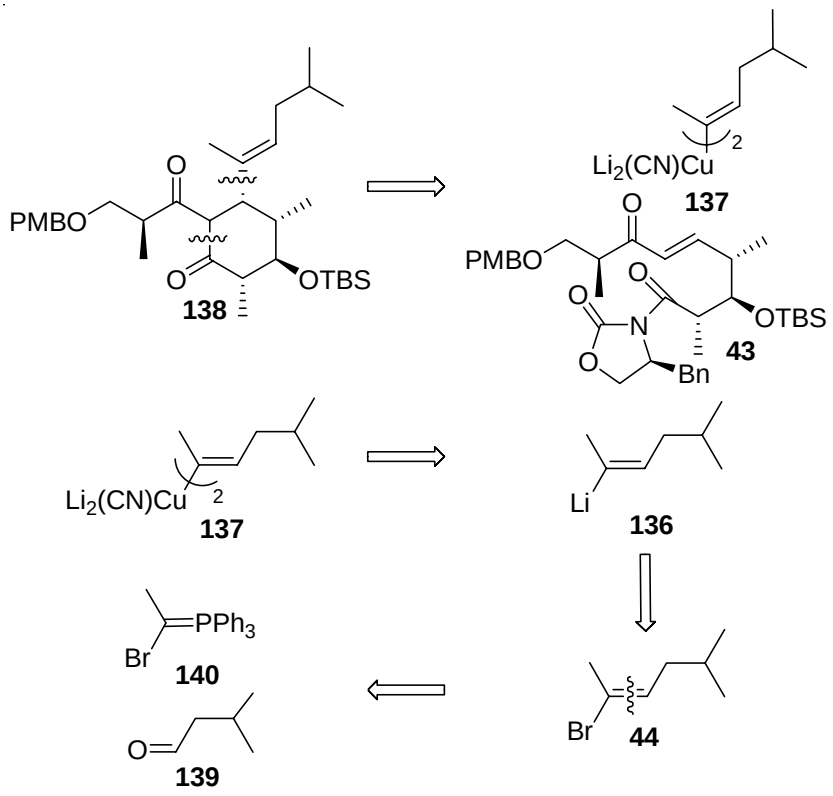
4.1 Application of Methodology Developed to Natural Product Synthesis

With considerable success in forming a model compound with the same bicyclic ring system as found in tridachiahydropyrone (**7**) utilising a cyclohexenone ring as a synthon, attention was turned to applying this knowledge to the actual synthesis of **7**. The fragments required to complete the task were enone **43** (P = PMB), already synthesised on multi-gram scale and discussed in Chapter 3, and the (*E*)-vinyl side-chain**,** which would be obtained as (*E*)-vinyl bromide **44** (Scheme 4.1). Conversion of vinyl bromide **44** to the corresponding organolithium **136** and subsequently to cuprate **137** would allow for the tandem conjugate addition-Dieckmann condensation of the cuprate with enone **43**, affording cyclohexanone **138** (Scheme 4.1). Chemistry discussed in Chapter 3 could then be employed to effect *trans* methylation/elimination and intramolecular cyclisation to form the pyrone ring of bicyclic **7.** The final requirement would be to *O*-methylate the pyrone that is formed, as has been achieved in the model system (Section 3.5.3).

4.1.1 Retrosynthetic Analysis of the Vinyl Side-Chain

To utilise the conjugate addition-cyclisation approach being developed, the appropriate vinyl side-chain needed to be synthesised. Thus, organolithium **136**, added as the corresponding cuprate **137** to enone **43**, can conceivably come from lithiation of vinyl bromide **44**, which could be obtained from the Wittig reaction between commercially available isovaleraldehyde (**139**) and the readily attainable triphenylphosphonium α-bromoalkylide[94] **140** (Scheme 4.1). Problems may arise with the use of such an α-

bromoalkylide with regard to the stereochemical integrity of the resulting bromoalkene, but any difficulties will be addressed in due course.



Scheme 4.1: *Retrosynthesis of the vinyl side-chain to isovaleraldehyde (**139**) and α-bromoalkylide **140**.*

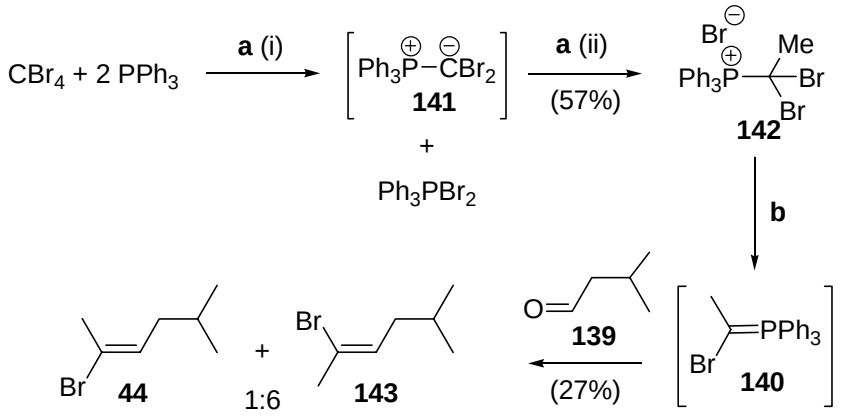
4.2 Synthesis of Vinyl Side-Chain 44

4.2.1 An Attempt Using α-Bromoalkylide 140

To begin, α-bromoalkylide **140** was synthesised by the method of Smithers.[94] A solution of PPh_3 in CH_2Cl_2 was added to carbon tetrabromide (CBr_4) in CH_2Cl_2 at 0°C to afford **141** as an orange solution. Without isolation of **141**, methyl bromide was bubbled into the reaction mixture at 0°C, causing decolouration of the mixture over two hours, to yield crystalline triphenylphosphonium salt **142** (57%, Scheme 4.2). The next step involved forming the ylide *in situ* before reacting it with isovaleraldehyde (**139**) and the method of Smithers[94] was again employed.

Firstly, phosphonium salt **142** was stirred rapidly in THF at room temperature to pulverise the material. Treatment of the pulverised salt with *n*-BuLi at –40°C required careful monitoring to maintain the internal temperature between –45°C and –40°C

(Scheme 4.2). Indeed, without accurate internal temperature monitoring and control by slow addition of the *n*-BuLi, the reaction always failed. Successful ylide formation was indicated by a colour change from deep red to orange. At this stage, isovaleraldehyde (**139**) was added in THF at –60°C and the colour discharged immediately to yellow/brown. The reaction was stirred at –60°C for 10 minutes and slowly warmed to room temperature. This method led to a very low yield (27%) of a 6:1 mixture of *Z*:*E* isomers **143** and **44**, which were inseparable by chromatography on silica. The low yield was due primarily to the volatility of the two compounds. Clearly the *Z*:*E* mixture was the greatest concern of this reaction, because ideally pure (*E*)-isomer **44** was needed. It was apparent that a stereochemically-defined route to vinyl bromide **44** was required.



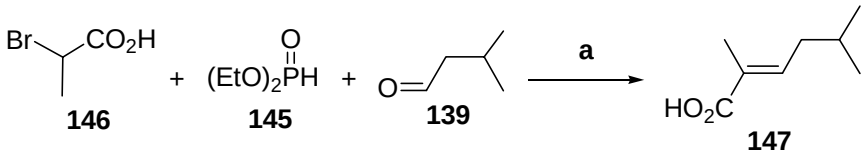
Reagents and conditions: a. i. CH_2Cl_2, 0°C, 15 min; ii. MeBr (excess), 0°C, 2h; **b.** i. THF, rt, stirring, 20 min; ii. *n*-BuLi (1 eq), -40°C, 10 min; iii. Aldehdye **140** (1.5 eq), -60°C, 10 min to rt.

Scheme 4.2: *Utilisation of α-bromoalkylide **140** in the synthesis of a mixture of (Z)-vinyl bromide **143** and (E)-vinyl bromide **44**.*

4.2.2 A Highly Stereoselective Route to (*E*)-Vinyl Bromide 44

For greater stereocontrol in the synthesis of vinyl bromide **44**, the method of Kim *et al*. for the stereoselective formation of (*E*)- and (*Z*)-bromoalkenes[95] was employed. As a starting point, known α,β-unsaturated acid[96] **147** was synthesised by the one pot, phosphite-mediated *in situ* carboxyvinylation method of Brittelli.[97] The reaction involved adding diethyl phosphite (**145**) in dimethoxyethane (DME) to a slurry of NaH in DME at 0°C, followed by 2-bromopropionic acid (**146**) in DME (Scheme 4.3). The mixture was stirred at room temperature until hydrogen evolution ceased and isovaleraldehyde (**139**) in DME was added. Stirring continued at room temperature for

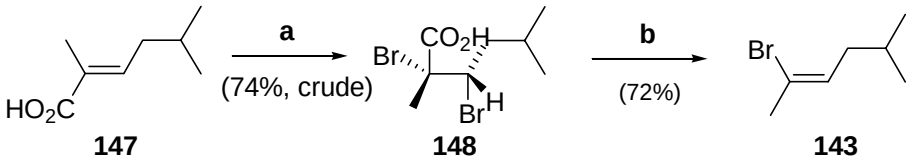
one hour to afford (*E*)-acid **147** (82%, Scheme 4.3). The acid was purified by distillation under reduced pressure and was prepared on a 15-gram scale.



Reagents and conditions: a. i. NaH (3.5 eq), DME, 0°C, 1 h; ii. Phosphite **145** (1 eq), DME, 0°C then acid **146** (1 eq), DME, 0°C to rt, 1 h; iii. Aldehyde **139** (1.2 eq), rt, 2 h; iv. H_3O^+

Scheme 4.3: *Phosphite mediated carboxyvinylation to afford (E)-acid **147**.*

Acid **147** was stereospecifically brominated by treatment with Br_2 in CH_2Cl_2 at –78°C[95] to afford crystalline dibromide **148** (74%, crude, Scheme 4.4). Dibromide **148** was subjected to sodium bicarbonate ($NaHCO_3$) in dimethyl formamide (DMF) at 65°C to effect decarboxylative elimination,[98] yielding (*Z*)-bromide **143** (72%) as a volatile oil, purifiable by reduced pressure distillation. At this point it is worthwhile noting that the stereochemistry of (*Z*)-vinyl bromide **143** is of the opposite configuration to that required for the natural product. Conversion to the corresponding (*E*)-vinyl bromide required further manipulation, but importantly this method allows access to both side-chain configurations.

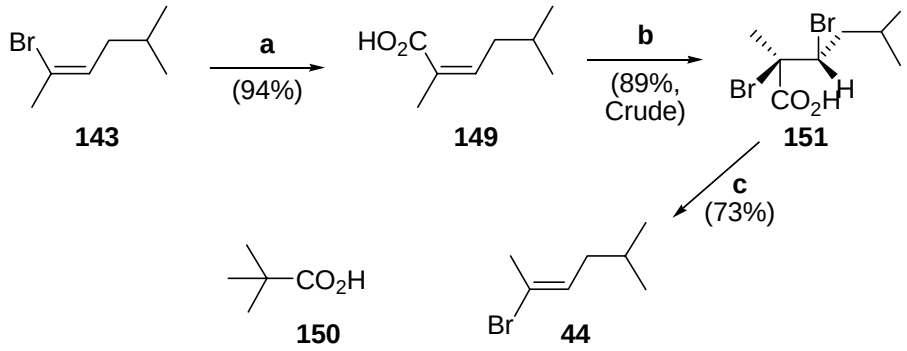


a. Br_2 (1.2 eq), CH_2Cl_2, -78°C, 1h; **b.** $NaHCO_3$, DMF, 65°C, 1 h;

Scheme 4.4: *Stereoselective synthesis of (Z)-vinyl bromide **143**.*

Subsequent carboxylation involved treating bromide **143** with *t*-BuLi in Et_2O at –78°C and, after stirring for 40 minutes, transferring the solution into solid CO_2.[95] Acidification of the mixture furnished (*Z*)-acid **149** (94%), also purifiable by reduced pressure distillation (Scheme 4.5). To avoid substantial quantities of pivalic acid (**150**) contaminant, derived from carboxylating *t*-BuLi itself, the concentration of the organolithium solution had to be determined, even for a new bottle. Therefore, the *t*-

BuLi was standardised by titration[99] prior to use, thus giving a reliable indication of its concentration.



Reagents and conditions: a. i. *t*-BuLi (2 eq), Et_2O, -78°C, 40 min; ii. $CO_{2(s)}$; iii. H_3O^+; **b.** Br_2 (1.2 eq), CH_2Cl_2, -78°C, 1 h; **c.** $NaHCO_3$, DMF, 65°C, 1 h.

Scheme 4.5: *Sequence for the conversion of (Z)-vinyl bromide **143** into* (*E*)*-isomer **44**.*

A repetition of the above bromination/decarboxylation procedure was used to acquire (*E*)-vinyl bromide **44**. Thus, (*Z*)-acid **149** was stereospecifically brominated[95] to give crystalline dibromide **151** (89%, crude, Scheme 4.5) followed by decarboxylative elimination[98] to afford volatile (*E*)-bromide **44** (73%, 27% over 6 steps), again purifiable by reduced pressure distillation. Vinyl bromides **44** and **143** were intriguing in that they had relatively high vapour pressures at room temperature and would evaporate quickly, but had reasonably high boiling points (*ca.* 70°C at 20 mmHg). Regardless, the sequence described above was amenable to multi-gram scale synthesis and from 15 grams of (*E*)-acid **147**, almost 6 grams of (*E*)-bromide **44** were produced.

The ^{1}H NMR spectra of (*Z*)-**143** and (*E*)-**44** were very similar, with the main difference being the chemical shift of the vinyl proton (Figures 4.1 and 4.2, respectively). The vinyl proton appeared as a triplet of quartets (tq) at δ 5.61 (*J* = 6.9, 1.4 Hz) in (*Z*)-**143** and δ 5.86 (*J* = 7.8, 1.4 Hz) in (*E*)-**44**, with the downfield shift in the (*E*)-isomer being due to the vinyl proton being oriented *cis* to the bromine atom. The vinyl methyl protons appear as a multiplet at δ 2.29 (q, *J* = 1.4 Hz) in (*Z*)-**143** and at δ 2.21-2.19 in (*E*)-**44**, while the methylene protons appear as a multiplet, at δ 2.03 (tq, *J* = 6.9, 1.4 Hz) in (*Z*)-**143** and δ 1.92-1.87 in (*E*)-**44**. The downfield shift of the methylene protons in (*Z*)-**143** is due to their being oriented *cis* to the bromine atom. The methine proton of the isopropyl group appears as a nonatet (n, *J* = 6.7 Hz), at δ 1.69 in (*Z*)-**143** and δ 1.65 in

(*E*)-**44**. The methyl protons of the isopropyl group appear as a 6H doublet (J = 6.7 Hz), at δ 0.91 in (*Z*)-**143** and δ 0.90 in (*E*)-**44**.

The splitting pattern observed for the vinyl proton in each spectrum arises from couplings to both the vinyl methyl and methylene protons. The vinyl methyl shows couplings to both the vinyl proton and methylene protons with apparently very similar coupling constants, hence the appearance of the quartet in (*Z*)-**143**. The methine proton of the isopropyl group couples to both the methyl groups and methylene protons, again with very similar coupling constants, so as to appear as nine lines. The infrared spectrum of each compound was very similar, with an absorption at *ca.* 1650 cm^{-1}, consistent with the presence of the double bond. Accurate mass measurements confirmed the expected molecular formula for each isomer as $C_7H_{13}Br$.

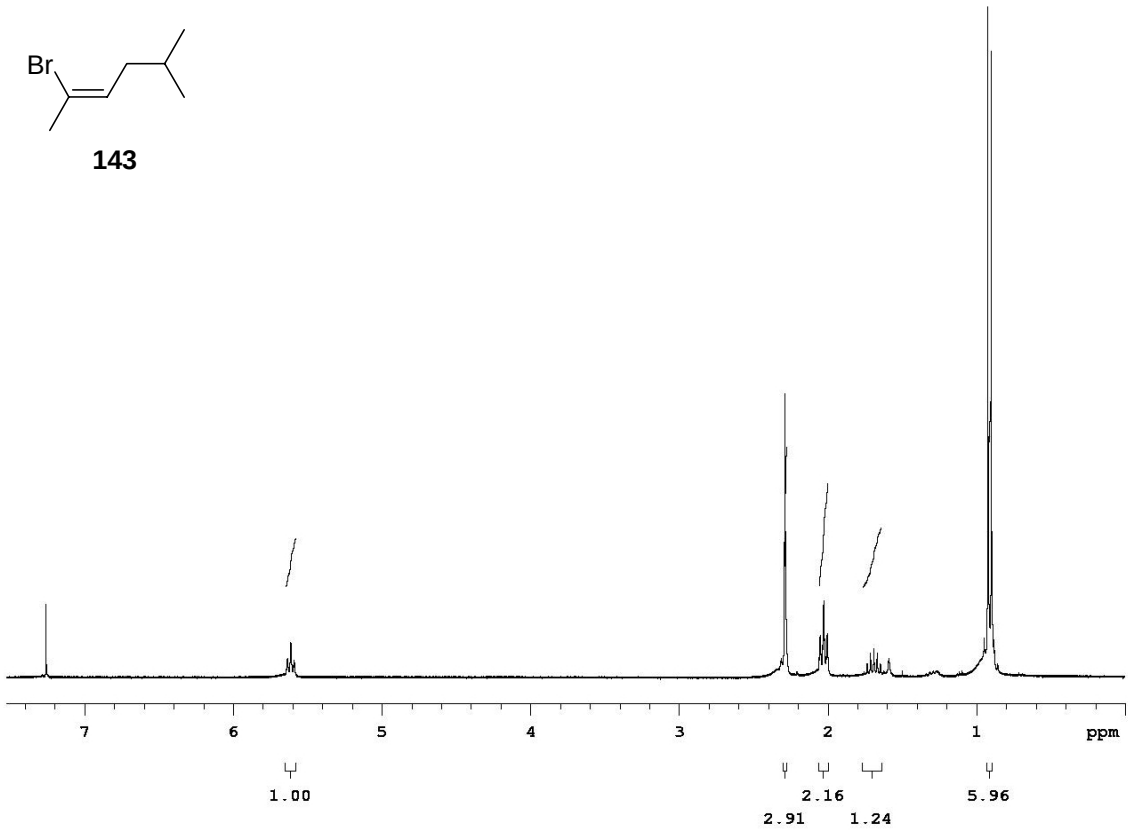


Figure 4.1: *300 MHz ^1H NMR spectrum of (Z)-vinyl bromide **144** in $CDCl_3$.*

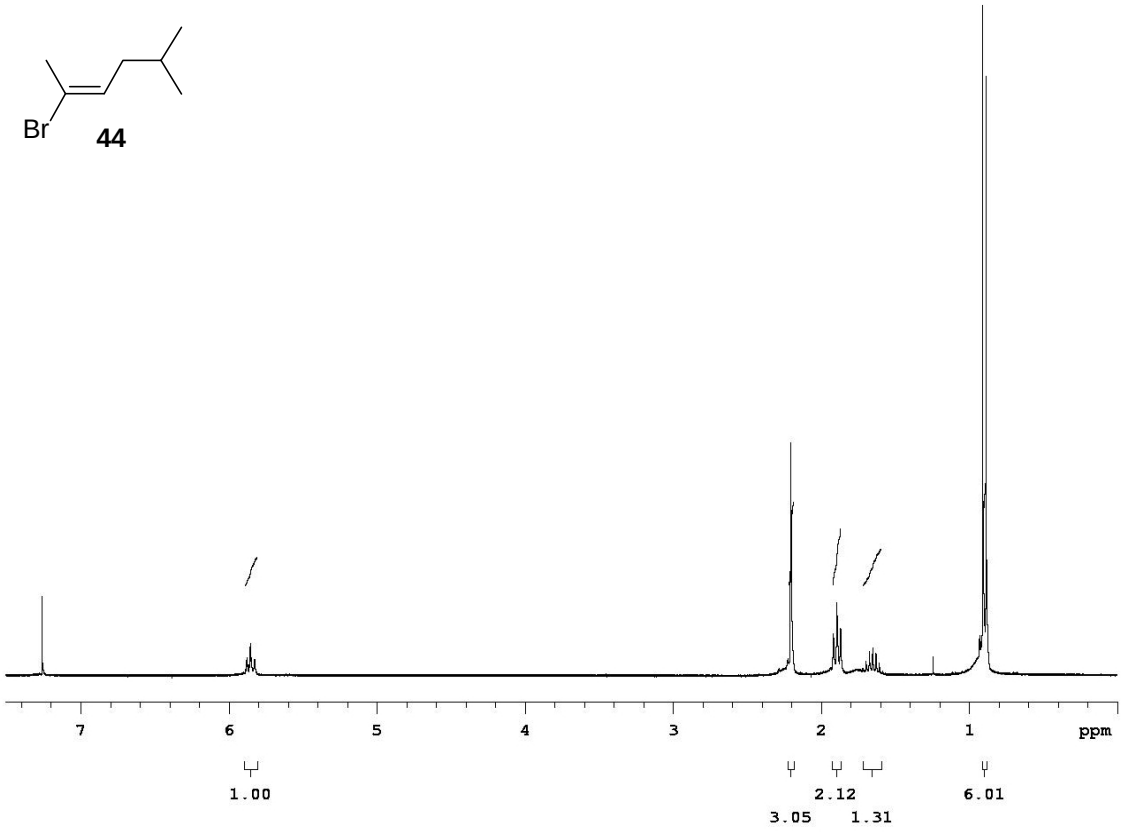


Figure 4.2: *300 MHz ^1H NMR spectrum of (E)-vinyl bromide **44** in $CDCl_3$.*

4.3 Addition Reactions with Vinyl Cuprates and Simple Enone

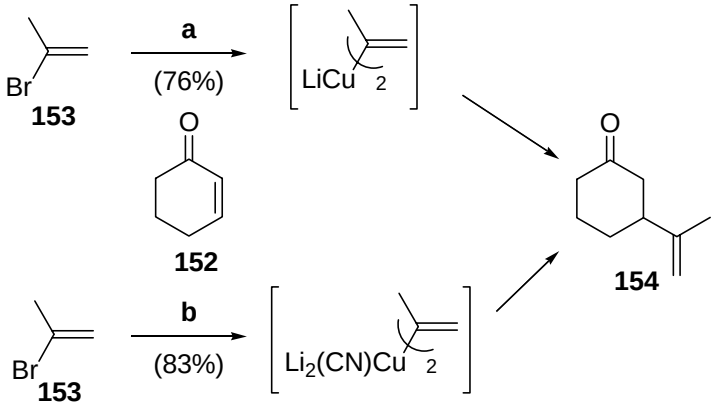
With substantial quantities of (*E)*-vinyl bromide **44** in hand, attention was focused on forming the desired cuprate and effecting tandem conjugate addition-Dieckmann condensation with enone **43**. To simplify proceedings, several factors were first examined. These included the lithium-halogen exchange time and temperature, reaction solvent and temperature, and choice of copper salt, using 2-cyclohexenone (**152**) as the substrate and 2-bromopropene (**153**) as the cuprate precursor. In all cases the stoichiometry of the cuprate formation was two equivalents of organolithium to one equivalent of copper salt, except when the dummy thiophene ligand was used. In this case the stoichiometry was one equivalent each of the organolithium, lithiothiophene and copper salt.

4.3.1 Model Vinyl Cuprate Addition Reactions

The lithium-halogen exchange was straightforward and performed by reacting 2-bromopropene (**153**) with freshly standardised[99] *t*-BuLi in THF at –78°C for 1 hour under nitrogen, resulting in a bright yellow solution. The solution was transferred into a

slurry of CuI in Et_2O and Me_2S at –78°C and the resulting deep orange solution was warmed to –20°C and stirred for 30 minutes to form the cuprate (known as a Gilman cuprate). Addition of 2-cyclohexenone (**152**) neat at –78°C, followed by stirring at –40°C for 30 minutes gave the known addition product[100] **154** in good yield (76%, Scheme 4.6).

Alternatively, the lithium-halogen exchange was effected as above, but the yellow organolithium solution was added to a slurry of CuCN in Et_2O at –78°C and the resulting pale yellow, homogeneous cuprate (known as a higher order (HO) Gilman cuprate) solution was stirred for 30 minutes (Scheme 4.6). Addition of 2-cyclohexenone (**152**) neat at –78°C resulted in an immediate bright yellow colouration and the reaction was warmed slowly to room temperature. This procedure afforded addition product **154** (83%) as before, but the use of CuCN as the salt resulted in a homogeneous solution and less insoluble material after quenching. It did appear that CuCN would be the salt of choice, not only for its reactive properties, but also as it required no special purification procedures and was not hygroscopic, unlike CuI.[101]



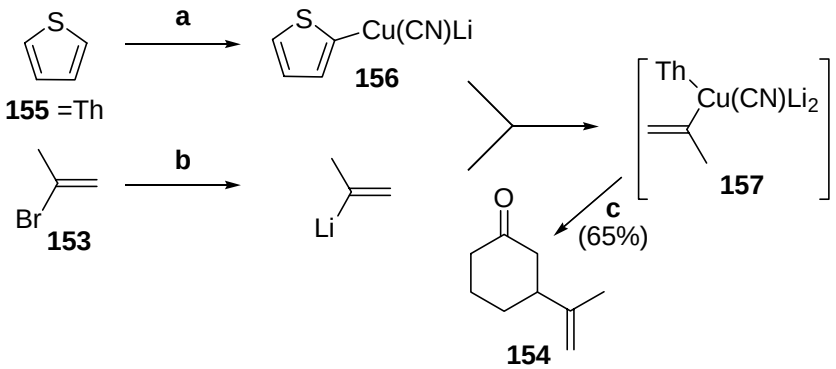
Reagents and conditions: a. i. *t*-BuLi (2 eq), THF, -78°C, 1 h; ii. CuI (0.5 eq), Et_2O, Me_2S, -78°C to -20°C, 30 min; iii. Enone **152** (0.25 eq), -78°C to -40°C, 30 min; **b.** i. *t*-BuLi (2 eq), THF, -78°C, 1 h; ii. CuCN (0.5 eq), Et_2O, -78°C, 30 min; iii. Enone **152** (0.25 eq), -78°C to rt.

Scheme 4.6: *Formation of cuprates from 2-bromopropene (**153**) and reaction with 2-cyclohexenone (**152**).*

With acceptable results using the divinyl (HO Gilman) cuprate, the use of a Lipshutz[102] (mixed HO Gilman) cuprate was explored. The advantage of a Lipshutz cuprate was that only one equivalent of organolithium was required. The other copper ligand, which is non-transferable in cuprate reactions,[102] can be derived from thiophene (**155**), for

instance (Scheme 4.7). Thus, if the organolithium species is difficult to obtain or highly valuable, less is required when employing such a Lipshutz cuprate. In fact, lithium 2-thienylcyanocuprate (**156**), or 'cuprate in a bottle', was commercially available as a THF solution, such is its stability. In practice, more reliable results were obtained from forming the lower order (LO) cuprate **156** when required.

To this end, mixed higher order cuprate **157** was formed by firstly making the LO cuprate **156** (Scheme 4.7). Thiophene (**155**) in THF was treated with *n*-BuLi at –78°C and the mixture was stirred for 15 minutes at –78°C and 30 minutes at –20°C, before being transferred into a slurry of CuCN in THF at –78°C. Warming the reaction mixture to –40°C afforded a brown, homogeneous solution of LO cuprate **156**. This solution was reserved at –40°C while the following lithiation was performed. Lithium-halogen exchange was effected on 2-bromopropene (**153**) as previously described and the yellow solution was added to the LO cuprate **156** at –78°C and stirred at –40°C for 30 minutes, thereby forming a homogeneous tan solution of mixed HO cuprate **157**. Addition of 2-cyclohexenone (**152**) neat at –78°C resulted in a yellow solution, which was stirred at –78°C for 10 minutes and slowly warmed to 0°C, affording **154** in modest yield (65%, Scheme 4.7).



Reagents and conditions: a. i. *n*-BuLi (1 eq), THF, -78°C, 15 min to -20°C, 30 min; ii. CuCN (1 eq), THF, -78°C to -40°C; **b.** i. *t*-BuLi (2 eq), THF, -78°C, 30 min; ii. Added to **156**, -78°C to -40°C, 30 min; **c.** Enone **152** (0.5 eq), -78°C, 10 min to 0°C.

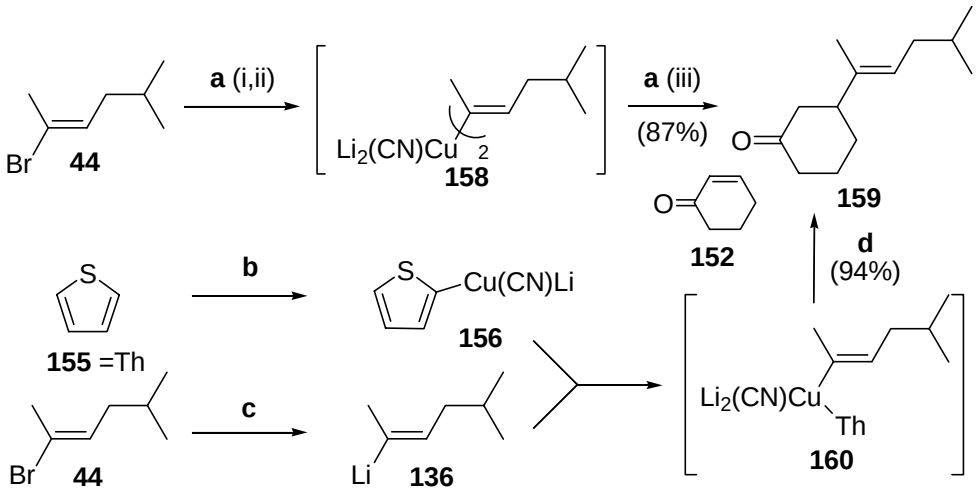
Scheme 4.7: *Formation of mixed HO cuprate from 2-bromopropene (**153**) and reaction with 2-cyclohexenone (**152**).*

4.3.2 Cuprates Derived from (*E*)-Vinyl Bromide 44

With some practical experience for the formation of several types of cuprate now available, the reaction of the cuprate derived from vinyl bromide **44** was attempted with

2-cyclohexenone (**152**). As was mentioned, CuCN was the copper salt of choice and this was employed in both HO Gilman and Lipshutz cuprate formation. Firstly, (*E*)-vinyl bromide **44** was treated with *t*-BuLi in THF at –78°C as before (Scheme 4.8). The resulting bright yellow solution was transferred into a slurry of CuCN in Et_2O at –78°C and stirred for 30 minutes, affording a pale yellow, homogeneous solution of cuprate **158**. Addition of 2-cyclohexenone (**152**) neat at –78°C caused a bright orange colouration, and the mixture was slowly warmed to room temperature to give addition product **159** in good yield (87%, Scheme 4.8).

Mixed HO cuprate **160** was formed in the same manner as previously described for cuprate **157**, by first making the LO cuprate **156** (Scheme 4.8). Separately, lithium-halogen exchange was performed on (*E*)-vinyl bromide **44** as above and the derived solution of organolithium **136** was added to the LO cuprate solution at –78°C, followed by warming to –40°C and stirring for 30 minutes. Once again, 2-cyclohexenone (**152**) was added neat at –78°C and the olive green solution was stirred at –78°C for 30 minutes and warmed slowly to 0°C, yielding **159** in excellent yield (94%, Scheme 4.8).



Reagents and conditions: a. i. *t*-BuLi (2 eq), THF, -78°C, 1 h; ii. CuCN (0.5 eq), Et_2O, -78°C, 30 min; iii. Enone **153** (0.25 eq), -78°C to rt; **b.** i. *n*-BuLi (1 eq), THF, -78°C, 15 min to -20°C, 30 min; ii. CuCN (1 eq), THF, -78°C to -40°C; **c.** i. *t*-BuLi (2 eq), THF, -78°C, 30 min; ii. Added to **156**, -78°C to -40°C, 30 min; **d.** Enone **152** (0.5 eq), -78°C, 30 min to 0°C.

Scheme 4.8: *Formation of cuprates from (E)-vinyl bromide **44** and reaction with 2-cyclohexenone (**152**).*

Several important observations were gleaned from the reactions with 2-cyclohexenone (**152**). Successful reactions always involved a bright yellow solution after lithium-halogen exchange of vinyl bromide **44** with *t*-BuLi in THF, and a homogeneous, pale

yellow solution of cuprate **158** or homogeneous tan solution for mixed cuprate **160**. Subsequently, addition of 2-cyclohexenone (**152**) resulted in an obvious change of colour of the reaction mixture to bright yellow/orange or olive green. These observations were excellent indicators for the progress of each stage of the reaction and would become invaluable when it came to the synthesis of natural product **7**.

4.4 Addition-Cyclisation Route to Synthetic Target

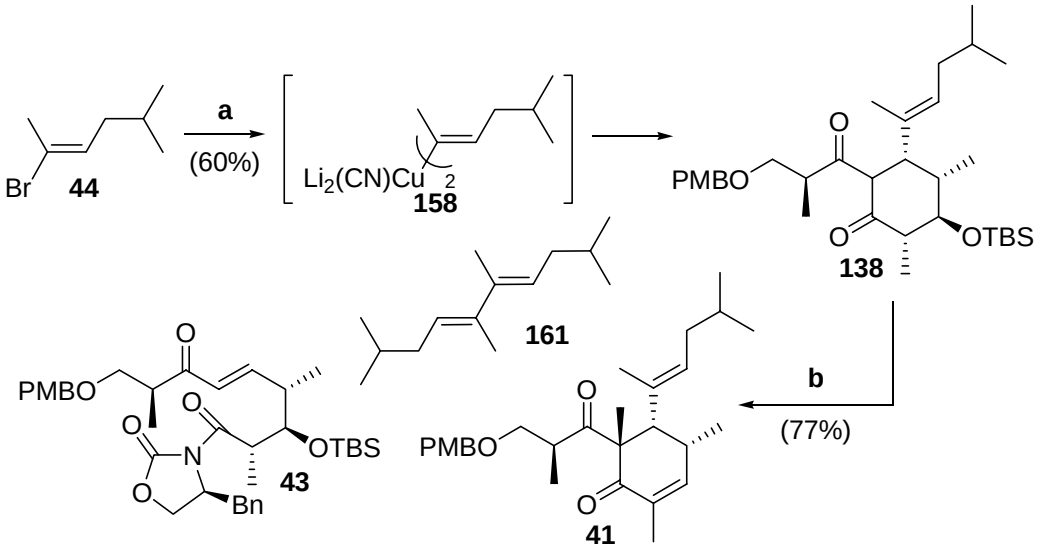
4.4.1 Tandem Conjugate Addition-Cyclisation Step

With the conditions apparently optimised for successful conjugate addition reactions with (*E*)-vinyl bromide **44**, the next task was to effect a similar conjugate addition reaction using enone **43** as the substrate, with subsequent cyclisation to natural product cyclohexanone intermediate **138**. To begin, cuprate **158** was formed in exactly the same manner as above and reacted with enone **43**. This reaction proved to be more troublesome than expected, with problems arising from the thermal instability of the organolithium solution derived from bromide **44,** leading to unreproducible results. The problem was overcome by lowering the temperature of the lithium-halogen exchange reaction to –100°C and stirring for only 15 minutes under an argon atmosphere (Scheme 4.9). The apparent difference in stability of the organolithium when compared to reactions involving 2-cyclohexenone (**152**) was unknown, but concentration may have an effect.

In order to maintain the required low temperature during transferral *via* cannula of the bright yellow organolithium solution, the cannula was pre-cooled to –78°C. Quickly transferring the organolithium solution through the pre-cooled cannula was sufficient to minimise decomposition. In fact, if the solution emerged from the cannula pale yellow or colourless, as it did on occasions when the transfer was not *via* a pre-cooled cannula, the subsequent cuprate formation did not occur as reliably and reaction with enone **43** afforded very little product **138**.

Upon successful transferral of the bright yellow organolithium solution into the CuCN/Et_2O slurry at –78°C, the mixture was warmed to –50°C and stirred for 15 minutes, giving a pale yellow, homogeneous solution of cuprate **158** (Scheme 4.9). Addition of enone **43** at –50°C resulted in an immediate bright yellow colouration of the solution, and stirring at –50°C for 90 minutes and 0°C for 90 minutes afforded

cyclohexanone **138** (60%, Scheme 4.9) as a mixture of *keto* and *enol* tautomers. The presence of the *enol* OH proton at δ 16.76 in the ^{1}H NMR spectrum of the crude material was once again evidence of successful cyclisation.



Reagents and conditions: a. i. *t*-BuLi (2 eq), THF, -100°C, 15 min; ii. CuCN (0.5 eq), Et_2O, -78°C to -50°C, 15 min; iii. Enone **43** (0.25 eq), Et_2O, -50°C, 90 min to 0°C, 90 min; **b.** i. NaH (1.3 eq), THF, rt, 10 min; ii. MeI (10 eq), rt, 16 h.

Scheme 4.9: *Tandem conjugate addition-cyclisation reaction of cuprate **158** with enone **43** and subsequent trans methylation to afford cyclohexenone **41**.*

Extensive monitoring of the reaction by tlc indicated that at –50°C the addition was occurring, but the subsequent cyclisation was quite slow. Hence, there was a need to warm the reaction to 0°C, but only after addition was judged to be complete by tlc analysis. The reaction could not be stirred at 0°C for the duration because of the instability of the cuprate, which appeared stable up to about –40°C. A small amount of dimer **161** (*ca*. 20 milligrams) was also obtained in these reactions, presumably due to some organolithium reacting with the precursor vinyl bromide. Inexplicably, the use of Lipshutz cuprate **160** failed to yield any desired cyclohexanone **138.** This was not a major concern, however, because access to large quantities of vinyl bromide **44** was relatively facile.

4.4.2 *Trans* Methylation and Functional Group Manipulation

The next step was to *trans* methylate cyclohexanone **138** and this was accomplished in the usual manner with NaH and MeI in THF. As has been the case, methylation occurred with β-elimination of the OTBS group to afford cyclohexenone **41** (77%,

Scheme 4.9), with the stereochemistry of the methylation confirmed by NOE experiments (Figure 4.3). Unlike the case with cyclohexanone **116** and the poor *trans* selectivity observed (Section 3.4.2), this methylation was highly selective for the *trans* product **41**, presumably due to the larger steric bulk of the side-chain.

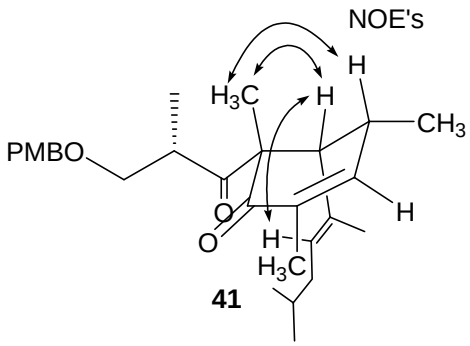


Figure 4.3: *NOE correlations (indicated by arrows) observed for cyclohexenone **41**.*

The ^{1}H NMR spectrum of cyclohexenone **41** has the diagnostic vinyl proton of the α,β-unsaturated carbonyl functionality, which appears as a singlet at δ 6.32 (Figure 4.4). The corresponding vinyl methyl protons α to the carbonyl appear as a multiplet at δ 1.81-1.79. The diastereotopic oxymethylene protons appear as multiplets at δ 3.37 (dd, *J* = 9.0, 4.2 Hz) and δ 3.27 (app t, *J* = 9.0 Hz) and show reciprocal coupling to each other and to the methyl methine proton multiplet at δ 3.19-3.09. This methine in turn displays coupling to the protons of the methyl doublet at δ 1.26 (*J* = 6.6 Hz). The two allylic methine protons show reciprocal coupling to each other and appear as multiplets at δ 3.01-2.90 and δ 2.64 (d, *J* = 6.0Hz), with the former coupling to the protons of the methyl doublet at δ 1.01 (*J* = 7.5 Hz) and to the vinyl proton at δ 6.32. The side-chain vinyl proton appears as a triplet at δ 5.09 (*J* = 7.1 Hz) while the corresponding vinyl methyl protons appear as a singlet at δ 1.37. The side-chain methylene protons appear together as a multiplet at δ 1.75-1.60 and show coupling to the vinyl proton at δ 5.09 and to the isopropyl methine proton multiplet at δ 1.56-1.45. The isopropyl methine proton in turn shows reciprocal coupling to the isopropyl methyl protons which appear as an apparent 6H triplet at δ 0.79 (*J* = 6.6 Hz). The quaternary methyl protons appear as a singlet at δ 1.43 while the remaining resonances at δ 7.20 (2H), δ 6.83 (2H), δ 4.36 (2H) and δ 3.76 (3H) are due to the PMB protecting group The infrared spectrum displayed absorptions at 1719 and 1695 cm^{-1}, consistent with the presence of two carbonyl groups. An accurate mass measurement confirmed the expected molecular formula of $C_{28}H_{40}O_4$.

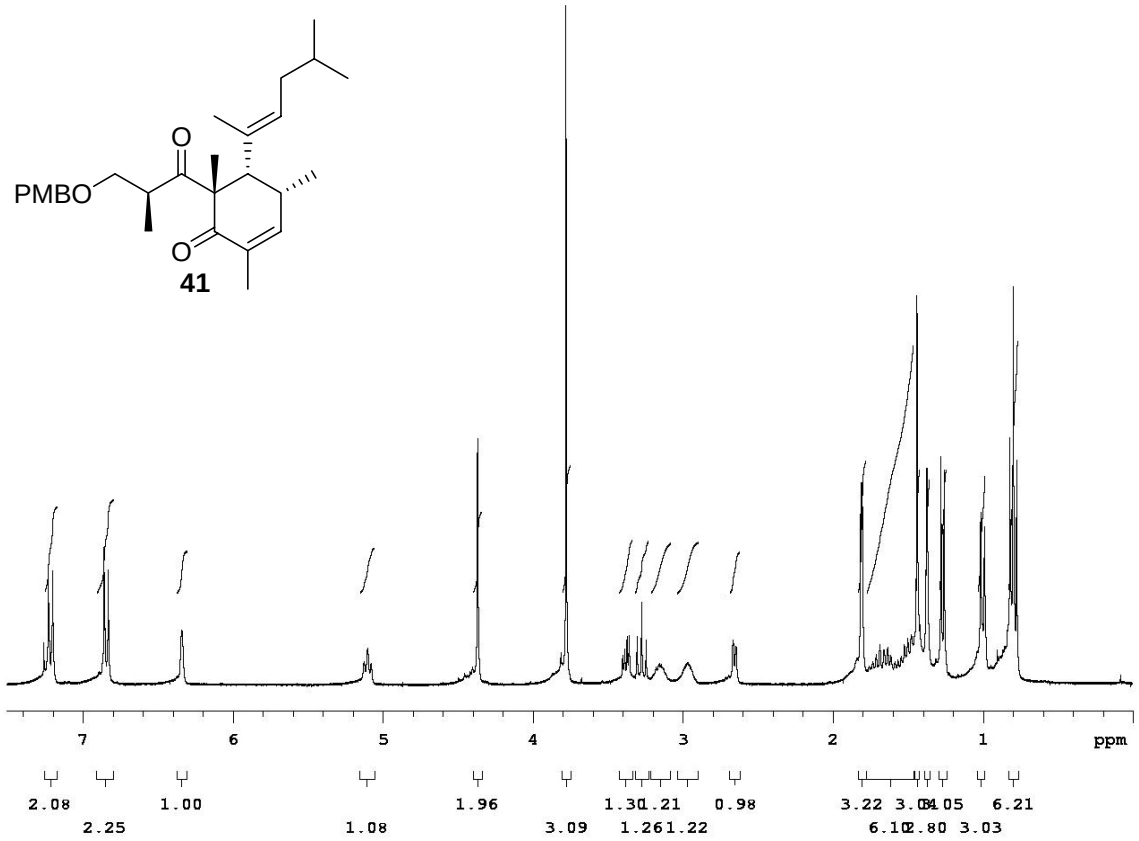
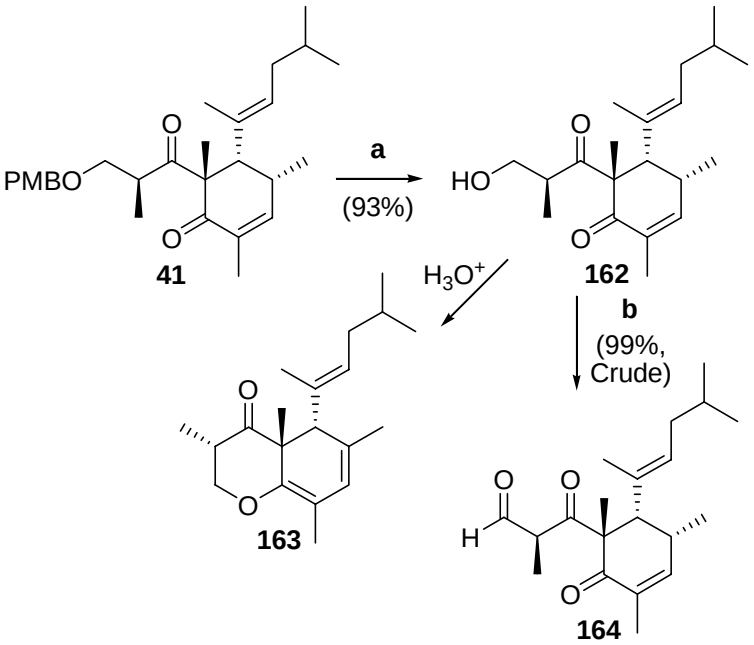


Figure 4.4: *300 MHz ^{1}H NMR spectrum of cyclohexenone **41** in $CDCl_3$.*

Removal of the PMB protecting group was accomplished in the usual manner with DDQ in CH_2Cl_2/pH 7 buffer at 0°C[74] with stirring for 4 hours to afford crystalline primary alcohol **162** (93%, Scheme 4.10). Although crystals of alcohol **162** were small and weakly diffracting, a single crystal X-ray structure determination$^{\phi}$ confirmed the structure and relative stereochemistry (Figure 4.5). Alcohol **162** had a tendency to cyclise to bicyclic pyrone **163** in $CDCl_3$, but as before with pyrone **130** (Section 3.5.1), this has no synthetic utility in the current approach to **7**. Dess-Martin oxidation[65] of alcohol **162** in CH_2Cl_2 at room temperature with stirring for 90 minutes afforded aldehyde **164** (*ca.* 100%, crude) as a crystalline solid with few impurities, so the aldehyde was used crude for the following oxidation. There was no detection of bicyclic **163** and no apparent epimerisation of **164** in the ^{1}H NMR spectrum of the crude material, such was the mildness of the Dess-Martin reagent.

$^{\phi}$ CIF files containing X-ray crystallographic data are contained on the compact disc found inside the back cover of this thesis.



Reagents and conditions: a. DDQ (1.2 eq), CH_2Cl_2, pH 7 buffer, 0°C, 4 h;
b. Dess-Martin periodinane (1.5 eq), CH_2Cl_2, rt, 1.5 h.

Scheme 4.10: *Functional group manipulation of cyclohexenone **41** to afford aldehyde **164**.*

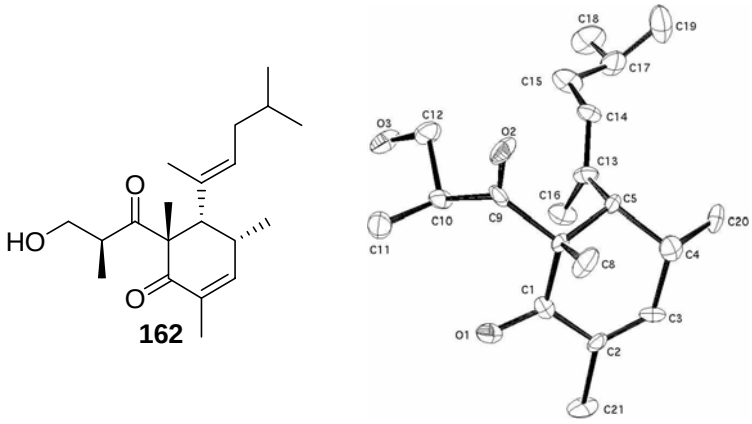
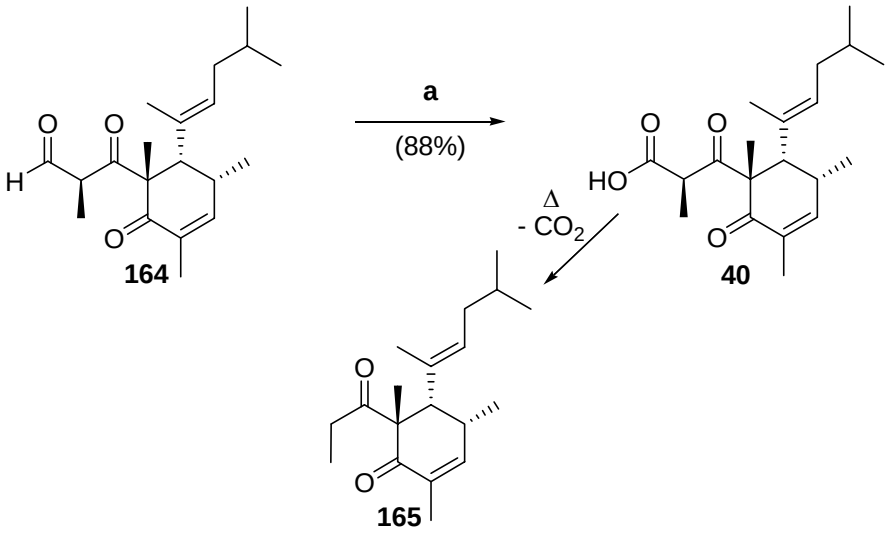


Figure 4.5: *Single crystal X-ray structure of alcohol **162**.*

Oxidation of aldehyde **164** using $NaClO_2$ and NaH_2PO_4 in t-BuOH/H_2O and Me_2C=CHMe[86] was performed as usual but with an altered product isolation,[103] which suppressed epimerisation of the tertiary stereocentre between the two carbonyls. This afforded diastereomerically pure acid **40** in good yield (88%, Scheme 4.9). The altered product isolation involved acidifying the reaction mixture to pH 3-4 with trifluoroacetic acid (TFA), instead of the usual HCl, prior to extraction with CH_2Cl_2. Acid **40** was prone to decarboxylation at room temperature over several days, yielding compound **165**. This was a common observation for these types of β-ketoacid.



Reagents and conditions: a. $NaClO_2$ (5 eq), NaH_2PO_4 (3.8 eq), *t*-BuOH, H_2O, Me_2C=CHMe, rt, 1.5 h.

Scheme 4.11: *Oxidation of aldehyde **164** to acid **40**, and decarboxylation product **165**.*

The ^{1}H NMR spectrum of acid **40** displays the appropriate resonances (Figure 4.6). The acidic proton appears as a broad singlet at ~ δ 9 while the vinyl proton of the ring appears as a singlet at δ 6.44. The corresponding ring vinyl methyl protons appear as a multiplet at δ 1.83-1.81 while the allylic methine protons appear as multiplets at δ 3.06-2.97 and δ 2.68 (d, *J* = 6.0 Hz) and show coupling to each other. The methine at δ 3.06-2.97 shows reciprocal coupling to the protons of the methyl doublet at δ 1.03 (*J* = 7.5 Hz) and to the ring vinyl proton at δ 6.44. The methyl methine proton α to the acid moiety appears as a multiplet at δ 3.85-3.73 and shows coupling to the methyl proton doublet at δ 1.55 (*J* = 6.9 Hz) while the quaternary methyl protons appear as a singlet at δ 1.46. The side-chain vinyl proton appears as a triplet at δ 5.13 (*J* = 6.9 Hz) and the corresponding vinyl methyl appears as a singlet at δ 1.42. The methylene protons of the side-chain appear as a multiplet at δ 1.82-1.69 and show reciprocal coupling to the vinyl proton at δ 5.13 and to the isopropyl methine proton multiplet at δ 1.50-1.45. The methine proton also couples to the isopropyl methyl protons which appear as a 6H doublet at δ 0.78 (*J* = 6.6 Hz). The infrared spectrum displays a broad absorption at 3270 cm^{-1} due to the OH stretch and absorptions at 1733, 1720 and 1702 cm^{-1}, consistent with the presence of three carbonyl groups. An accurate mass measurement could not be obtained for the parent acid but instead confirmed the expected molecular formula of the decarboxylated material **165** as $C_{19}H_{30}O_2$.

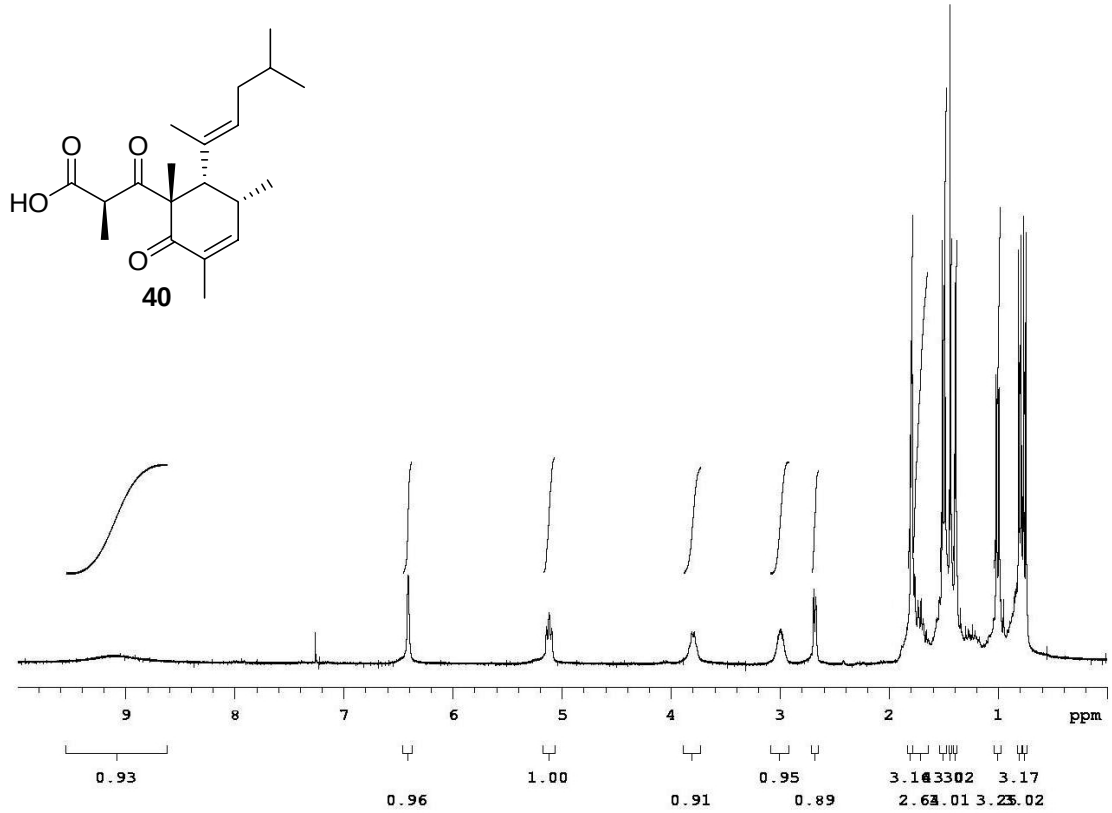
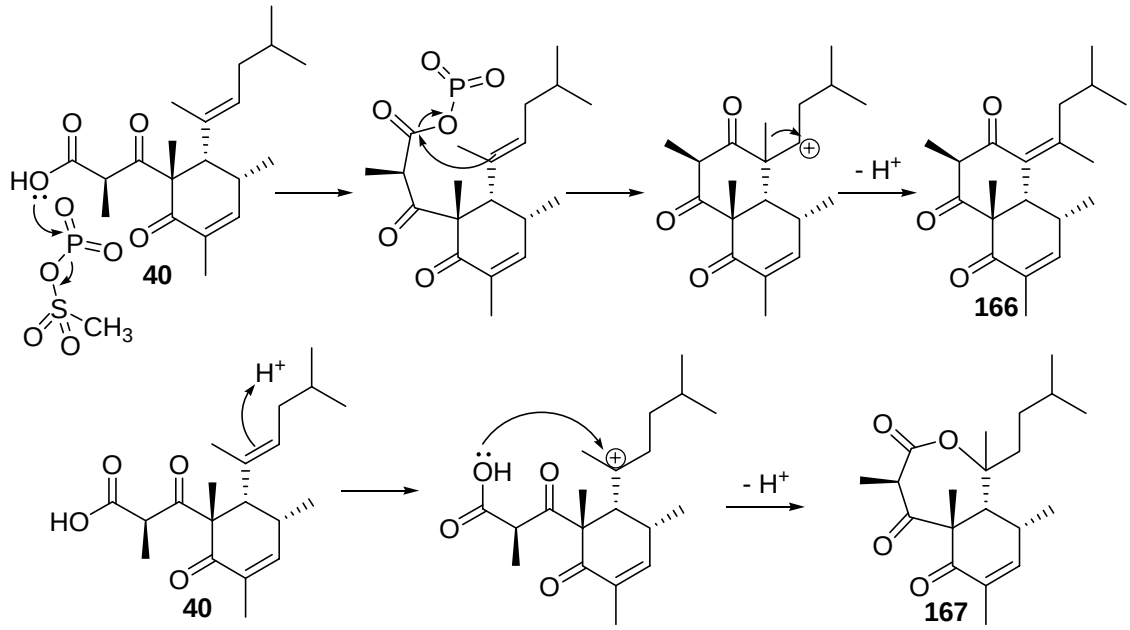


Figure 4.6: *300 MHz ^1H NMR spectrum of acid **40** in $CDCl_3$.*

4.5 Intramolecular Cyclisation to Afford a Bicyclic Pyrone

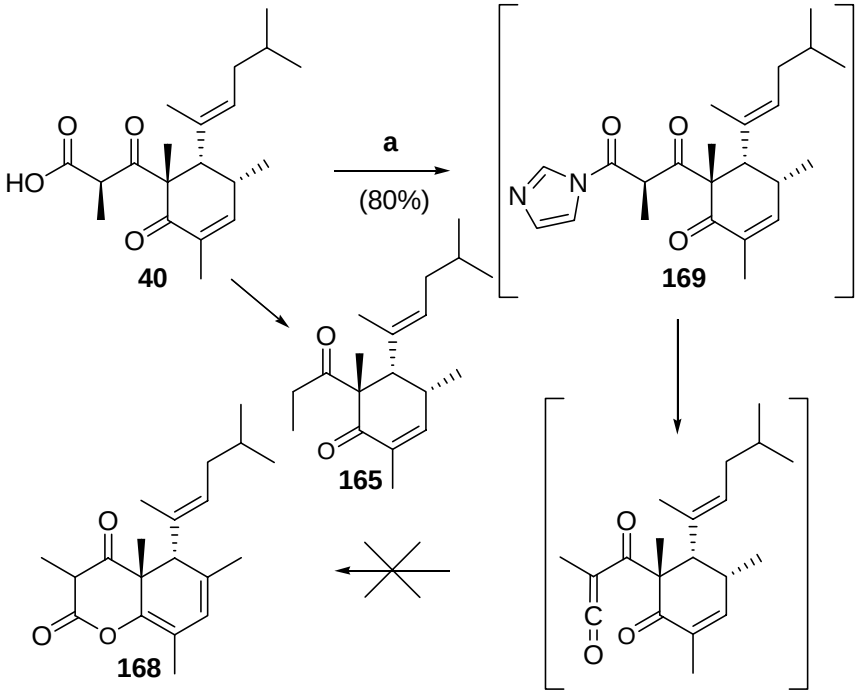
4.5.1 Initial Attempts to Cyclise Acid 40

Cyclisation of acid **40** with Eaton's reagent[91] as described in Chapter 3 (Section 3.5.3) did not proceed as expected. While the two main products of the reaction were not purified or characterised, the absence of the side-chain vinyl proton at δ 5.13, along with the presence of the ring vinyl proton at δ 6.44 in the ^{1}H NMR spectrum of the crude material indicated a different cyclisation mode. Analysis of the reaction mixture by GC/MS indicated two main peaks in the GC trace; one with a molecular ion at *m/z* 334 (isomeric with parent acid) and the other at *m/z* 316 (isomeric with the desired product). Plausible products that explain the above observations are shown in Scheme 4.12. It is postulated that attack of the alkene onto the mixed anhydride intermediate (proposed in Section 3.5.3), followed by a methyl migration and loss of a proton gives **166** (MW = 316). Alternatively, protonation of the alkene, followed by cyclisation of the acid onto the cation formed and loss of a proton affords **167** (MW = 334). In any case, it was evident that the acidic conditions were not compatible with the presence of the vinyl side-chain in this system.



Scheme 4.12: *Attempted Eaton's reagent cyclisation of acid **40**, forming postulated bicyclic products **166** and **167**.*

Another cyclisation attempt to form pyrone **168** involved *in situ* ketene formation *via* imidazolide **169** (Scheme 4.13). Although ketene formation was previously unsuccessful, leading to decarboxylation of acid **40** (Section 3.5.2), options for cyclisation were extremely limited. Treatment of acid **40** in THF with 1,1'-carbonyldiimidazole (CDI) at room temperature, followed by LiHMDS at –78°C resulted in the formation of a yellow solution, which was stirred at –78°C for one hour. The reaction was then stirred for 21 hours at room temperature, whereby the colour slowly discharged, to give the sole product **165** (80%, Scheme 4.13), which arose from decarboxylation of the parent acid **40**. Once again, an activated acid derivative in the presence of base was obviously not conducive to cyclisation, so attempts to effect cyclisation *via* a ketene intermediate were not the answer.



Reagents and conditions: a. i. CDI (1 eq), THF, rt, 20 min; ii. LiHMDS (2 eq), -78°C, 1 h to rt, 21 h.

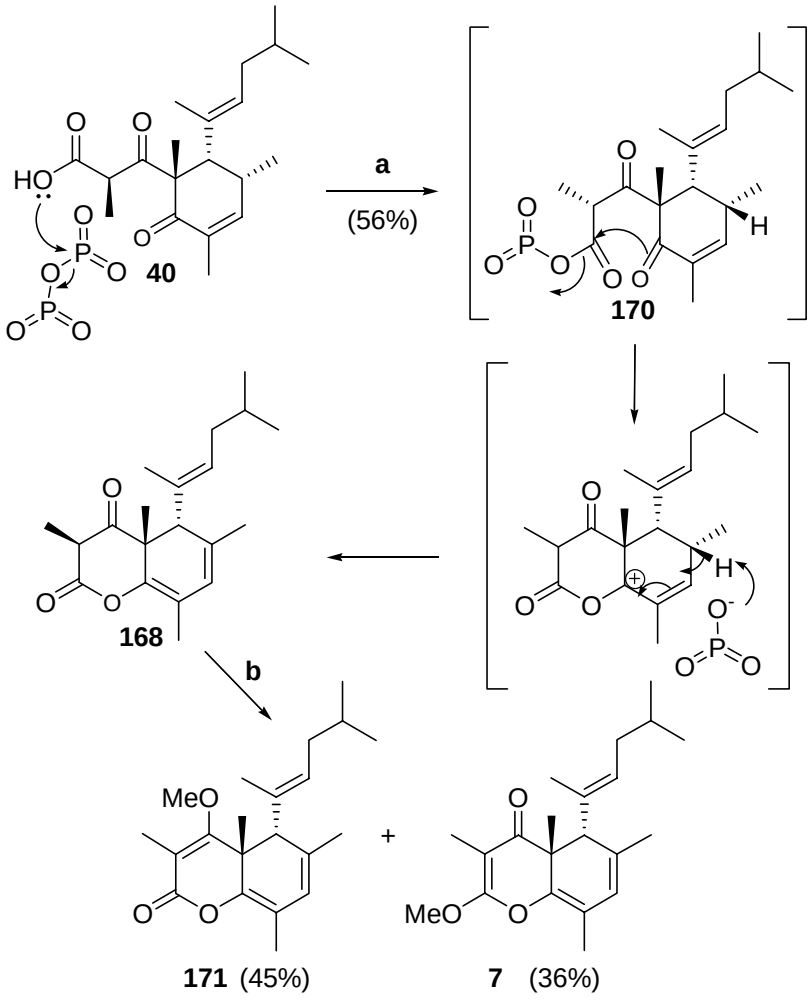
Scheme 4.13: *Attempted cyclisation of acid **40** via in situ ketene formation.*

4.5.2 Unique P_2O_5-Mediated Cyclisation of Acid 40

In light of the success of Eaton's reagent in the model system (Section 3.5.3), much thought was given to overcoming the current dilemma. It was apparent that acidic conditions were undesirable, but the mechanism proposed earlier could apply to P_2O_5 in the absence of methanesulfonic acid. Eaton's reagent was just a convenient, easy to handle, soluble source of P_2O_5. Attention was therefore focused on using P_2O_5 alone and the question of how best to do this was answered by means of supporting P_2O_5 on oven-dried celite.[104] Thus, after P_2O_5 was stirred rapidly with oven-dried celite for several minutes, acid **40** was added to the mixture as a CH_2Cl_2 solution at room temperature and the reaction was stirred for one hour to afford pyrone **168** (56%, Scheme 4.14), predominantly as the *keto* tautomer. Semi-empirical calculations at the Hartree-Fock level (*Gaussian98W*) indicated the favoured *keto* tautomer to be the one depicted, where the methyl group was equatorial.

This simple procedure to overcome the problems associated with effecting intramolecular cyclisation of acid **40** adds weight to the proposed mechanism shown in Chapter 3 (Section 3.5.3) with a slight modification; the mechanism is equally likely if P_2O_5 is used to form a mixed anhydride intermediate such as **170** (Scheme 4.14). As before, methylation of pyrone **168** was performed by treatment with CH_2N_2 in Et_2O at

room temperature for one hour (Scheme 4.14). This afforded a readily separable mixture of γ-pyrone **7** (39%) and α-pyrone **171** (45%). The spectral data for γ-pyrone **7** will be addressed after discussion of the spectra of α-pyrone **171**.



Reagents and conditions: a. P_2O_5 (5 eq)-celite, CH_2Cl_2 , rt, 1 h; **b.** CH_2N_2 (excess), Et_2O, rt, 1 h.

Scheme 4.14: *P_2O_5-mediated cyclisation of acid **40** to pyrone **168** and subsequent O-methylation to afford methoxypyrones **7** and **171**.*

4.5.3 Structural Assignment: α-Pyrone 171

The ^{1}H NMR spectrum of α-pyrone **171** displays the appropriate resonances (Figure 4.7). The ring vinyl proton appears as a multiplet at δ 5.54-5.42 and couples with the cyclohexadiene ring vinyl methyl proton doublet at δ 1.71 (J = 1.5 Hz). The remaining cyclohexadiene ring vinyl methyl protons appear as a singlet at δ 1.73. The pyrone ring vinyl methyl protons appear as a singlet at δ 1.92 while the quaternary stereocentre methyl protons appear as a singlet at δ 1.34. The doubly allylic methine proton appears as a singlet at δ 2.72 while the methoxy methyl protons appear as a singlet at δ 3.87.

The side-chain vinyl proton appears as a triplet at δ 5.33 (J = 7.2 Hz) and shows reciprocal coupling to the vinyl methyl proton singlet at δ 1.45. The side-chain vinyl proton also couples to the methylene protons, which appear as a triplet at δ 1.83 (J = 7.2 Hz), while these methylene protons show reciprocal coupling to the isopropyl methine proton septet at δ 1.58 (J = 6.6 Hz). The isopropyl methine proton couples to the isopropyl methyl proton doublets (J = 6.6 Hz) at δ 0.86 and δ 0.85.

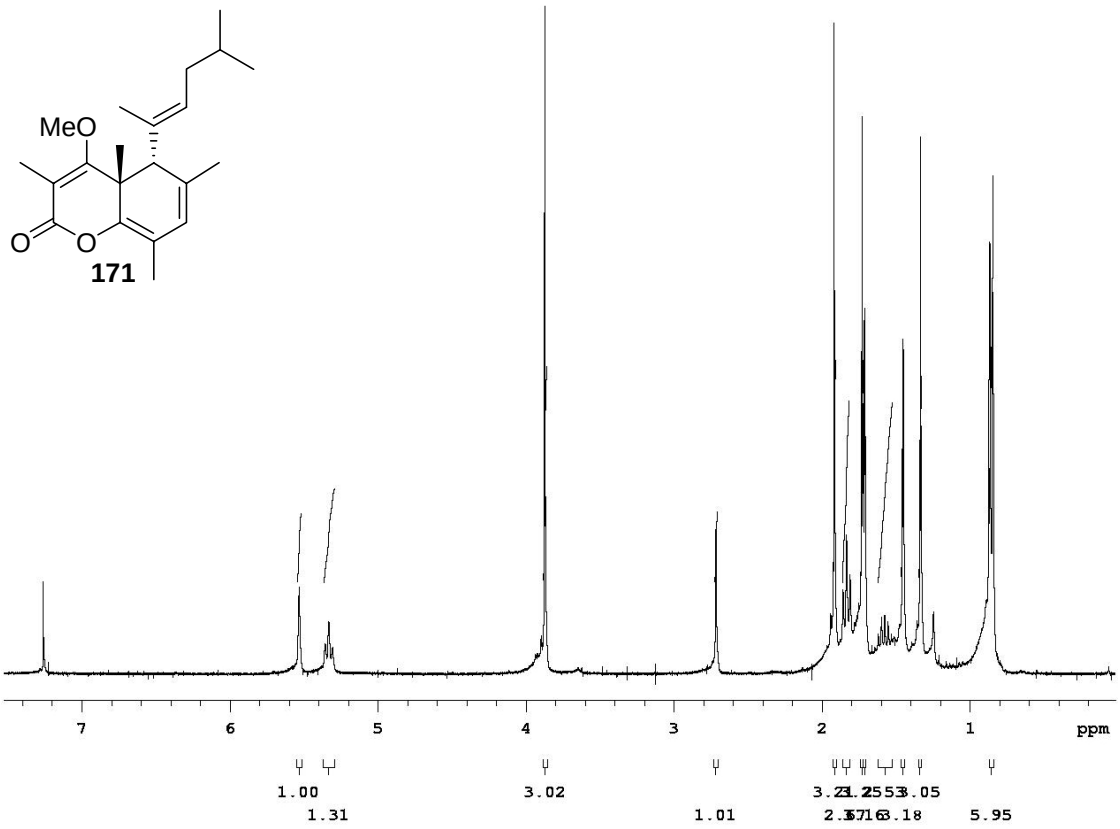


Figure 4.7: *300 MHz ^{1}H NMR spectrum of α-pyrone **171** in $CDCl_3$.*

The ^{13}C NMR spectra of α-pyrone **171** displays the requisite 21 resonances (Figure 4.8). The pyrone carbonyl carbon (C-1) appears at δ 165.4, the quaternary vinyl carbon bearing the β-vinyl methyl (C-2) appears at δ 103.6 and the carbon of the β-vinyl methyl (C-20) itself occurs at δ 11.7. The carbon bearing the γ-methoxy group (C-3) appears at δ 172.8, the carbon of the quaternary stereocentre (C-4) resonates at δ 43.2, the adjacent quaternary vinyl carbon (C-5) appears at δ 143.4 and the methoxy methyl carbon appears at δ 61.6. The cyclohexadiene contains two quaternary, methyl-bearing carbons, which appear at δ 110.4 (C-6) and δ 131.2 (C-8), a tertiary vinyl carbon (C-7) at δ 122.8 and a tertiary, doubly allylic carbon (C-9) at δ 59.2. The remaining ring vinyl

methyl carbons appear at δ 21.4 (C-18) and δ 13.6 (C-19) and methyl carbon of the quaternary stereocentre (C-17) appears at δ 24.0. The vinyl side-chain consists of the quaternary vinyl carbon (C-10), which appears at δ 132.5, the vinyl methyl carbon (C-16) at δ 12.7 and the tertiary vinyl carbon (C-11) at δ 129.0. It also contains the allylic secondary carbon (C-12) at δ 36.8, the tertiary carbon (C-13) at δ 28.9 and the remaining methyl carbons at δ 22.3 and δ 22.2 (C-14/15). The infrared spectrum of α-pyrone **171** displayed an absorption at 1725 cm^{-1}, consistent with the presence of the carbonyl group. The EI mass spectrum displayed a molecular ion at *m/z* 330 and base peak at *m/z* 182. An accurate mass measurement confirmed the expected molecular formula of $C_{21}H_{30}O_3$. An absorption in the UV/Vis spectrum occurred at 242 nm (MeOH) and a specific rotation of –716 (*c* 0.65, $CHCl_3$) was observed. The structural assignment of α-pyrone **171** was aided by ^{1}H-^{1}H correlation (COSY), ^{1}H-^{13}C correlation (HMQC), long range ^{1}H-^{13}C coupling (HMBC) and NOESY experiments.

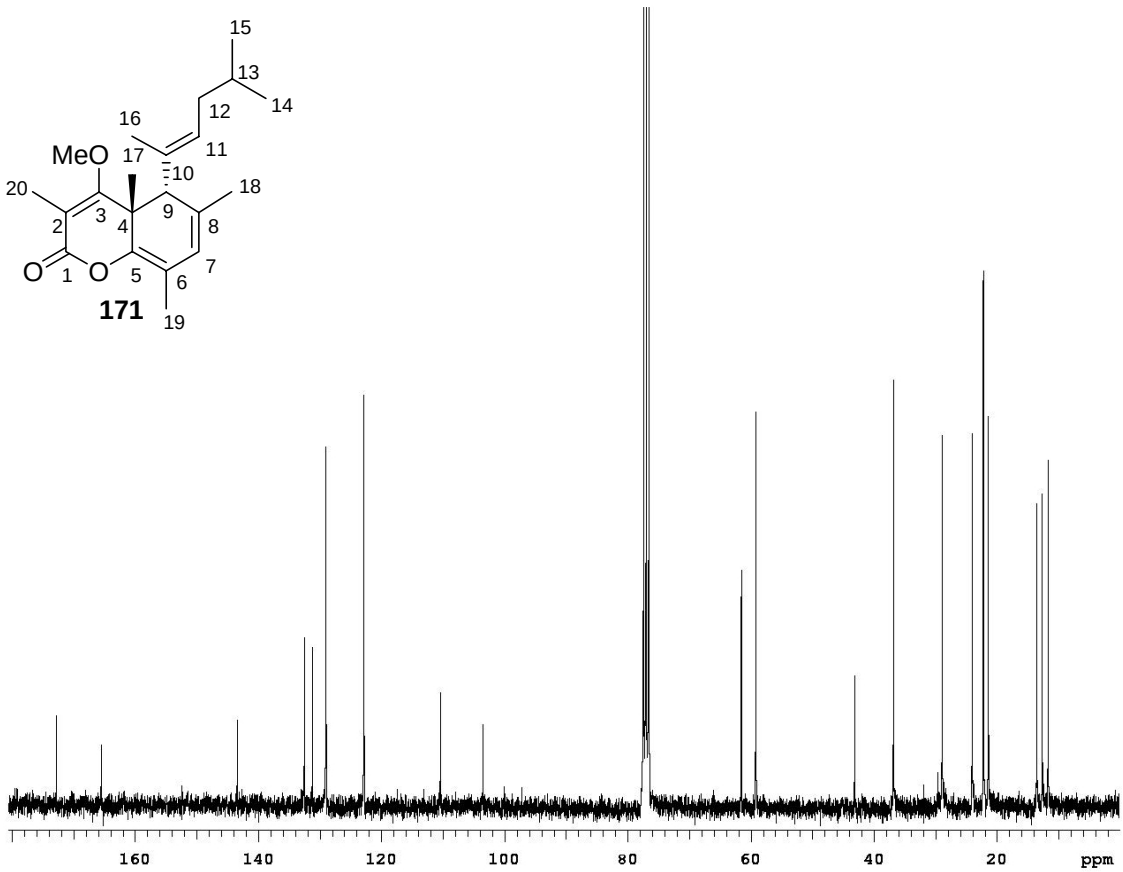


Figure 4.8: *75.5 MHz ^{13}C NMR spectrum of α-pyrone **171** in $CDCl_3$.*

4.5.4 Structural Assignment: γ-Pyrone 7

The ^{1}H NMR spectrum of γ-pyrone **7** displays the expected resonances (Figure 4.9). The ring vinyl proton appears as a multiplet at δ 5.49-5.46 and couples with the cyclohexadiene ring vinyl methyl proton multiplet at δ 1.76-1.73. The remaining cyclohexadiene ring vinyl methyl protons appear within the multiplet at δ 1.76-1.73. The pyrone ring vinyl methyl protons appear as a singlet at δ 1.60 while the quaternary stereocentre methyl protons appear as a singlet at δ 1.35. The doubly allylic methine proton appears as a singlet at δ 2.91 while the methoxy methyl protons appear as a singlet at δ 3.94. The side-chain vinyl proton appears as a triplet at δ 5.39 (J = 7.2 Hz) and shows reciprocal coupling to the vinyl methyl proton singlet at δ 1.47. The side-chain vinyl proton also couples to the methylene protons, which appear as a triplet at δ 1.80 (J = 7.2 Hz), while these methylene protons show reciprocal coupling to the isopropyl methine proton multiplet at δ 1.61-1.52. The isopropyl methine proton couples to the isopropyl methyl proton doublets (J = 6.6 Hz) at δ 0.82 and δ 0.81.

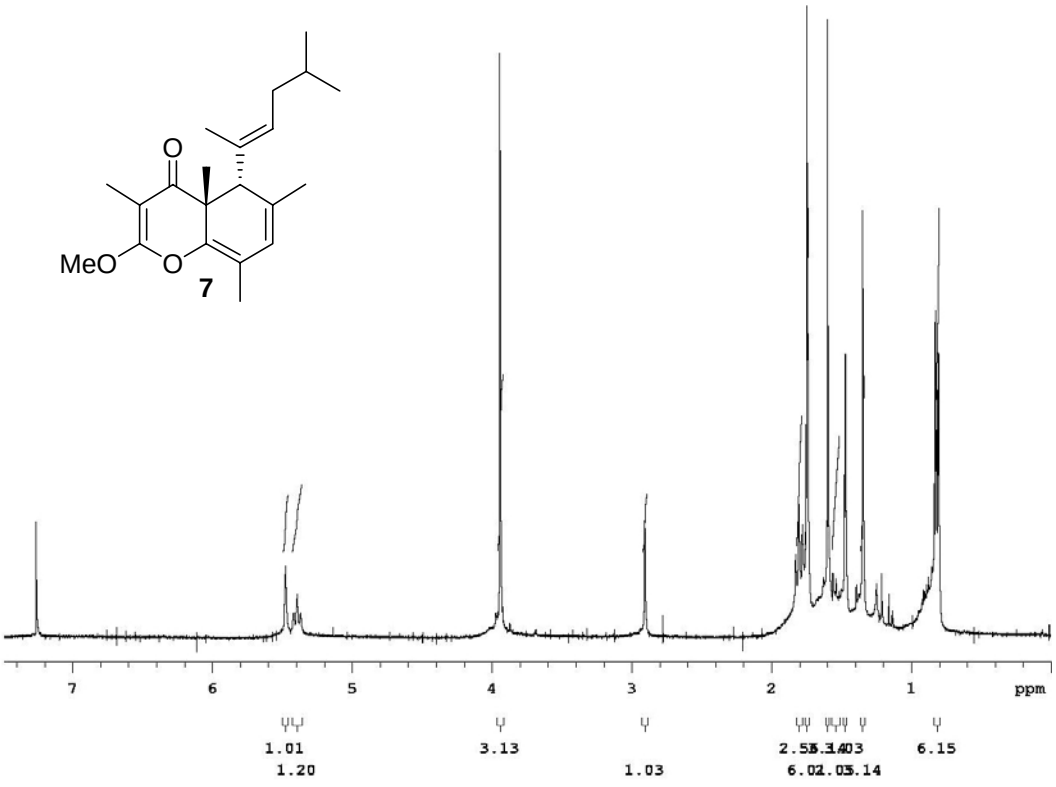


Figure 4.9: *300 MHz ^{1}H NMR spectrum of γ-pyrone **7** in $CDCl_3$.*

The ^{13}C NMR spectra of γ-pyrone **7** displays the required 21 resonances (Figure 4.10). The α-methoxy bearing carbon (C-1) appears at δ 164.2, the quaternary vinyl carbon bearing the β-vinyl methyl (C-2) appears at δ 88.9 and the carbon of the β-vinyl methyl

(C-20) itself occurs at δ 6.5. The carbonyl carbon (C-3) appears at δ 192.8, the carbon of the quaternary stereocentre (C-4) resonates at δ 46.2, the adjacent quaternary vinyl carbon (C-5) appears at δ 145.8 and the methoxy methyl carbon appears at δ 54.7. The cyclohexadiene contains two quaternary, methyl-bearing carbons, which appear at δ 112.1 (C-6) and δ 133.6 (C-8), a tertiary vinyl carbon (C-7) at δ 121.4 and a tertiary, doubly allylic carbon (C-9) at δ 58.8. The remaining ring vinyl methyl carbons appear at δ 21.7 (C-18) and δ 14.3 (C-19) and the methyl carbon of the quaternary stereocentre (C-17) appears at δ 25.4. The vinyl side-chain consists of the quaternary vinyl carbon (C-10), which appears at δ 132.5, the vinyl methyl carbon (C-16) at δ 13.4 and the tertiary vinyl carbon (C-11) at δ 128.0. It also contains the allylic secondary carbon (C-12) at δ 36.9, the tertiary carbon (C-13) at δ 28.9 and the remaining methyl carbons at δ 22.3 and δ 22.2 (C-14/15). The infrared spectrum of γ-pyrone **7** displayed an absorption at 1610 cm^{-1}, consistent with the presence of the carbonyl group in this α-methoxy-β-methyl-γ-pyrone system. The EI mass spectrum displayed a molecular ion at *m/z* 330 and base peak at *m/z* 41. An accurate mass measurement confirmed the expected molecular formula of $C_{21}H_{30}O_3$. An absorption in the UV/Vis spectrum occurred at 262 nm (MeOH) and a specific rotation of –542 (*c* 0.26, $CHCl_3$) was observed. Thus, the structure of γ-pyrone **7** was unequivocally assigned, aided by COSY, HMQC, HMBC and NOESY experiments.

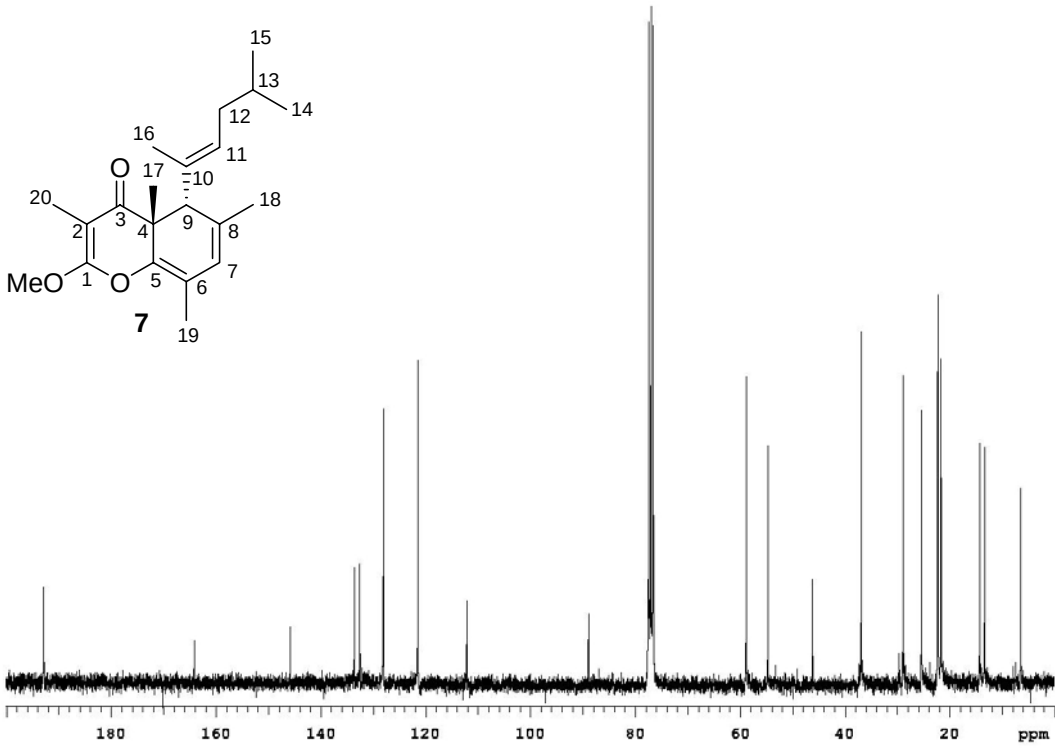


Figure 4.10: *75.5 MHz ^{13}C NMR spectrum of γ-pyrone **7** in $CDCl_3$.*

4.5.5 Natural Product Spectral Comparison

At this point, comparison of the spectral data of γ-pyrone **7** with that reported[23] for natural the product was quite disconcerting. In particular, the ^{1}H NMR spectrum of the natural product displayed several conspicuous differences (Figure 4.11) such as the chemical shifts for the two vinyl protons, which appear as multiplets at δ 5.44 (δ 5.48 in **7**) and δ 5.51 (δ 5.39 in **7**). The most significant difference, however, is the doubly allylic methine proton singlet which appears at δ 3.91 (δ 2.91 in **7**). Other notable differences include the quaternary stereocentre methyl proton singlet at δ 1.20 (δ 1.35 in **7**) and the ring vinyl methyl protons adjacent to the tertiary stereocentre at δ 1.63 (1.76-1.73 in **7**)

The ^{13}C NMR spectrum of the natural product (Figure 4.12) was similar to γ-pyrone **7**, with notable differences being the doubly allylic carbon stereocentre (C-9) at δ 53.4 (δ 58.8 in **7**) and the quaternary stereocentre methyl (C-17) at δ 21.2 (δ 25.4 in **7**). The NMR comparisons of γ-pyrone **7** and the natural product are summarised in Table 4.1 (main differences in bold) and Figure 4.13. Interestingly, the EI mass spectra of both natural product and γ-pyrone **7** were almost identical and the infrared spectra were similar. However, the natural product had an absorption in its UV/Vis spectrum at 271 nm (262 nm in **7**) and a specific rotation of –476 (*c* 0.49, $CHCl_3$) ($[\alpha]_D$ = –542 (*c* 0.26, $CHCl_3$) for **7**). Furthermore, the natural product was reported[23] to be crystalline, while γ-pyrone **7** failed to solidify and decomposed in $CDCl_3$ (or $CHCl_3$), partially reverting to parent pyrone **168**. The spectral data, however, indicated that the natural product was an isomer of γ-pyrone **7** and that the carbon skeleton of **7** was common to both compounds.

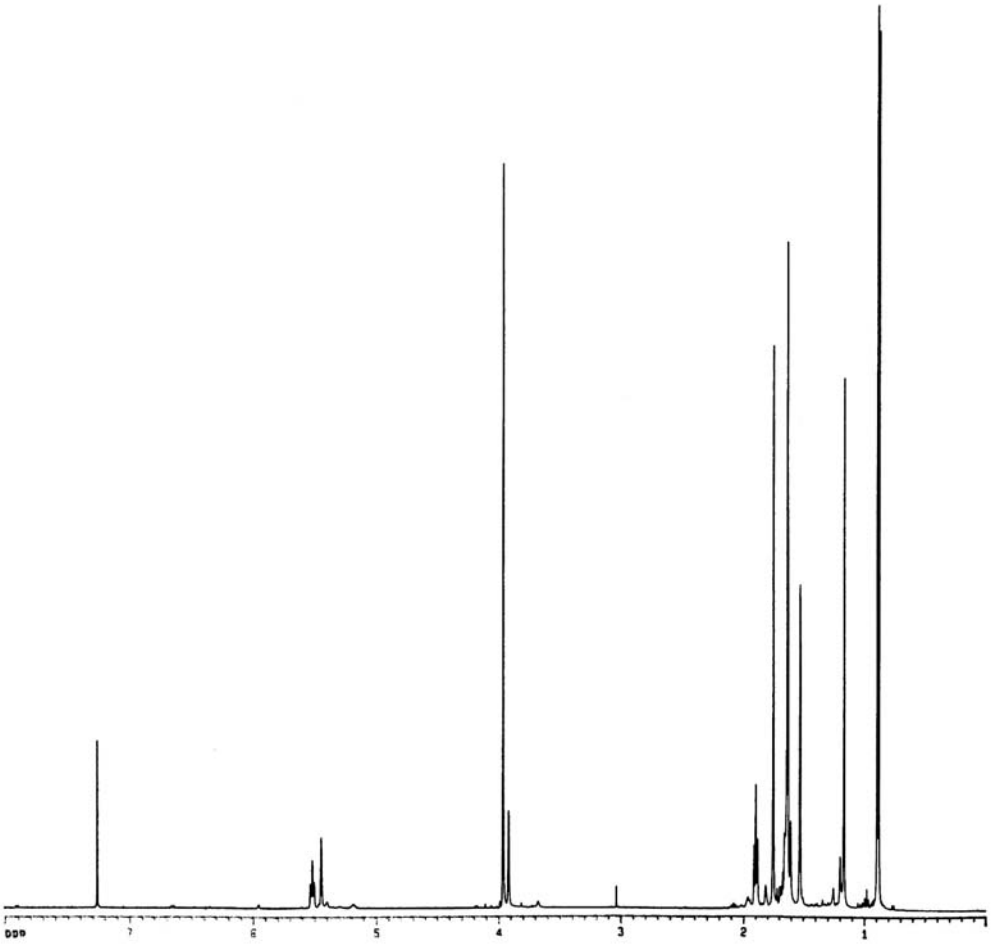


Figure 4.11: *500 MHz (Bruker AMX 500 MHz) ^{1}H NMR spectrum of tridachiahydropyrone in $CDCl_3$ provided by M. Gavagnin.*

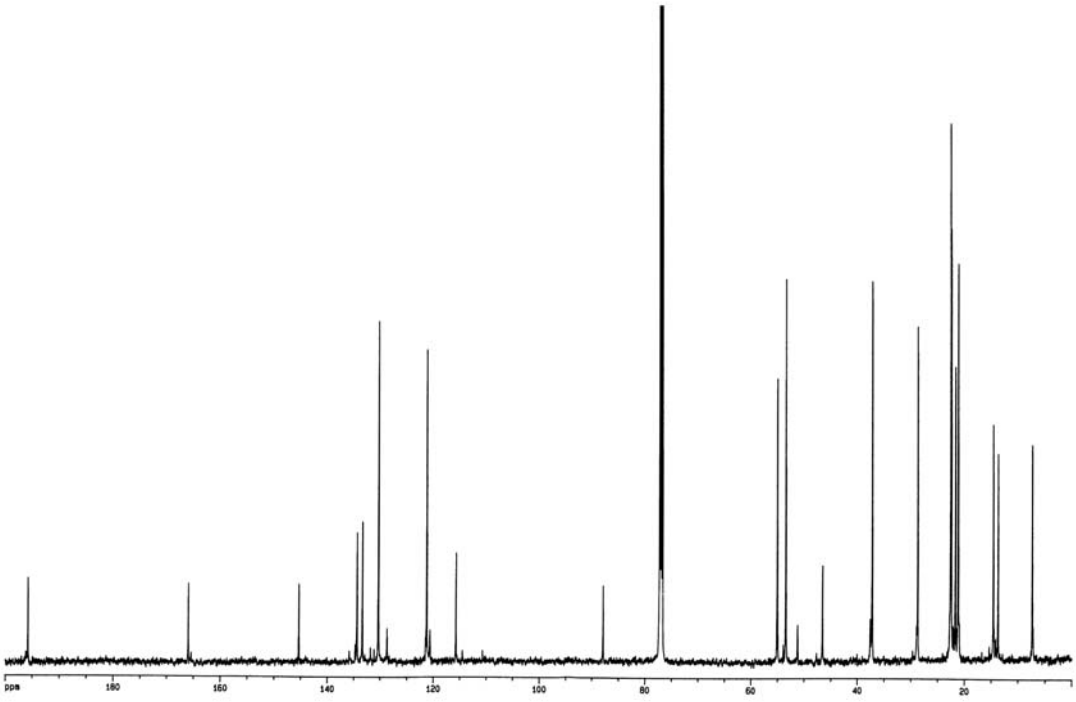
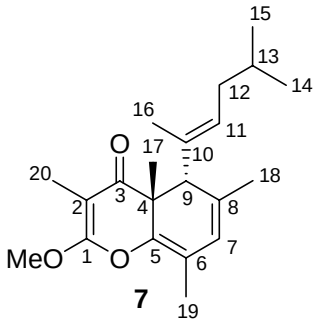


Figure 4.12: *125 MHz (Bruker AMX 500 MHz) ^{13}C NMR spectrum of tridachiahydropyrone in $CDCl_3$ provided by M. Gavagnin.*



7

Position	Tridachia-hydropyrone[a] δ ^{1}H[c]	Tridachia-hydropyrone[a] δ ^{13}C[c]	Synthetic 7[b] δ ^{1}H[c]	Synthetic 7[b] δ ^{13}C[c]
1	-	**165.97**	-	**164.17**
2	-	**87.88**	-	**88.94**
3	-	**195.79**	-	**192.83**
4	-	46.56	-	46.17
5	-	145.33	-	145.80
6	-	**115.74**	-	**112.14**
7	5.44	121.28	5.48	121.45
8	-	134.42	-	133.59
9	**3.91**	**53.45**	**2.91**	**58.82**
10	-	133.42	-	132.54
11	**5.51**	**130.37**	**5.39**	**128.05**
12	**1.90**	37.24	**1.80**	36.90
13	1.64	28.72	1.63	28.94
14	0.88	22.59	0.82	22.24
15	0.88	22.47	0.82	22.30
16	1.53	13.71	1.47	13.38
17	**1.20**	**21.21**	**1.35**	**25.40**
18	**1.63**	21.72	**1.75**	21.67
19	1.75	14.62	1.75	14.31
20	1.63	7.40	1.60	6.46
OMe	3.96	55.08	3.94	54.69

[a] Bruker AMX 500 MHz NMR Spectrometer. [b] Varian Gemini 300 MHz NMR Spectrometer. Assignments assisted by ^{1}H-^{1}H COSY, ^{1}H-^{13}C HMBC and HSQC using a Varian Inova 600 MHz NMR Spectrometer. [c] Chemical shifts in ppm referenced to C*H*Cl$_3$ (δ 7.26) for proton and to *C*DCl$_3$ (δ 77.0) for carbon.

Table 4.1: *Comparison of ^{1}H and ^{13}C NMR chemical shifts for tridachiahydropyrone and γ-pyrone **7** (main differences in bold).*

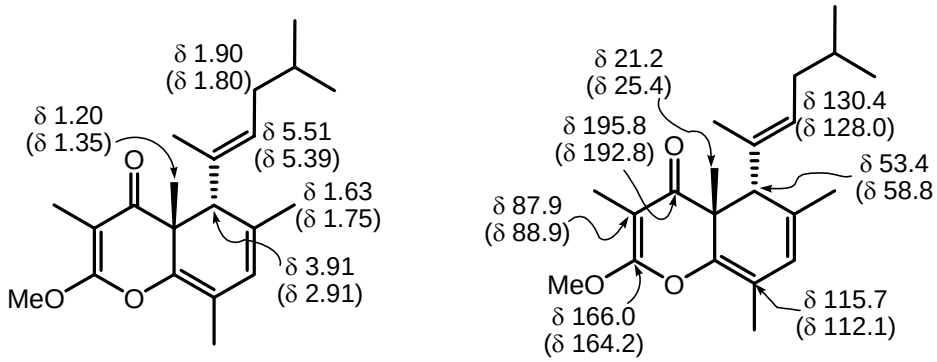
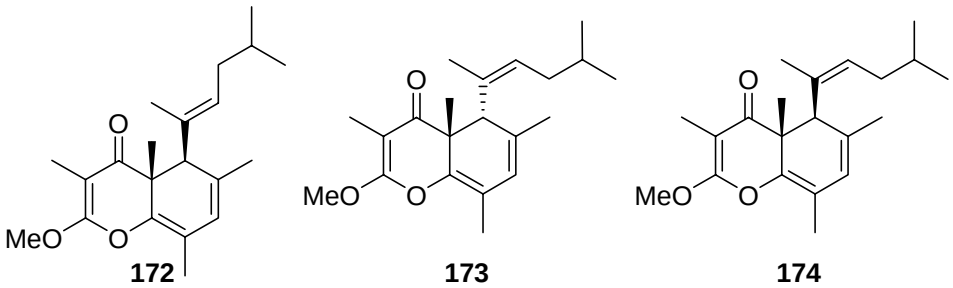


Figure 4.13: *Comparison of ^{1}H and ^{13}C NMR chemical shifts for tridachiahydropyrone and γ-pyrone **7** (bracketed).*

4.6 The Identity of Tridachiahydropyrone

In light of the findings above that tridachiahydropyrone was not the same as γ-pyrone **7**, the true structure of tridachiahydropyrone was deemed to differ only in its relative stereochemistry or double bond geometry, leading to three isomers (Figure 4.14). These isomers contain either the alternate relative stereochemistry of the ring stereocentres as in **172**, the alternate side-chain double bond geometry as in **173**, or both of these as in **174**. The possible differences between γ-pyrone **7** and tridachiahydropyrone were seen to be strongly related to the two stereocentres. Indeed, the sole basis for assignment of the natural product relative stereochemistry was the observation[23] of NOE effects between the methyl at C-4 and H-9, indicating they had the same orientation. Based on the differences discussed above relating to the stereocentres, however, there was a strong possibility that the relative stereochemistry of the natural product was *cis*, as seen in **172**.



172 **173** **174**

Figure 4.14: *Isomers of γ-pyrone **7** that could potentially be the natural product tridachiahydropyrone.*

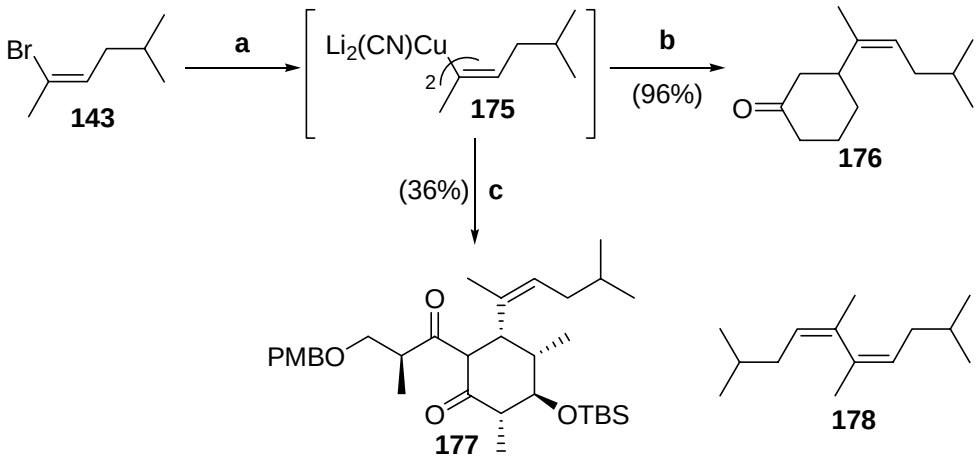
Although less likely, there was the possibility that the vinyl side-chain had (*Z*)-double bond geometry, rather than the reported (*E*)-double bond. The approach being

developed was amenable to the use of various cuprates and in fact the (*Z*)-vinyl bromide **143**, required for the formation of **173**, was already synthesised in the pursuit of (*E*)-vinyl bromide **44** (Section 4.2.2). Thus, the more expedient option to explore at this point was to use the alternate geometry of the side-chain to see how spectral data for product **173** compared to the natural product data.

4.6.1 Alternate Side-Chain Double Bond Geometry

It was envisaged that the chemistry described for the synthesis of γ-pyrone **7** could equally apply to the synthesis of the (*Z*)-side-chain isomer, beginning with (*Z*)-vinyl bromide **143** and enone **43**. Initially, brief experimentation began with adding (*Z*)-vinyl bromide **143** as cuprate **175** to 2-cyclohexenone (**152**), under the same conditions as used previously (Section 4.3.2), to give compound **176** in excellent yield (96%, Scheme 4.13). Reaction of cuprate **175** with enone **43**, however, was not as reliable as for the previous case, with yields varying between 40-60%. Indeed, the only way to get acceptable yields was to use 5 to 10 equivalents of cuprate **175**, and in the largest scale reaction (250 milligrams of enone **43**), cyclohexanone **177** was afforded in rather modest yield (36%, Scheme 4.13).

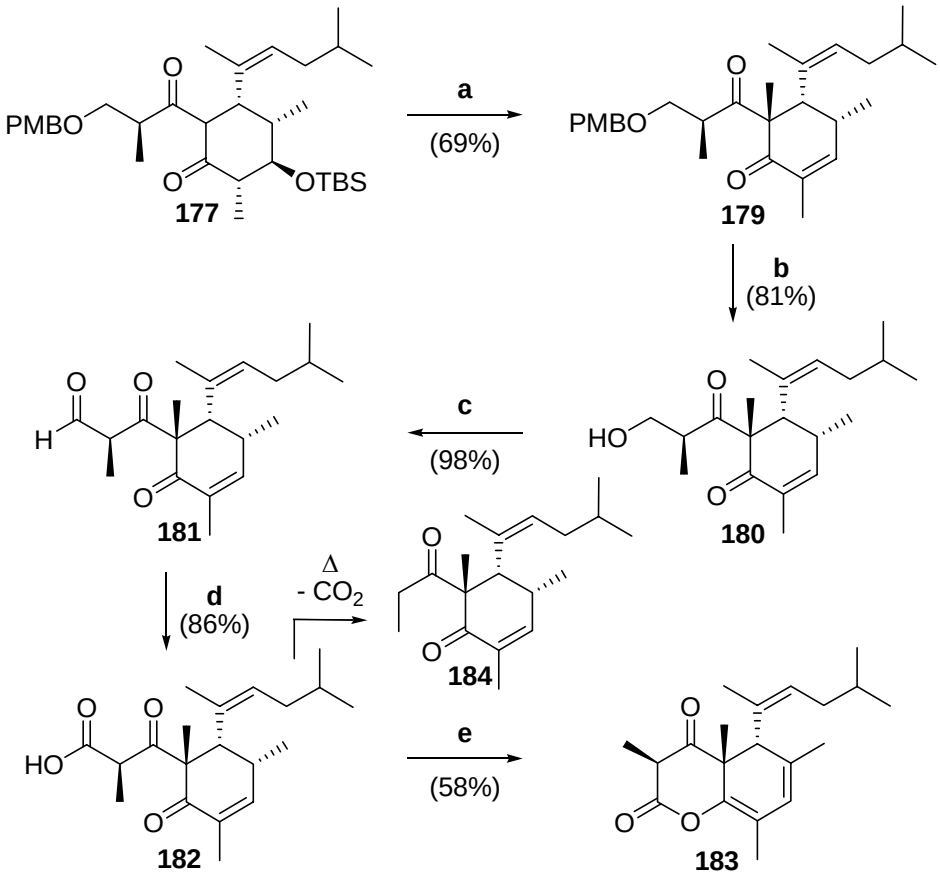
The difficulty with this particular reaction may be due to greater steric hindrance of the (*Z*)-configured cuprate, as evidenced by the addition step taking at least 3 hours (determined from tlc monitoring). Unusually, even though pure (*Z*)-vinyl bromide **143** was used, a small amount of cyclohexanone **138** (Section 4.4.1) was obtained on occasions, presumably from isomerisation of the double bond prior to the conjugate addition. This by-product formation could be suppressed by excluding light as much as possible during all stages of the reaction. As before, a small amount of dimer **178** was also obtained, but apart from that, there were few other by-products and no starting enone **43**. The reaction was not optimised further and no Lipshutz cuprate addition was attempted.



Reagents and conditions: a. i. *t*-BuLi (2 eq), THF, -100°C, 15 min; ii. CuCN (0.5 eq), Et_2O, -78°C to -50°C, 15 min; **b.** Cyclohexenone **152** (0.25 eq), Et_2O, -50°C, 15 min to rt; **c.** Enone **43** (0.1 eq), Et_2O, -50°C, 3 h to 0°C, 90 min.

Scheme 4.13: *Reactions of cuprate **175** affording addition products **176** and **177**.*

After overcoming the conjugate addition hurdle, the remaining sequence of methylation/elimination and functional group manipulation was performed exactly as before (Section 4.4.2). Thus, methylation/elimination afforded cyclohexenone **179** (69%), deprotection with DDQ[74] gave alcohol **180** (81%), Dess-Martin oxidation[65] gave aldehyde **181** (98%), chlorite oxidation[86,103] gave acid **182** (86%) and cyclisation with P_2O_5 afforded pyrone **183** (58%, Scheme 4.14). Pyrone **183** existed predominantly as the *keto* tautomer, with the stereochemistry depicted based on NOESY experiments and supported by semi-empirical calculations at the Hartree-Fock level (*Gaussian98W)*, where the favoured *keto* tautomer has the methyl group in the equatorial position. Perhaps not surprisingly, the methylene protons of the side-chain appeared diastereotopic in this series of compounds. Acid **182** was sensitive to heat and decarboxylated to compound **184** over several days at room temperature, as has been observed with similar β-ketoacids.

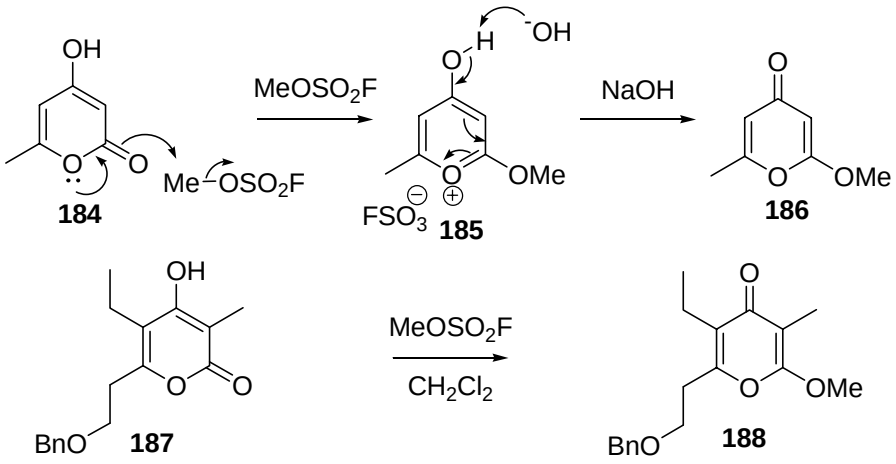


Reagents and conditions: a. i. NaH (1.5 eq), THF, rt, 10 min; ii. MeI (10 eq), rt, 17 h; **b.** DDQ (1.3 eq), CH_2Cl_2, pH 7 buffer, 0°C, 3 h; **c.** Dess-Martin periodinane (1.5 eq), CH_2Cl_2, rt, 1 h; **d.** $NaClO_2$ (5 eq), NaH_2PO_4 (3.8 eq), *t*-BuOH, H_2O, Me_2C=CHMe, rt, 1 h; **e.** P_2O_5(5 eq)-celite, CH_2Cl_2 , rt, 2 h.

Scheme 4.14: *Methylation/elimination and functional group manipulation of cyclohexanone **177** to afford pyrone **183**.*

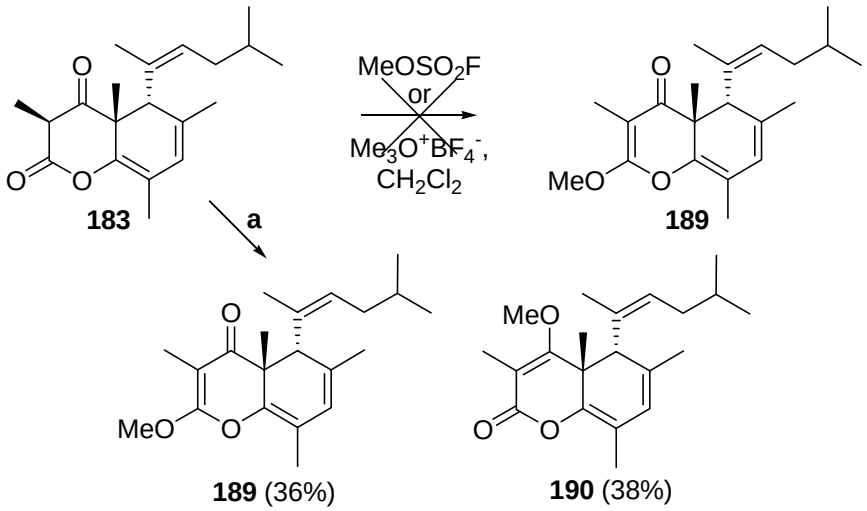
4.6.2 Attempted Regioselective Methylation

In an attempt to maximise formation of the γ-pyrone regioisomer, several attempts were undertaken to effect a regioselective methylation. There are several reports of regioselective methylation of pyrones with methyl fluorosulfonate ($MeOSO_2F$) to afford specifically the γ-pyrone,[35,105,106] with the selectivity explained by participation of the ring oxygen[106] (Scheme 4.15). For example, work by Beak *et al.* [106] on the methylation of pyrone **184** with $MeOSO_2F$ yielded intermediate cation **185**, which was stabilised by the aromatic character of the system. At this point the methylating agent was removed *in vacuo* (to avoid over methylation) and the resulting residue was washed with base to liberate the α-methoxy-γ-pyrone **186** in excellent reported yield (98%). Similarly, pyrone **187** was regiospecifically methylated by Ishibashi *et al.* [35] with $MeOSO_2F$ to afford α-methoxy-γ-pyrone **188** with a reported 61% yield.



Scheme 4.15: *Regiospecific O-methylation of pyrones **184** and **187** to afford α-methoxy-γ-pyrones **185** and **188**.*

Treatment of pyrone **183** however, with several methylating agents such as methyl triflate ($MeOSO_2CF_3$, similar in reactivity to $MeOSO_2F$) and Meerwein's salt (trimethyloxonium tetrafluoroborate, $Me_3O^+BF_4^-$) only returned starting material (Scheme 4.16). The difference can be attributed to the fact that pyrone **183** has a quaternary carbon whereas 'normal pyrones' such as **184** and **187** have a double bond at this position, giving the intermediate aromatic character. Attention was thus returned to the use of CH_2N_2 in Et_2O for the *O*-methylation, which afforded readily separable regioisomeric γ-pyrone **189** (36%) and α-pyrone **190** (38%, Scheme 4.16).



Reagents and conditions: **a.** CH_2N_2 (excess), Et_2O, rt, 1 h.

Scheme 4.16: *O-methylation of pyrone **183** with CH_2N_2 to afford γ-pyrone **189** and α-pyrone **190**.*

4.6.3 Structural Assignment: (*Z*)-Configured α-pyrone 190

The spectra of α-pyrone **190** will be discussed only briefly. The ^{1}H NMR and ^{13}C NMR spectra of α-pyrone **190** (Figures 4.15 and 4.16, respectively) display the appropriate resonances and are similar to the (*E*)-configured isomer **171**. The main differences between the proton spectra of the two isomers are the chemical shifts of the side-chain vinyl protons, the side-chain methylene protons and the doubly allylic methine protons. The side-chain vinyl proton appears as a triplet of quartets at δ 5.12 (J = 6.4, 1.5 Hz) in α-pyrone **190** (δ 5.33 in **171**) and couples to the side-chain diastereotopic methylene protons, which appear as a multiplet δ 2.20-1.95 (δ 1.83 in **171**). The doubly allylic methine proton appears as a singlet at δ 3.24 in α-pyrone **190** (δ 2.72 in **171**), while the remaining resonances relate the protons not discussed here.

The main differences in the carbon spectrum between α-pyrone **190** and its (*E*)-isomer **171** relate particularly to the doubly allylic secondary carbon (C-9), which appears at δ 49.0 (δ 59.2 in **171**), and the side-chain vinyl methyl (C-16), which appears at δ 20.0 (δ 12.7 in **171**). The remaining resonances relate to carbons not discussed, some of which also display small differences. The infrared spectrum of α-pyrone **190** displayed an absorption at 1725 cm^{-1}, consistent with the presence of the carbonyl group. The EI mass spectrum displayed a molecular ion at *m/z* 330 and base peak at *m/z* 41. An accurate mass measurement confirmed the expected molecular formula of $C_{21}H_{30}O_3$. An absorption in the UV/Vis spectrum occurred at 245 nm (MeOH) and a specific rotation of –609 (*c* 0.32, $CHCl_3$) was observed. The structural assignment of α-pyrone **190** was aided by COSY, HMQC, HMBC and NOESY experiments.

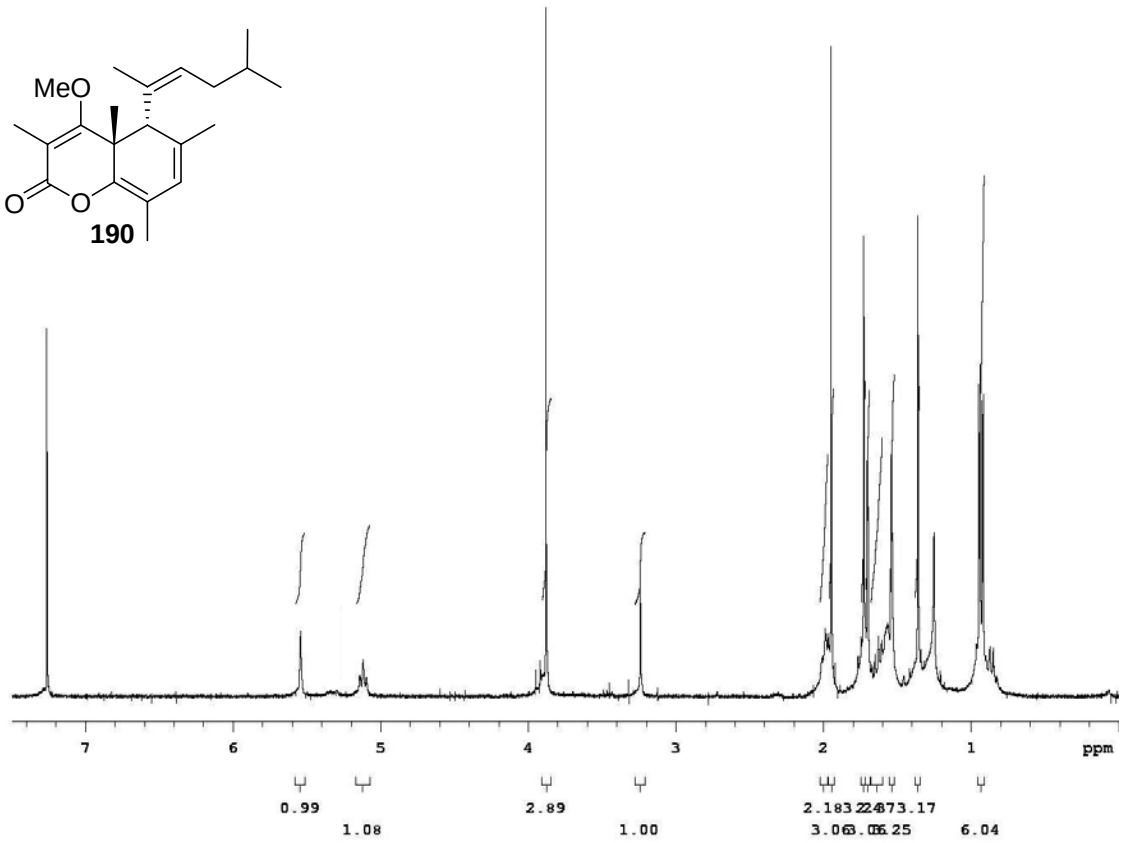


Figure 4.15: *300 MHz ^{1}H NMR spectrum of α-pyrone **190** in $CDCl_3$.*

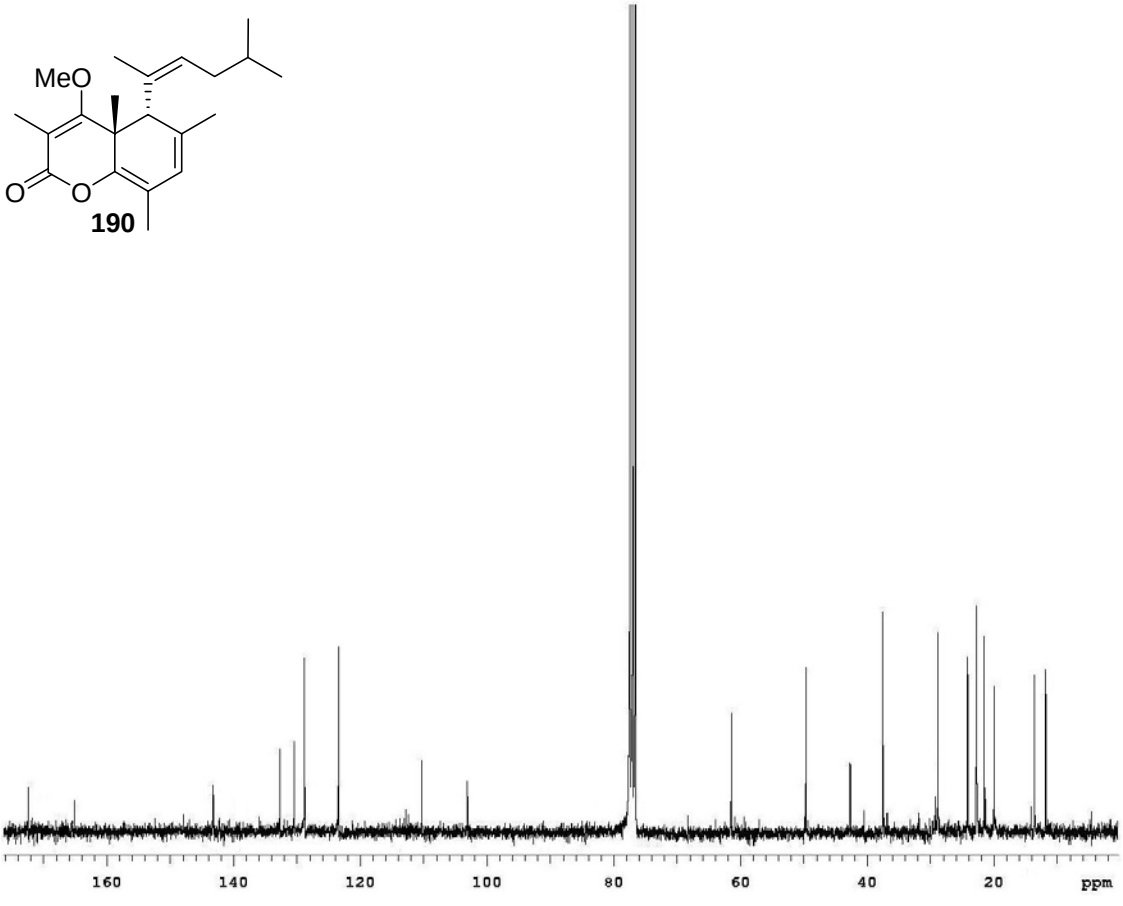


Figure 4.16: *75.5 MHz ^{13}C NMR spectrum of α-pyrone **190** in $CDCl_3$.*

4.6.4 Structural Assignment: (*Z*)-Configured γ-pyrone 189

The ^{1}H NMR spectra of γ-pyrone **189** displays the required resonances (Figure 4.17). The ring vinyl proton appears as a multiplet at δ 5.51-5.48 and couples with one of the two cyclohexadiene vinyl methyl groups, which appear as an apparent 6H singlet at δ 1.74. The protons of the pyrone ring vinyl methyl appear as a singlet at δ 1.62, while the quaternary stereocentre methyl protons appear as a singlet at δ 1.35. The doubly allylic methine proton appears as a singlet at δ 3.43 and the methoxy methyl protons appear as a singlet at δ 3.94. The side-chain vinyl proton appears as a triplet of quartets at δ 5.08 (J = 6.6, 1.5 Hz) and shows reciprocal coupling to the protons of the side-chain vinyl methyl quartet at δ 1.52 (J = 1.5 Hz). The side-chain diastereotopic methylene protons appear as multiplets at δ 2.21-2.10 and δ 2.09-1.98 and couple to the vinyl methyl proton and the isopropyl methine proton multiplet at δ 1.71-1.60. The isopropyl methine proton couples to the isopropyl methyl protons, which appear as doublets (J = 6.6 Hz) at δ 0.95 and δ 0.90.

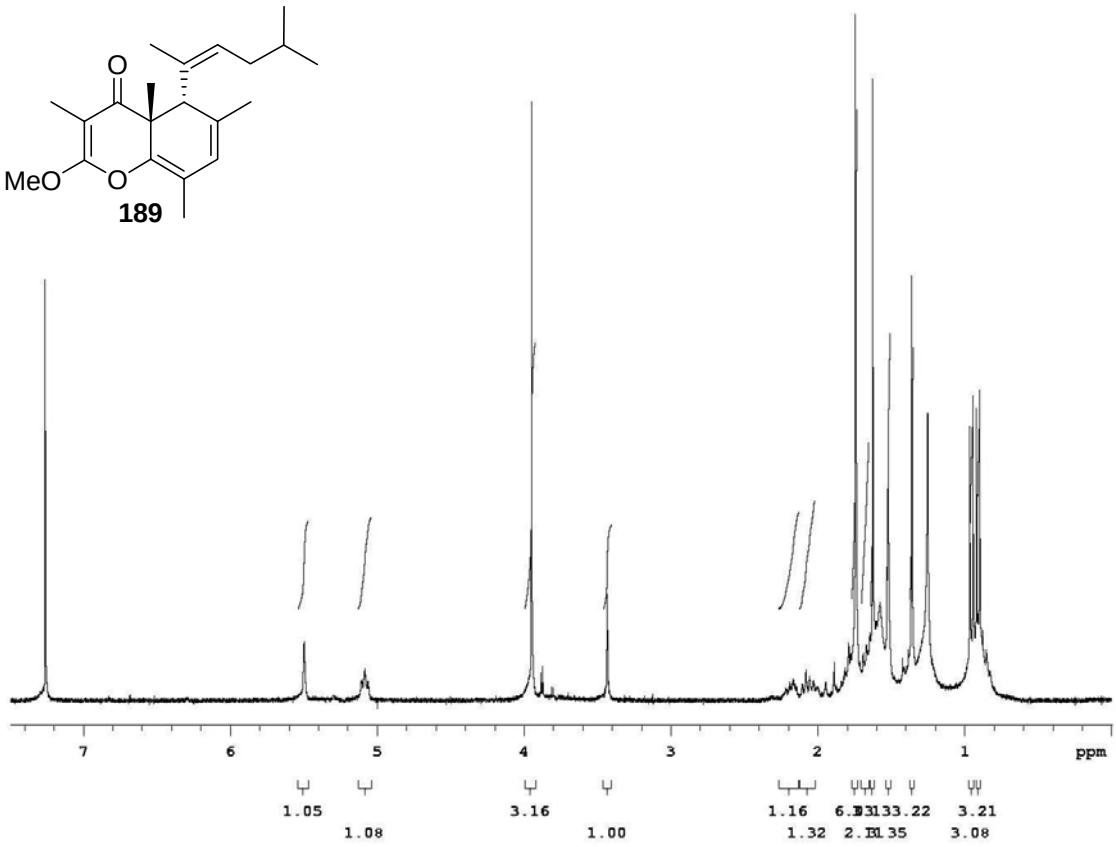


Figure 4.17: *300 MHz ^{1}H NMR spectrum of γ-pyrone **189** in $CDCl_3$.*

The ^{13}C NMR spectra of γ-pyrone **189** displays the appropriate 21 resonances (Figure 4.18). The α-methoxy bearing carbon (C-1) appears at δ 163.9, the quaternary vinyl carbon bearing the β-vinyl methyl (C-2) appears at δ 88.4 and the carbon of the β-vinyl methyl (C-20) itself occurs at δ 6.6. The carbonyl carbon (C-3) appears at δ 192.5, the carbon of the quaternary stereocentre (C-4) resonates at δ 45.5, the adjacent quaternary vinyl carbon (C-5) appears at δ 145.5 and the methoxy methyl carbon appears at δ 54.7. The cyclohexadiene contains two quaternary, methyl-bearing carbons, which appear at δ 111.9 (C-6) and δ 132.2 (C-8), a tertiary vinyl carbon (C-7) at δ 122.2 and a tertiary, doubly allylic carbon (C-9) at δ 49.9. The remaining ring vinyl methyl carbons appear at δ 21.6 (C-18) and δ 13.4 (C-19) and the methyl carbon of the quaternary stereocentre (C-17) appears at δ 25.5. The vinyl side-chain consists of the quaternary vinyl carbon (C-10), which appears at δ 132.5, the vinyl methyl carbon (C-16) at δ 20.4 and the tertiary vinyl carbon (C-11) at δ 128.8. It also contains the allylic secondary carbon (C-12) at δ 37.6, the tertiary carbon (C-13) at δ 28.8 and the remaining methyl carbons at δ 22.8 and δ 22.7 (C-14/15). The infrared spectrum of γ-pyrone **189** displayed an absorption at 1611 cm^{-1}, consistent with the presence of the carbonyl group in this α-methoxy-β-methyl-γ-pyrone system. The EI mass spectrum displayed a molecular ion at *m/z* 330 and base peak at *m/z* 41. An accurate mass measurement confirmed the expected molecular formula of $C_{21}H_{30}O_3$. An absorption in the UV/Vis spectrum occurred at 255 nm (MeOH) and a specific rotation of –517 (*c* 0.30, $CHCl_3$) was observed. Thus, the structure of γ-pyrone **189** was unequivocally assigned, aided by COSY, HMQC, HMBC and NOESY experiments.

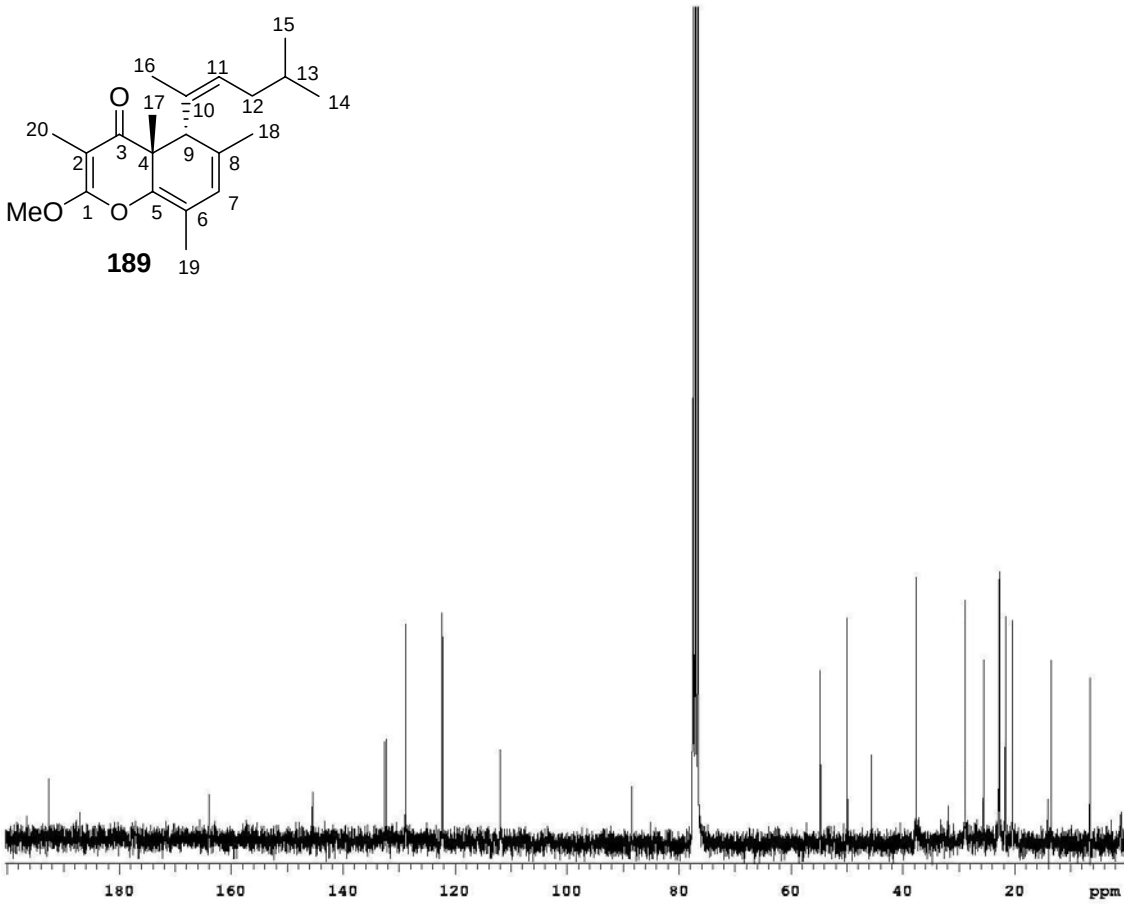


Figure 4.18: *75.5 MHz ^{13}C NMR spectrum of γ-pyrone **189** in $CDCl_3$.*

4.6.5 Comparison With Previous Spectral Data

Comparison of the spectral data of (*Z*)-configured γ-pyrone **189** with that already discussed for (*E*)-isomer **7** and the natural product was undertaken. The two side-chain isomers **189** and **7** had similar spectra. Notable differences in the ^{1}H NMR spectra for **189** are the chemical shift of the side-chain vinyl proton, which appears as a multiplet at δ 5.08 (δ 5.39 in **7**), the methylene protons, which occur as a multiplet at δ 2.03 (δ 1.80 in **7**) and the isopropyl methyl doublets at δ 0.95 and δ 0.90 (δ 0.82 and δ 0.81 in **7**). The most significant difference, however, is the doubly allylic methine proton singlet which appears at δ 3.43 (δ 2.91 in **7**). It is noteworthy to observe that the change of double bond geometry has little effect on many proton resonances, with the effects seemingly localised to the side-chain. For instance, the quaternary stereocentre methyl proton singlet in **189** occurs at δ 1.35 (δ 1.35 in **7**), both cyclohexadiene ring vinyl methyl protons appear as a singlet at δ 1.74 (1.76-1.73 in **7**) and the methoxy methyl protons appear at δ 3.94 (δ 3.94 in **7**).

The ^{13}C NMR spectrum contained conspicuous differences for **189** such as the doubly allylic carbon stereocentre (C-9) at δ 49.9 (δ 58.8 in **7**) and the side-chain vinyl methyl (C-16) at δ 13.4 (δ 20.4 in **7**). Other small differences were associated with some side-chain and cyclohexadiene carbons. From the comparison of the data for the two double-bond geometries, a generalisation could be made that the (*Z*)-geometry has the effect of shifting the C-9 carbon resonance downfield and the C-16 resonance upfield, while not greatly influencing anything else. A summary of the different proton and carbon chemical shifts can be seen in Figure 4.19.

Unfortunately, it was apparent that the spectral data for (*Z*)-configured γ-pyrone **189** did not match the data reported for tridachiahydropyrone, with the greatest differences being related to resonances of the vinyl side-chain and the two stereocentres in both carbon and proton spectra. In fact, the side-chain vinyl methyl carbon (C-16) resonance was all that was required to differentiate between the (*E*)- (~ δ 13) and (*Z*)- (~ δ 20) isomers, with (*E*)-isomer **7** experiencing an upfield shift due to steric interactions of C-16 with C-12. This difference between the side-chain isomers was evident throughout the entire series of synthetic intermediates.

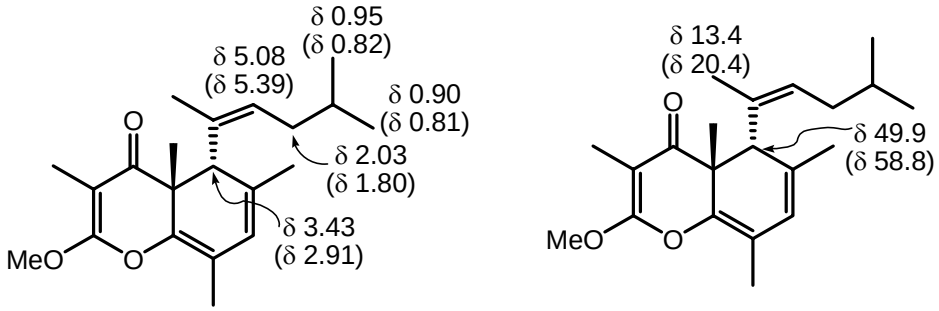


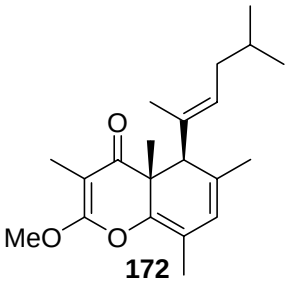
Figure 4.19: *Comparison of ^{1}H and ^{13}C NMR chemical shifts for (Z)-configured pyrone **189** and (E)-configured pyrone **7** (bracketed).*

4.6.6 Summary of Synthetic Findings

The preceding experiments document the unambiguous synthesis of several analogues of the natural product and in particular, γ-pyrone **7**, which has the putative structure reported for the natural product. An X-ray crystal structure of intermediate alcohol **162** confirmed the *trans* relative stereochemistry and (*E*)-configuration of the side-chain double bond. Indeed, formation of the two regioisomeric pyrones **7** and **171** offered two

opportunities to fully examine and confirm the core carbon framework of these molecules, which was consistent with the structure reported for the natural product.

The synthesis and extensive characterisation of the (*Z*)-configured side-chain regioisomers **189** and **190** was further confirmation of the structure of these related compounds. Careful analysis of the spectral data of the two isomeric γ-pyrones **7** and **189** and comparison with that reported for the natural product leads to the hypothesis that the natural product has *cis* relative stereochemistry between the two stereocentres as in **172**, rather than *trans*, as reported in the isolation paper. This follows from having eliminated the possibility that the natural product has the (*Z*)-configured side-chain, which was less likely at the outset.



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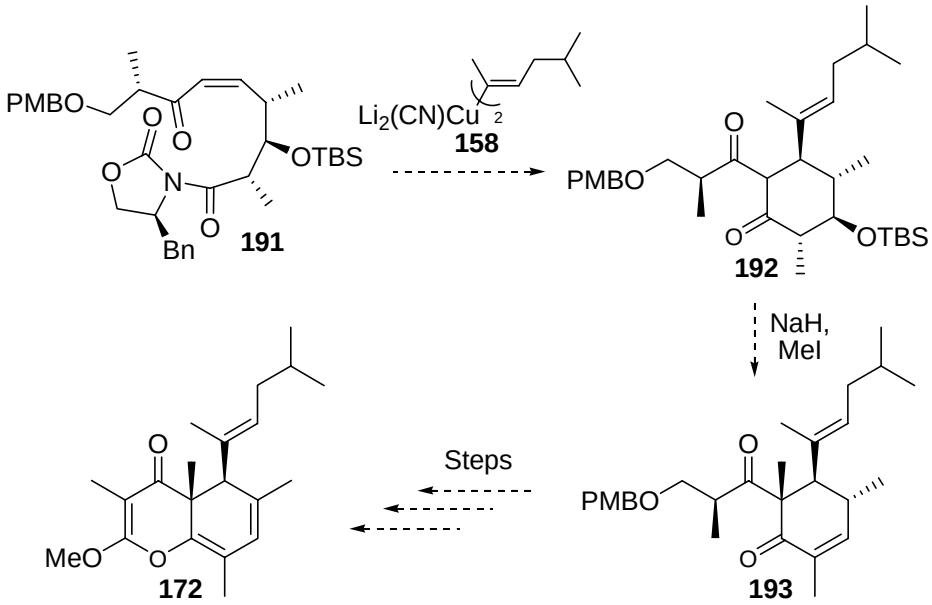
Furthermore, analogy may be drawn between the effect on C-16 chemical shifts due to different configurations of the side-chain double bond and the chemical shift of the methyl of the quaternary stereocentre (C-17). In γ-pyrone **7**, C-17 resonates at δ 25.4, whereas in the natural product, C-17 appears at δ 21.2. This upfield shift of C-17 in the natural product relative to γ-pyrone **7** was indicative that there was a greater steric interaction between C-17 and C-10 of the side-chain in the natural product. This supports the hypothesis that the natural product has *cis* relative stereochemistry.

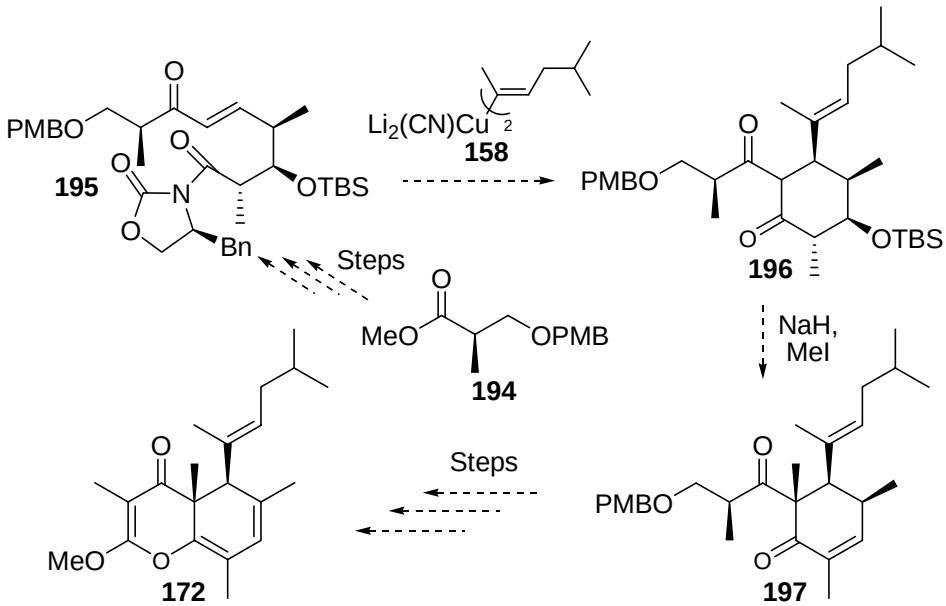
4.7 Possibilities for Forming a *Cis* Product

Considering the observation that the relative stereochemistry between the methyl and side-chain was most likely *cis*, there appeared to be two possibilities to access such a product using the methodology developed herein. Either (*Z*)-enone **191** could be used, where addition of cuprate **158** could afford anti-Felkin like product[76] **192** (Scheme 4.17). Subsequent *axial* methylation (if methylation is truly *axial*) should afford *cis* methylated product **193**, which could be transformed into γ-pyrone **172** using the techniques already described. Alternatively, chiral hydroxy ester **194** (the enantiomer of that used previously, Section 2.4.4) could be used initially. Subsequent manipulation to

(*E*)-enone **195** followed by addition of cuprate **158** should afford the Felkin like product[76] **196**, which may be *axially* methylated to provide *cis* methylated **197** (Scheme 4.18).



Scheme 4.17: *Possible conversion of (Z)-enone **191** to γ-pyrone **172** with cis relative stereochemistry*

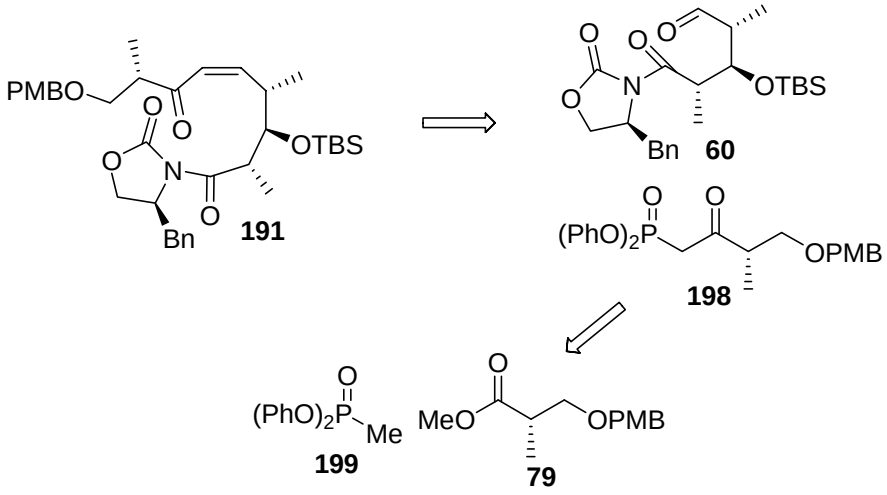


Scheme 4.18: *Possible conversion of (E)-enone **195** to γ-pyrone **172** with cis relative stereochemistry.*

4.6.1 Preliminary Investigations into Forming a *Cis*-Methylated Product

With limited time available, the more expedient route to **172** appeared to be *via* (*Z*)-enone **191**, the reason being that quantities of aldehyde **60** were already available and β-ketophosphonate **198** seemed attainable (Scheme 4.19). The only drawback with this

proposal was that it required a more unusual (*Z*)-selective H/W/E reaction. Several effective reagents have been reported for (*Z*)-selective H/W/E reactions, with the ligands on phosphorous ranging from trifluoroethoxy (CF_3CH_2O)[107] to aryloxy (ArO)[108] groups. Apparently the greater electronegativity of these groups, when compared to the usual alkoxy (MeO, EtO) groups, enhances the electrophilicity of the phosphorous, rendering the initial carbon-carbon bond formation irreversible due to rapid oxaphosphetane formation and stabilisation.[109,110]



Scheme 4.19: *Retrosynthetic analysis of (Z)-enone **191** to phosphonate **198** and chiral ester **79**.*

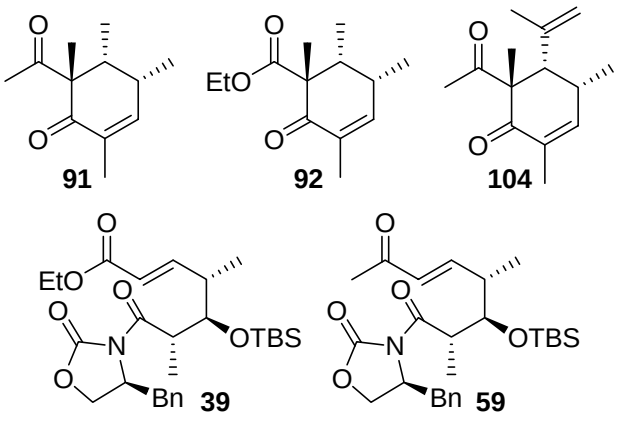
Unfortunately, attempts to couple diphenyl methylphosphonate (**199**) with chiral ester **79** (as in Section 3.3.1) led to decomposition of the phosphonate. It was apparent from the literature that this type of transformation had not been undertaken. The literature examples only involved β-phosphonoesters, rather than β-ketophosphonates such as the required **198**, where the usual substrates were diaryl methylphosphonates such as **199** and various chloroformates. It was evident that the desired transformation was not going to be straightforward, and as such was not pursued further due to time constraints.

Chapter Five

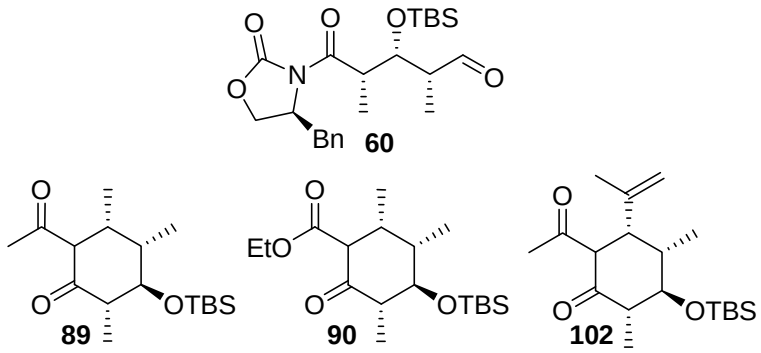
Conclusions and Future Work

Methodology has been developed for utilising enantiopure cyclohexenone derivatives as synthons in the formation of tridachione type natural products. Several model compounds have been synthesised as single enantiomers and a novel cyclisation route has been discovered, which furnishes fused, bicyclic pyrone ring systems as found in the natural products. The total synthesis of the putative structure of tridachiahydropyrone has been accomplished, and spectral data comparisons show the structure was misassigned in the isolation paper.

A synthetic approach to tridachione marine natural products has been developed. The strategy employed chiral cyclohexenone rings as synthons in the formation of some analogues of these types of natural product. The methodology was developed to form cyclohexenone rings, utilising a tandem conjugate addition-Dieckmann condensation reaction. This unusual route to highly substituted, chiral cyclohexenone rings such as **91**, **92**, and **104** underpinned the whole strategy. The methodology utilised stereochemistry of an acyclic precursor to facilitate cyclisation to a cyclohexanone, upon addition of a cuprate to the double bond of the corresponding α,β-unsaturated carbonyl compounds **39** and **59**.



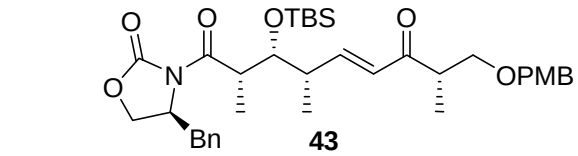
The unsaturated ketone **59** and ester **39** came from common aldehyde **60**, assembled using Evans' aldol chemistry, and a Wittig reaction between commercially available ylides. An Evans chiral auxiliary was used in the stereoselective aldol and also acted as a leaving group in the cyclisation step. After addition of methyl or vinyl cuprates, the cyclohexanones **89**, **90** and **102** were *trans* methylated, which occurred with β-elimination of the OTBS group to afford the desired cyclohexenones **91**, **92** and **104**. These may be further functionalised in a variety of ways, such as by reaction with another cuprate at the enone functionality or by reduction and dehydration to form substituted cyclohexadiene rings. Indeed, the latter aspect could be useful in forming some of the tethered analogues of tridachione marine natural products.



As alluded to above, this stereoselective route to cyclohexenones is not only useful for the current approach, but may also find utility in other natural product syntheses. The method of forming six-membered carbocycles with several stereocentres and in-built regions of reactivity could no doubt be adapted to many applications. The conjugate addition-cyclisation approach allows for a multitude of different cuprates to be added, depending on what substituent is required on the ring. As such, the method successfully provides chiral cyclohexenone derivatives that may be used as synthons in natural product syntheses.

A model study exemplified the synthetic utility of the approach that has been developed. In this case, the plan involved incorporating the whole carbon skeleton of a fused, bicyclic pyrone ring system into an acyclic precursor. The acyclic enone **43** this time was derived from a H/W/E reaction between chiral β-ketophosphonate **113** and the same aldehyde **60** used previously. Addition of methyl cuprate and subsequent *trans* methylation afforded the requisite cyclohexenone **117** that would act as a synthon. The

selectivity for the *trans* methylated product was optimised with an unusual two step methylation/elimination protocol.



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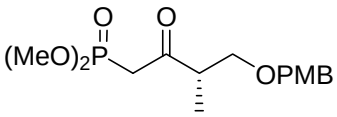
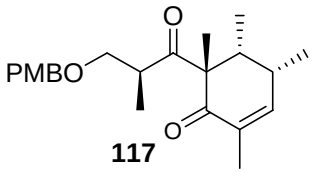


113



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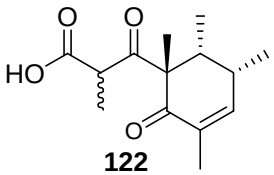
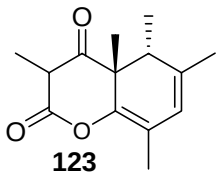
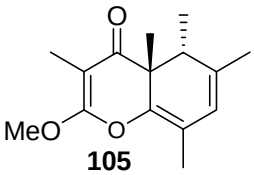
The benzyloxyketone moiety of cyclohexenone **117** was manipulated to the corresponding β-ketoacid **122**, in readiness for the cyclisation. In an unprecedented reaction, the cyclohexenone carbonyl oxygen of **122** underwent intramolecular cyclisation onto the acid carbonyl, with the loss of water, to complete the formation of the pyrone and cyclohexadiene rings in **123**. A plausible mechanism has been postulated to account for this transformation. Subsequent *O*-methylation yielded α-methoxy-β-methyl-γ-pyrone **105** and the regioisomeric α-pyrone **135**, as single enantiomers, thus completing the methodology for forming a bicyclic, pyrone-containing ring system. Both compounds were crystalline and single crystal X-ray analysis provided confirmation of the ring structure and relative stereochemistry of the two regioisomers.



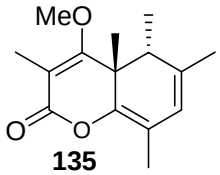
122



123



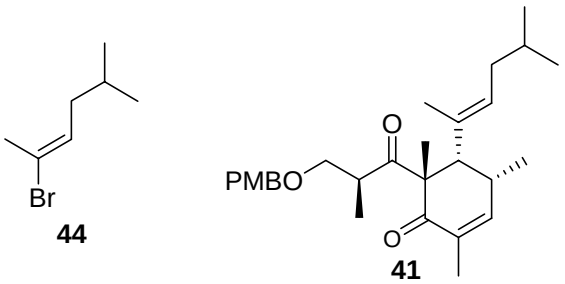
105



135

Finally, the methodology developed was applied to the synthesis of the structure purported to be tridachiahydropyrone. Following on with the theme of using fragments that have already been employed successfully in model systems, one of the key fragments was the (*E*)-enone **43** (shown above). This fragment had the entire carbon

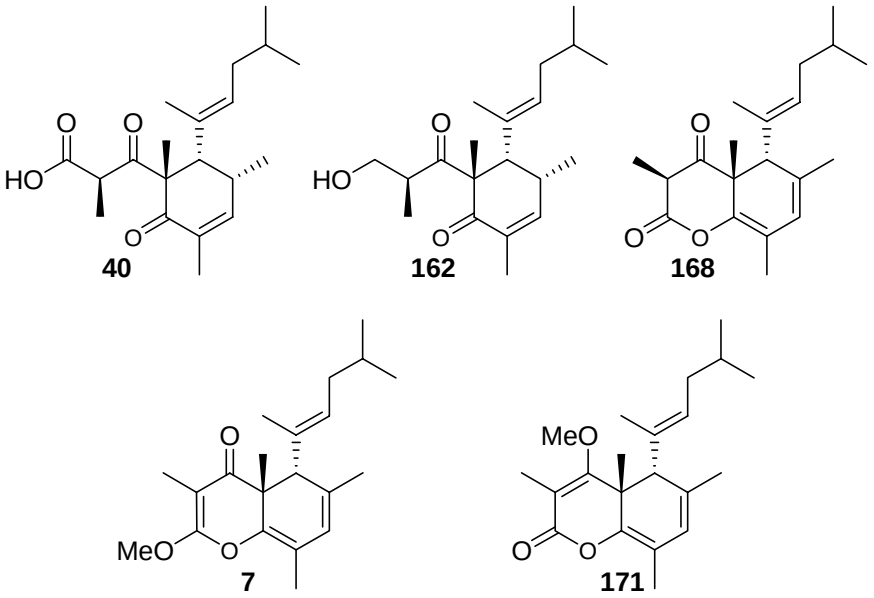
framework required to form the core bicyclic ring structure. The other fragment required for the conjugate addition-cyclisation step was yet to be synthesised. An excellent, stereoselective route to (*E*)- and (*Z*)-vinyl bromides was adapted to access the (*E*)-vinyl side-chain **44** of the reported natural product structure. A tandem conjugate addition-cyclisation reaction was followed by *trans* methylation to afford the desired cyclohexenone **41**.



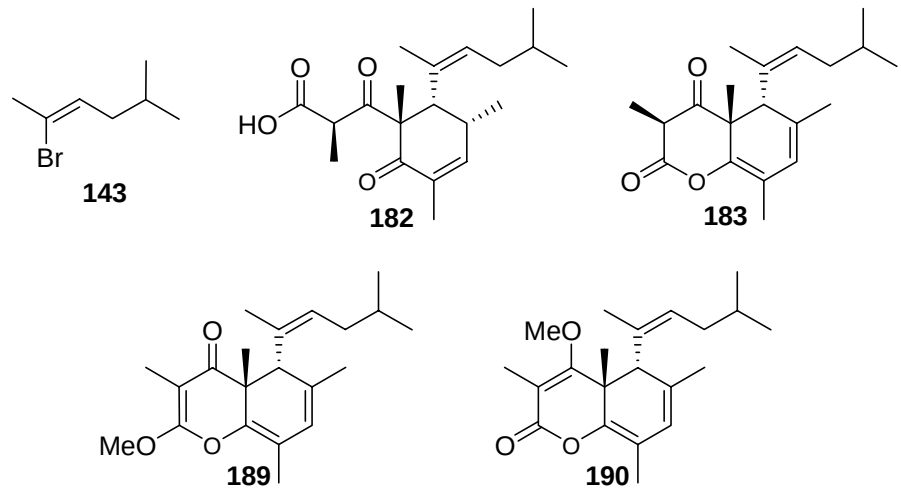
44 **41**

Transformation once again of the benzyloxyketone moiety to the corresponding β-ketoacid **40** furnished the monocyclic precursor to the purported natural product. The primary alcohol intermediate **162** afforded X-ray quality crystals, analysis of which confirmed the structure and relative stereochemistry of the alcohol. A unique P_2O_5-mediated cyclisation of the cyclohexenone carbonyl oxygen onto the acid moiety completed the desired annulation.

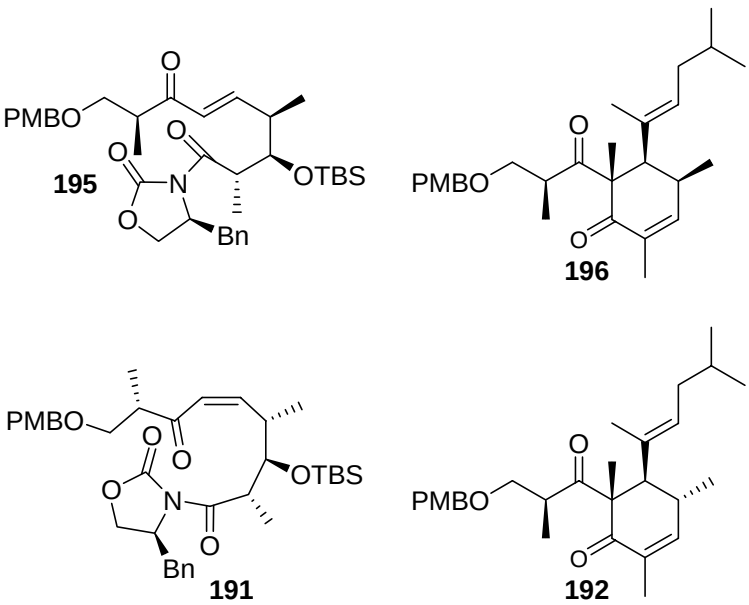
O-methylation afforded two regioisomeric pyrones **7** and **171** as single enantiomers, with the α-methoxy-β-methyl-γ-pyrone **7** having the structure reported in the isolation paper. The compounds were synthesised *via* an unambiguous synthetic route and the structures were unequivocally assigned by extensive NMR analysis. Unfortunately, the spectral data of **7** failed to match that reported for the natural product. It was easy to conclude that the gross structures were identical but there was obviously some difference. The possible differences were associated with either the relative stereochemistry or the side-chain double bond geometry.



Attempts were made to determine the true structure of tridachiahydropyrone through synthesis. Initially, the simpler avenue to explore was the alternate double bond geometry, because the required (*Z*)-vinyl bromide **143** was already on hand. Reinforcing the general utility of the approach, the (*Z*)-vinyl cuprate was added to (*E*)-enone **43** to effect addition-cyclisation. *Trans* methylation and functional group manipulation yielded the corresponding β-ketoacid pyrone precursor **182**. Cyclisation of the enone oxygen onto the acid was carried out as before by P_2O_5-mediated annulation to give **183**. *O*-methylation, performed in the usual manner, afforded yet another pair of regioisomeric, bicyclic pyrones **189** and **190**, as single enantiomers, but once again data for the α-methoxy-β-methyl-γ-pyrone **189** did not compare favourably with the natural product spectral data.



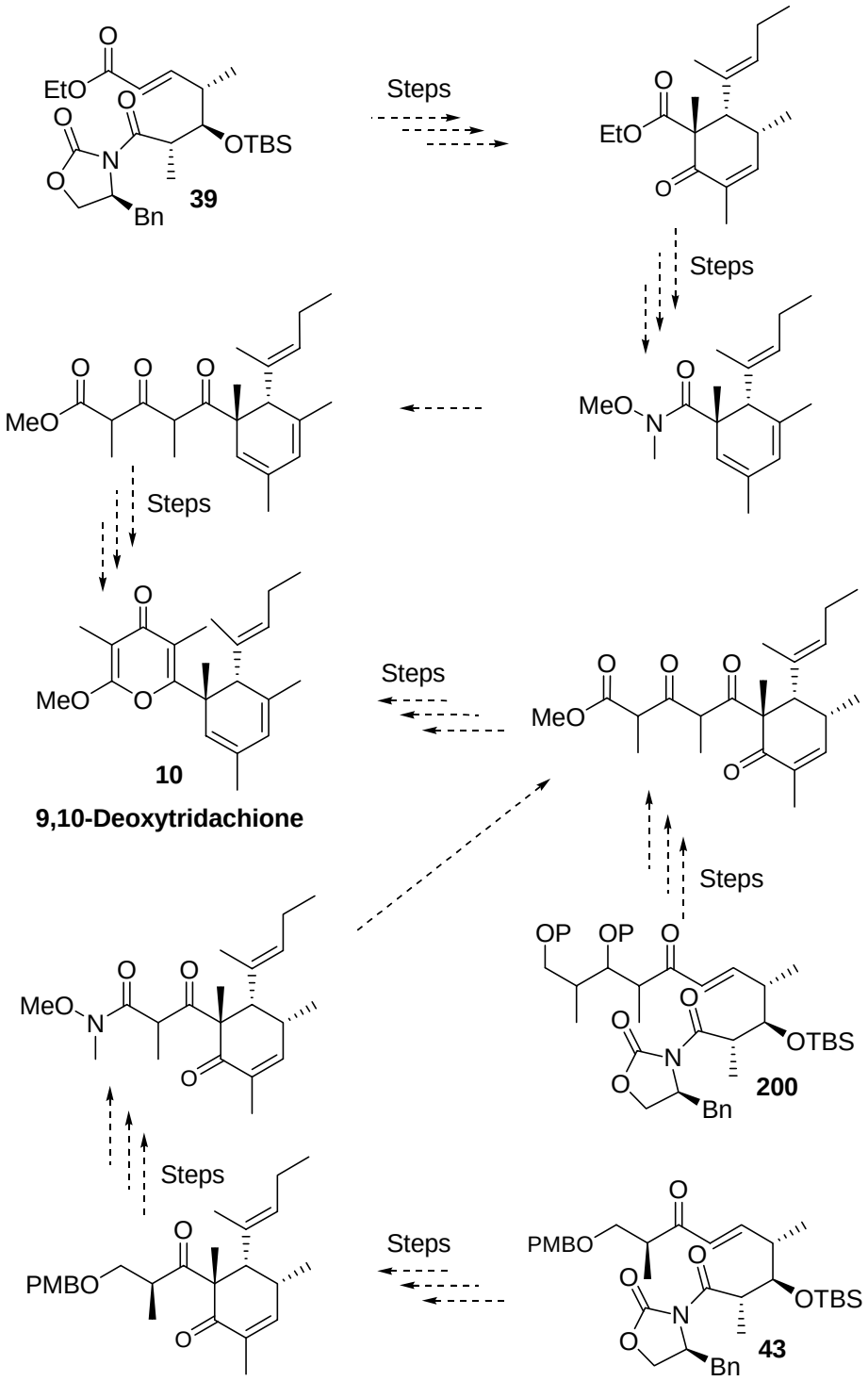
This outcome alluded to the possibility that the relative stereochemistry was in fact *cis*, so several strategies were envisaged that still maintained the conjugate addition-cyclisation approach. The likely possibilities included altering the stereochemistry of the acyclic precursor to afford (*E*)-enone **195**, thus altering the facial selectivity of the attacking cuprate. This could lead to a substrate that may be *cis* methylated to afford cyclohexenone **196,** due to the favoured *axial* approach of the methylating agent. Alternatively, the acyclic precursor double bond geometry could be altered by employing a (*Z*)-selective H/W/E reaction to form (*Z*)-enone **191.** This approach may also favour opposite facial attack of the cuprate and subsequent *axial* methylation could give the appropriate *cis* relative stereochemistry of the product **192**. Either route could be completed with chemistry already discussed for forming fused, bicyclic pyrone ring systems.



The latter option was pursued first, but it quickly became clear that the new series of reactions required more investigation than was possible with the limited time available. Needless to say, the methodology now exists for formation of these types of fused bicycles so further investigations would be backed by adequate precedent. The methodology appears robust and adaptable and its application to the synthesis of various systems seems limitless. Future work could examine the effects of altering the acyclic precursor stereochemistry to ascertain what effect this has on the cyclisation step.

Future work could also focus on utilising different cuprates in the conjugate addition-cyclisation to access other natural products of the tridachione series. As mentioned in the Introduction (Section 1.7.1), it was envisaged that the methodology developed for the synthesis of tridachione marine natural products was not limited to the bicyclic target that was the focus of this thesis. Indeed the method should prove amenable to the formation of tethered varieties of these natural products. The strategy design was such that from a common acyclic precursor and with the addition of the appropriate vinyl side-chain, a whole variety of tridachione natural products can conceivably be accessed (Scheme 5.1).

Thus, the common acyclic precursor could consist of the simple α,β-unsaturated ester **39**, the same α,β-unsaturated ketone **43** as used herein or the more complex α,β-unsaturated ketone **200**, with the advantage of the latter being it contains the total carbon framework for the two ring systems (Scheme 5.1). Addition of the relevant vinyl side-chain for the natural product being sought could be followed by *trans* methylation, functional group manipulation, pyrone formation and *O*-methylation to form tethered varieties of tridachione natural products, such as 9,10-deoxytridahcione (**10**). These possibilities are outlined in Scheme 5.1 and indicate the general applicability of the methodology devised for the total synthesis of these types of natural product. As can be seen with these postulated syntheses, there are several points during the synthesis that the cyclohexadiene ring could be completed, the details of which would need to be addressed during the synthesis.



Scheme 5.1: *Strategies for the synthesis of tethered pyrone-containing compounds such as 9,10-deoxytridachione (**10**).*

Chapter 6

Experimental Procedures for Chapters Two to Four

6.1 General Procedures

Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a Varian Gemini 300 spectrometer operating at 300 MHz for proton and 75.5 MHz for carbon nuclei. Chemical shifts were recorded as δ values in parts per million (ppm). Spectra were acquired in deuterochloroform ($CDCl_3$) at ambient temperature unless otherwise specified. For ^{1}H NMR spectra recorded in $CDCl_3$, the peak due to residual $CHCl_3$ (δ 7.26) was used as the internal reference. ^{1}H NMR data are recorded as follows: chemical shift (δ), multiplicity (defined as: s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sex = sextet, sept = septet, non = nonatet, m = multiplet, bs = broad singlet, app. = apparent), relative integral, coupling constant(s) *J* (Hz), assignment. For proton-decoupled ^{13}C NMR spectra recorded in $CDCl_3$, the central peak (δ 77.0) of the $CDCl_3$ triplet was used as the internal reference and the data are given as chemical shift (δ). The assignments of signals observed in various NMR spectra were assisted by conducting homonuclear (^{1}H-^{1}H) correlation spectroscopy (COSY), nuclear Overhauser effect (NOE) spectroscopy (NOESY), attached proton test (APT), heteronuclear (^{1}H-^{13}C) correlation spectroscopy (HETCOR or HMQC) and long-range heteronuclear (^{1}H-^{13}C) correlation spectroscopy (HMBC) experiments. Occasionally, these experiments were performed on a Varian Unity Inova 600 spectrometer operating at 600 MHz for proton and 150 MHz for carbon nuclei.

Low and/or high resolution mass spectra were recorded on one of the following instruments using either electron impact (EI), electrospray (ESI) or liquid secondary (LSI) ionisation techniques: Varian Saturn 4D GC/MS/MS fitted with a Zebron 30 m x 0.25 mm ID 5% phenyl polysiloxane column, (EI); Bruker BioApex II 47e FTMS fitted with an Analytica electrospray source (EI or ESI); Kratos 'Concept' high resolution double focussing mass spectrometer (EI or LSI); Micromass 'Quattro micro' (ESI). Mass spectral data are presented as follows: molecular formula, molecular ion (M^{+}, $M+H^{+}$ or $M+Na^{+}$), calculated mass and accurate mass; mass-to-charge ration (*m/z*), intensity relative to base peak.

Infrared spectra were recorded on a BIO-RAD FTS-40A Fourier Transform spectrophotometer with the absorptions recorded in wavenumbers (cm^{-1}). The bands associated with C-H stretching frequencies (2960-2850 cm^{-1}) were ubiquitous and have been omitted. Samples were analysed as thin films on NaCl discs, with solids being dissolved in CH_2Cl_2 or $CHCl_3$ before being applied to the disc and allowing the solvent to evaporate.

UV/Visible spectra were recorded using a Varian Cary 50 Scan spectrophotometer using the spectroscopic grade solvents specified.

Optical rotations were measured with a PolAAR 21 polarimeter, referenced to the sodium D line (589 nm) at 20°C, using the spectroscopic grade solvents specified and at the concentrations (*c*, g/100mL) indicated. The measurements were carried out in a cell with a 1 dm path length.

Melting points were recorded on a Reichert hot-stage apparatus and are uncorrected.

Elemental analyses were performed by the University of Otago, New Zealand.

Single crystal X-ray diffraction data were recorded and analysed at the University of Melbourne.

Analytical thin layer chromatography (tlc) was conducted on aluminium-backed 0.2 mm thick silica gel 60 F_{254} plates (Merck) and the plates were visualised under a 254 nm UV lamp and/or by treatment with either anisaldehyde dip (*p*-Anisaldehyde, 9.2 mL; H_2SO_4, 12.5 mL; AcOH, 3.75 mL; EtOH, 338 mL) or potassium permanganate dip ($KMnO_4$, 3 g; K_2CO_3, 20 g; 5% NaOH, 5 mL; H_2O, 300 mL), followed by heating with a heat gun. The retention factor (R_f) quoted is rounded to the nearest 0.01. Flash chromatography was conducted using silica gel 60 (mesh size 0.040-0.063 mm) as the stationary phase and the analytical reagent (AR) solvents indicated.

Many starting materials and reagents were available from the Sigma-Aldrich Chemical Company and were used as supplied, or dried and distilled using standard procedures.[111] Triethylamine (Et_3N) and pyridine were distilled from calcium hydride under nitrogen

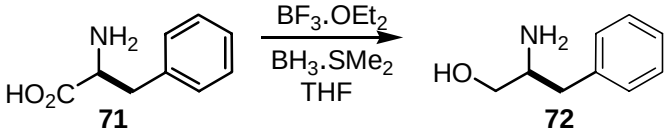
prior to use and commercially available aldehydes and acid chlorides were distilled from calcium chloride under nitrogen prior to use. Purchased organolithium reagents were freshly standardised by titration[99] prior to use, with the exception of methyl lithium (MeLi). Inorganic materials were used as received or purified according to recommended procedures.[111] Copper (I) iodide was purified by continuous extraction with THF for 12 hours.[101] Reactions employing air and/or moisture-sensitive reagents and intermediates were performed under an atmosphere of nitrogen (unless otherwise specified) in flame-dried apparatus. Anhydrous reagents were handled under nitrogen using standard techniques.

Room temperature (rt) varied between 19-25°C. Concentration *in vacuo* refers to the use of a rotary evaporator with the water bath temperature generally not exceeding 40°C.

Tetrahydrofuran (THF), diethyl ether (Et_2O) and 1,2-dimethoxyethane (DME) were dried using sodium metal wire and then distilled, as required, from sodium-benzophenone ketyl under nitrogen. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride under nitrogen as required. All other solvents used for reactions/extractions were distilled prior to use.

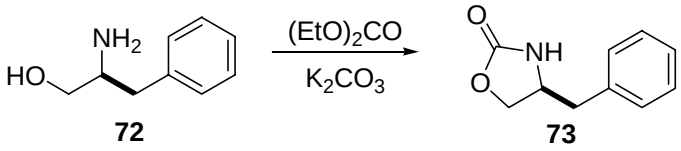
6.2 Experimental Procedures for Chapter Two

(*S*)-Phenylalanol (72)



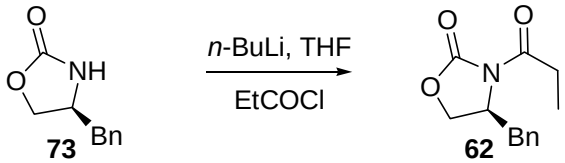
Alcohol **72** was prepared by the method of Evans and Gage[61] from (*S)*-phenylalanine (**71**) (20.00 g, 0.121 mol) as white crystals (16.50 g, 0.109 mol, 90%), after recrystallisation from EtOAc, mp 87-88.5°C (lit.[61] mp 88.5-91°C). Spectral data were identical to those reported in the literature.

(*S*)-4-(Phenylmethyl)-2-oxazolidinone (73)



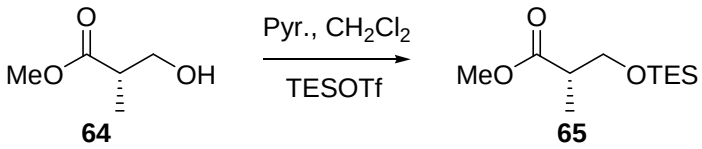
Oxazolidinone **73** was prepared by the method of Evans and Gage[61] from alcohol **72** (14.90 g, 0.098 mmol) as white crystals (15.74 g, 0.089 mol, 90%), after recrystallisation from EtOAc/hexanes (2:1), mp 84-86°C (lit.[61] mp 84.5-86.5°C). Spectral data were identical to those reported in the literature.

(*S*)-3-(1-Oxopropyl)-4-(phenylmethyl)-2-oxazolidinone (62)



N-acyloxazolidinone **62** was prepared by the method of Evans and Gage[61] from oxazolidinone **73** (15.40 g, 0.087 mol) as white needles (19.68 g, 0.084 mol, 97%), after trituration with ice-cold hexanes, mp 41-44°C (lit.[61] mp 44-46°C). Spectral data were identical to those reported in the literature. The product may be recrystallised from Et_2O/hexanes (3:1) but was generally used without further purification.

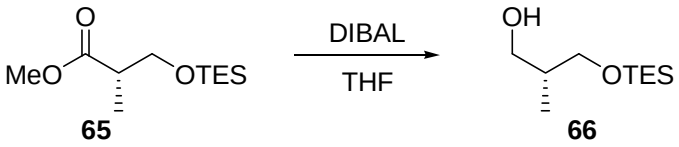
(*S*)-Methyl 3-triethylsilyloxy-2-methylpropionate (65)



64 **65**

To a stirred solution of alcohol **64** (2.00 g, 16.93 mmol) in dry CH_2Cl_2 (80 mL) under N_2 at –78°C was added pyridine (2.74 mL, 33.86 mmol) followed by TESOTf (4.59 mL, 20.32 mmol) in dry CH_2Cl_2 (15 mL) *via* cannula (5 mL rinse). The mixture was stirred at –78°C for 30 minutes and then at rt overnight. The reaction mixture was diluted with CH_2Cl_2 (100 mL), the phases were separated and the organic phase was washed with $CuSO_4$ (sat., 3 x 50 mL), $NaHCO_3$ (sat., 3 x 50 mL) and brine (50 mL). The dried ($MgSO_4$) organic extracts were filtered and concentrated *in vacuo* to yield a colourless oil. Purification by flash chromatography on silica (75% CH_2Cl_2/hexanes, R_f = 0.43) gave the title compound **65** (3.62 g, 15.58 mmol, 92%) as a colourless oil. Spectral data were identical to those reported in the literature.[62]

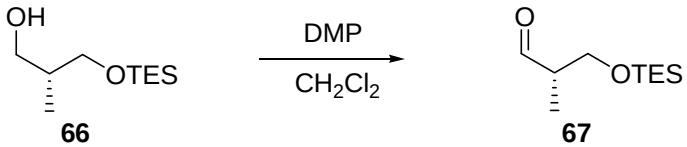
(*R*)-3-Triethylsilyloxypropan-1-ol (66)



65 **66**

Alcohol **66** was prepared by the method of Smith *et al.*[62] from ester **65** (3.20 g, 13.77 mmol) as a colourless oil (1.83 g, 8.95 mmol, 65%) after flash chromatography on silica (30% Et_2O/hexanes, R_f = 0.24). Spectral data were identical to those reported in the literature.[62]

(*S*)-3-Triethylsilyloxy-2-methylpropional (67)

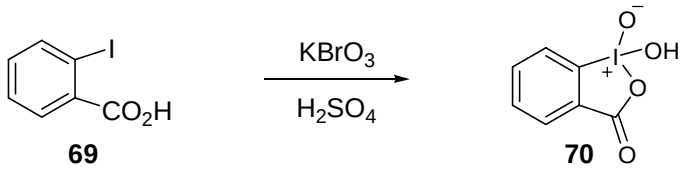


66 **67**

To a stirred suspension of Dess-Martin periodinane[65] (1.59 g, 3.67 mmol) in dry CH_2Cl_2 (10 mL) under N_2 was added a solution of alcohol **66** (0.500 g, 2.45 mmol) in dry CH_2Cl_2 (10 mL) *via* cannula (5 mL rinse) and the reaction was stirred at rt for 2 hours.

The reaction mixture was diluted with Et_2O (50 mL) and quenched with a solution of $NaHCO_3$ (sat., 50 mL) containing $Na_2S_2O_3.5H_2O$ (6.36 g, 25.62 mmol) and stirred for a further 5 minutes. The phases were separated and the organic phase was washed with $NaHCO_3$ (sat., 50 mL) and brine (50mL). The dried ($MgSO_4$) organic extracts were filtered and concentrated *in vacuo* to yield a colourless oil which was purified by flash chromatography on silica (75% CH_2Cl_2/hexanes, R_f = 0.45) to give the title compound **67** (0.396 g, 1.96 mmol, 80%) as a colourless oil. **^{1}H NMR** δ 9.74 (d, 1H, *J* = 1.6 Hz, C*H*O), 3.85-3.81 (m, 2H, C*H*$_2$OTES), 2.60-2.48 (m, 1H, C*H*(CH_3)), 1.09 (d, 3H, *J* = 7.2 Hz, CH(C*H*$_3$)), 0.94 (t, 9H, *J* = 7.9 Hz, C*H*$_3$CH$_2$Si), 0.59 (q, 6H, *J* = 7.9 Hz, CH$_3$C*H*$_2$Si); **^{13}C NMR** δ 204.7, 63.2, 48.5, 10.3, 6.7, 4.3.

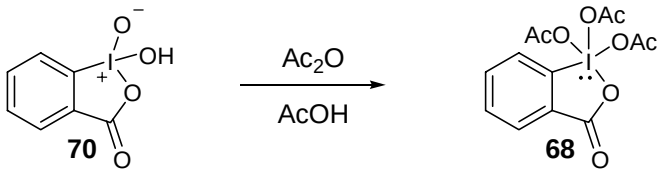
2-Iodoxybenzoic acid (70)



69 **70**

Acid **70** was prepared by the method of Dess and Martin[65] from 2-iodobenzoic acid **69** (30.00 g, 0.121 mol) as a white solid (29.49 g, 0.105 mol, 87%), mp 232-234°C (lit.[112] mp 233°C). Spectral data were identical to those reported in the literature.[65]

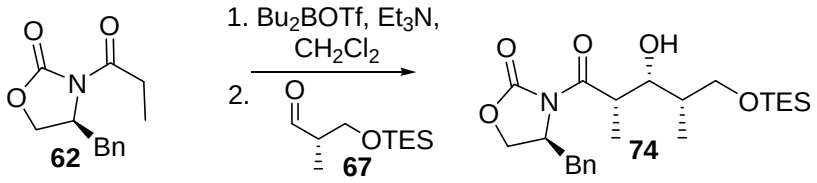
1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one (68)



70 **68**

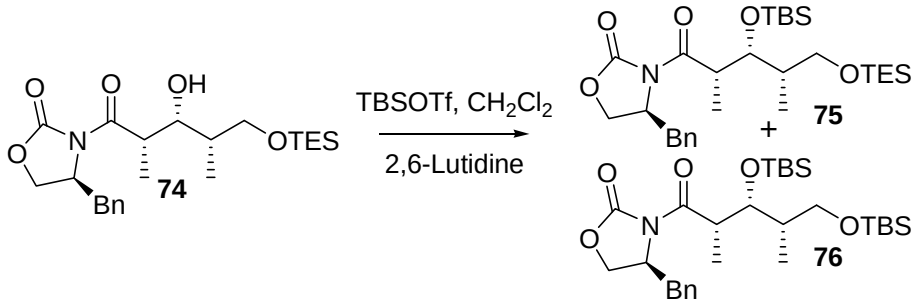
Tris acylated **68** was prepared by the method of Dess and Martin[65] from acid **70** (29.49 g, 0.105 mol) as white crystals (31.69 g, 0.0747 mol, 71%). Spectral data were identical to those reported in the literature.[65]

(*S*)-4-Benzyl-3-[(*2S*,3*R*,4*R*)-*3*-hydroxy-2,4-dimethyl-5-triethylsilyloxypentanoyl]-oxazolidin-2-one (74)



To a stirred solution of *N*-acyloxazolidinone **62** (2.29 g, 9.83 mmol) in dry CH_2Cl_2 (15 mL) under N_2 at 0°C was added Bu_2BOTf (1M in CH_2Cl_2, 11.80 mL, 11.80 mmol) followed by Et_3N (1.78 mL, 12.78 mmol) dropwise. The mixture was stirred at 0°C for 30 minutes, cooled to –78°C and aldehyde **67** (0.995 g, 4.92 mmol) in dry CH_2Cl_2 (5 mL) was added *via* cannula (5 mL rinse) over a 5 minute period. The solution was stirred at –78°C for 20 minutes and at 0°C for 4 hours before being quenched with pH 7 buffer (10 mL) and methanol (30 mL). To this cloudy solution was added *carefully* at 0°C a 2:1 mixture of methanol/30% H_2O_2 (30mL) and the resulting solution was stirred at rt for 1 hour. The volatile components were removed *in vacuo* and the resulting slurry was extracted with CH_2Cl_2 (3 x 75 mL). The organic extracts were washed with $NaHCO_3$ (sat., 100mL) and brine (100mL). The dried ($MgSO_4$) organic extracts were filtered and concentrated *in vacuo* to yield a yellow oil which was purified by flash chromatography on silica (5% Et_2O/CH_2Cl_2, R_f = 0.37) to give the title compound **74** (1.34 g, 3.08 mmol, 63%, >95% ds) as a colourless oil, plus recovered auxiliary **62** (1.18 g, R_f = 0.54). **IR** (film) 3510 (br), 1784, 1696, 1455, 1384, 1210 cm^{-1}; **^{1}H NMR** δ 7.38-7.17 (m, 5H, Ar*H*), 4.72-4.61 (m, 1H, aux. $PhCH_2CH$), 4.20-4.16 (m, 2H, aux. ring CH_2), 4.08 (dd, 1H, *J* = 7.0, 3.8 Hz, C*H*OH), 3.97 (app. qn, 1H, *J* = 6.9 Hz, $COCH(CH_3)$), 3.75 (dd, 1H, *J* = 9.9, 4.0 Hz, CH_AH_BOTES), 3.64 (dd, 1H, *J* = 9.9, 4.2 Hz, CH_AH_BOTES), 3.37 (bs, 1H, O*H*), 3.25 (dd, 1H, *J* = 13.2, 3.0 Hz, aux. $PhCH_AH_B$), 2.77 (dd, 1H, *J* = 13.2, 9.4 Hz, aux. $PhCH_AH_B$), 1.80-1.69 (m, 1H, $CH(CH_3)CH_2$), 1.34 (d, 3H, *J* = 6.6 Hz, $COCH(CH_3)$), 0.99 (d, 3H, *J* = 6.9 Hz, $CH(CH_3)CH_2$), 0.96 (t, 9H, *J* = 7.8 Hz, $SiCH_2CH_3$), 0.61, (q, 6H, *J* = 7.8 Hz $SiCH_2CH_3$); **^{13}C NMR** δ 176.7, 152.7, 135.1, 129.4, 128.9, 127.4, 74.6, 67.5, 66.0, 55.1, 41.0, 37.7, 37.4, 13.5, 11.3, 6.6, 4.2; **HRESIMS** calculated for $C_{23}H_{37}NO_5SiNa^+$ ($M+Na^+$): 458.2339; found: 458.2335; **EIMS** *m/z* (%): 435 (M^+, 1), 406 (6), 262 (13), 233 (10), 178 (25), 145 (22), 117 (28), 92 (100), 87 (82), 71 (22), 65 (23), 57 (35).

(*S*)-4-Benzyl-3-[(*2S*,3*R*,4*S*)-*3*-(*tert*-butyldimethylsilyloxy)-2,4-dimethyl-5-triethylsilyloxypentanoyl]-oxazolidin-2-one (75) and (*S*)-4-benzyl-3-[(*2S*,3*R*,4*S*)-*3*-(*tert*-butyldimethylsilyloxy)-2,4-dimethyl-5-*tert*-butyldimethylsilyloxypentanoyl]-oxazolidin-2-one (76)



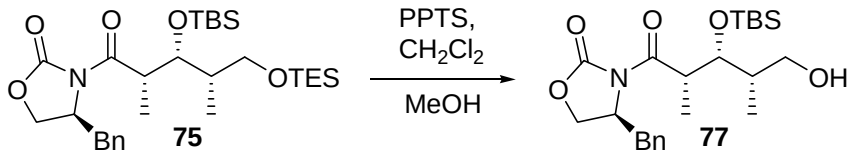
To a stirred solution of aldol adduct **74** (0.900 g, 2.06 mmol) in dry CH_2Cl_2 (10 mL) under N_2 at –78°C was added 2,6-lutidine (0.720 mL, 6.20 mmol) dropwise, followed by TBSOTf (0.710 mL, 3.10 mmol) dropwise. The mixture was stirred at –78°C for 1 hour and at rt for 1 hour before being diluted with CH_2Cl_2 (50 mL) and quenched with $NaHCO_3$ (sat., 30 mL). The phases were separated, the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic phases were washed with brine (30 mL). The dried ($MgSO_4$) organic extracts were filtered and concentrated *in vacuo* to yield a pale yellow oil which was purified by flash chromatography on silica (10% hexanes/CH_2Cl_2, R_f =0.57) to give an inseparable mixture (~ 4:1) of TES compound **75** and its isomeric di-TBS protected analogue **76** (1.05 g, 1.91 mmol, 92%) as a colourless oil. **IR** (film) 1786, 1699, 1457, 1383, 1252, 1210, 1115, 1090, 1049, 838, 775 cm^{-1}; **HRESIMS** calculated for $C_{29}H_{51}NO_5Si_2Na^+$ ($M+Na^+$): 572.3204; found: 572.3208; **EIMS** *m/z* (%): 550 (M^+, 1), 520 (39), 492 (66), 450 (29), 315 (40), 290 (78), 262 (49), 241 934), 199 (50), 185 (52), 117 (100), 91 (77).

TES compound **75**: **^{1}H NMR** δ 7.36-7.18 (m, 5H, Ar*H*), 4.66-4.58 (m, 1H, aux. $PhCH_2CH$), 4.22-4.14 (m, 2H, aux. ring CH_2), 4.09 (dd, 1H, *J* = 7.7, 2.6 Hz, C*H*OTBS), 3.99 (app. qn, 1H, *J* = 7.2 Hz, $COCH(CH_3)$), 3.58 (dd, 1H, *J* = 9.8, 6.2 Hz, CH_AH_BOTES), 3.38 (dd, 1H, *J* = 9.8, 8.3 Hz, CH_AH_BOTES), 3.26 (dd, 1H, *J* = 13.2, 3.0 Hz, aux. $PhCH_AH_B$), 2.76 (dd, 1H, *J* = 13.2, 9.6 Hz, aux. $PhCH_AH_B$), 1.74-1.64 (m, 1H, $CH(CH_3)CH_2$), 1.24 (d, 3H, *J* = 6.9 Hz, $COCH(CH_3)$), 0.95 (t, 9H, *J* = 8.0 Hz, $SiCH_2CH_3$), 0.91 (s, 9H, $SiC(CH_3)_3$), 0.88 (d, 3H, *J* = 6.9Hz, $CH(CH_3)CH_2$), 0.59 (q, 6H, *J* = 8.0 Hz, $SiCH_2CH_3$), 0.078 (s, 3H, $SiCH_3$), 0.067 (s, 3H, $SiCH_3$); **^{13}C NMR** δ

175.9, 152.8, 135.3, 129.4, 128.9, 127.3, 73.2, 65.9, 65.7, 55.5, 42.0, 41.2, 37.7, 26.1, 18.4, 14.9, 11.2, 6.8, 4.4, -3.9, -4.0.

Di-TBS analogue **76**: **^{1}H NMR** δ 7.36-7.18 (m, 5H, Ar*H*), 4.66-4.58 (m, 1H, aux. $PhCH_2CH$), 4.20-4.14 (m, 2H, aux. ring CH_2), 4.13 (dd, 1H, *J* = 7.8, 2.7 Hz, C*H*OTBS), 4.01 (app. qn, 1H, *J* = 7.0 Hz, $COCH(CH_3)$), 3.57 (dd, 1H, *J* = 9.9, 6.9 Hz, CH_AH_BOTBS), 3.39 (dd, 1H, *J* = 9.9, 7.7 Hz, CH_AH_BOTBS), 3.25 (dd, 1H, *J* = 13.2, 3.3 Hz, aux. $PhCH_AH_B$), 2.77 (dd, 1H, *J* = 13.2, 8.8 Hz, aux. $PhCH_AH_B$), 1.77-1.63 (m, 1H, $CH(CH_3)CH_2$), 1.25 (d, 3H, *J* = 7.0 Hz, $COCH(CH_3)$), 0.92 (s, 9H, $SiC(CH_3)_3$), 0.91 (s, 9H, $SiC(CH_3)_3$), 0.86 (d, 3H, *J* = 6.9 Hz, $CH(CH_3)CH_2$), 0.092 (s, 3H, $SiCH_3$), 0.080 (s, 3H, $SiCH_3$), 0.049 (s, 3H, $SiCH_3$), 0.046 (s, 3H, $SiCH_3$); **^{13}C NMR** δ 175.8, 152.8, 135.3, 129.4, 128.9, 127.3, 72.9, 65.8, 65.7, 55.5, 41.9, 41.1, 37.6, 26.1, 25.9, 18.4, 18.2, 14.8, 11.0, -3.9, -4.0, -5.3, -5.4.

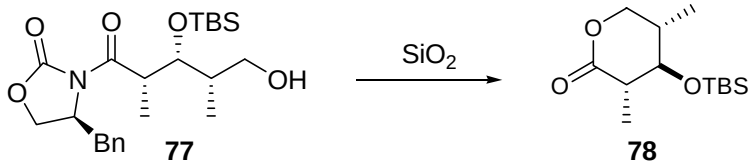
(*S*)-4-Benzyl-3-[(*2S*,3*R*,4*S*)-*3*-(*tert*-butyldimethylsilyloxy)-5-hydroxy-2,4-dimethyl-pentanoyl]-oxazolidin-2-one (77)



A solution of the di-protected aldol **75/76** mixture (1.05 g, 1.91 mmol) and PPTS (10 mg) in dry CH_2Cl_2 (15 mL) and dry MeOH (15 mL) was stirred under N_2 at rt for 14 hours. The reaction was quenched with $NaHCO_3$ (sat., 50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a pale yellow oil. Purification by flash chromatography on buffered silica (30% Et_2O/CH_2Cl_2, R_f = 0.44) gave the title compound **77** (0.496 g, 1.14 mmol, 72%, based on recovery of di-TBS product **76** [0.175 g, 0.318 mmol]) as a colourless oil. **$[\alpha]_D$** +55 (*c* 1.00, $CHCl_3$); **IR** (film) 3504 (br), 1782, 1697, 1387, 1352, 1253, 1211, 1110, 1049, 838, 775 cm^{-1}; **^{1}H NMR** δ 7.35-7.18 (m, 5H, Ar*H*), 4.67-4.60 (m, 1H, aux. $PhCH_2CH$), 4.18-4.15 (m, 3H, aux. ring CH_2, C*H*OTBS), 3.97 (app. qn, 1H, *J* = 6.9 Hz, $COCH(CH_3)$), 3.61-3.51 (m, 2H, CH_2OH), 3.24 (dd, 1H, *J* = 13.3, 3.2 Hz, aux. $PhCH_AH_B$), 2.76 (dd, 1H, *J* = 13.3, 9.4 Hz, aux. $PhCH_AH_B$), 2.10 (bs, 1H, O*H*), 1.87-1.75, (m, 1H, $CH(CH_3)CH_2$), 1.25 (d, 3H, *J* = 6.9 Hz, $COCH(CH_3)$), 0.91 (s, 9H, $SiC(CH_3)_3$), 0.88 (d, 3H, *J* = 7.2 Hz, $CH(CH_3)CH_2$), 0.093 (s, 3H, $SiCH_3$), 0.042 (s, 3H, $SiCH_3$); **^{13}C NMR** δ 175.6, 153.1, 135.1, 129.4, 128.9, 127.3, 73.2, 66.0, 65.3, 55.5,

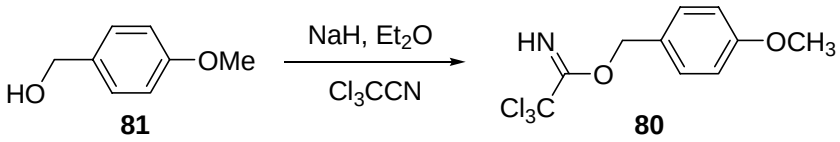
41.7, 40.8, 37.5, 26.0, 18.3, 13.7, 12.2, -4.0, -5.2; **HRESIMS** calculated for $C_{23}H_{37}NO_5SiNa^+$ ($M+Na^+$): 458.2339; found: 458.2343; **EIMS** *m/z* (%): 201 (13), 157 (56), 145 (86), 115 (100), 83 (69), 75 (65), 57 (32), 49 (52).

(3*S*,4*R*,5*S*)-4-(*tert*-Butyldimethylsilyloxy)-3,5-dimethyltetrahydropyran-2-one (78)



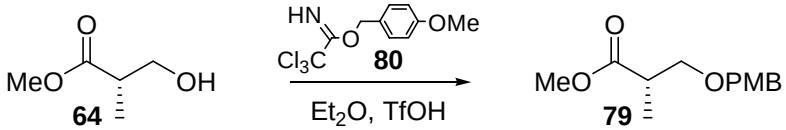
On occasions where buffered silica was not used or the column not performed swiftly enough (or by treatment of an NMR sample with *p*-TsOH) the primary alcohol underwent acid-catalysed cyclisation to the known lactone[69] **78** with identical spectral properties to those reported in the literature.[113] The chiral auxiliary **62** was also recovered during chromatography.

4-Methoxybenzyl-2,2,2-trichloroacetimidate (80)



Acetimidate **80** was prepared by the method of Nakajima *et al.*[71] from 4-methoxybenzyl alcohol (**81**) (20.00 g, 0.145 mmol) as a yellow oil (39.93 g, 0.141 mmol, 98%). The acetimidate was used without further purification. **^{1}H NMR** δ 8.36 (s, 1H, N*H*), 7.38 (d, 2H, *J* = 8.7 Hz, Ar*H*), 6.91 (d, 2H, *J* = 8.7 Hz, Ar*H*), 5.28 (s, 2H CH_2Ar), 3.82 (s, 3H, OCH_3); **^{13}C NMR** δ 162.6, 159.7, 129.7, 127.5, 113.9, 70.7, 55.2.

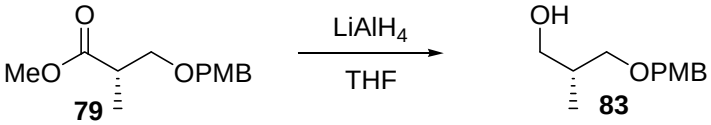
(*S*)-Methyl 3-(4-methoxybenzyloxy)-2-methylpropionate (79)



To a stirred solution of alcohol **64** (11.00 g, 0.093 mol) and acetimidate **80** (39.46g, 0.140 mol) in dry Et_2O (170 mL) under N_2 at 0°C was added TfOH (25 μL, 0.279 mmol) dropwise and the mixture was stirred at rt for 45 minutes. After this time another

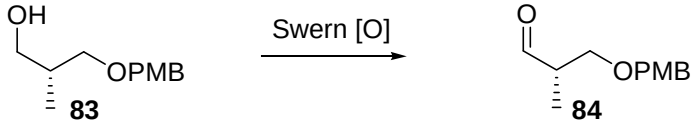
portion of TfOH (25 μL, 0.279 mmol) was added dropwise and the reaction went quickly to completion (tlc). The reaction was quenched with $NaHCO_3$ (sat., 100mL), the organic phase was separated and washed with brine (50 mL) and dried ($MgSO_4$). The dried organic extracts were filtered and concentrated *in vacuo* to yield a yellow oil which was distilled under reduced pressure to give the title compound **79** (18.44 g, 0.077 mol, 83%) as a colourless oil bp 100-108°C at 0.07 mmHg (lit.[72] bp 98-110°C at 0.07 mmHg). Spectral data were identical to those reported in the literature[72] with the exception of the peak at 4.45 ppm which should read (s, 2H) instead of (s, 3H).

(*R*)-3-(4-Methoxybenzyloxy)-2-methylpropan-1-ol (83)



To a stirred solution of $LiAlH_4$ (0.876 g, 0.023 mol) in dry THF (35 mL) under N_2 at 0°C was added a solution of ester **79** (5.00 g, 0.021 mol) in dry THF (25 mL) at 0°C *via* cannula (10 mL rinse) over 10 minutes. The solution was warmed to rt and stirred for 30 minutes. The mixture was cooled to 0°C and quenched by the successive dropwise addition of water (1mL), 15% NaOH (1 mL) and more water (3 mL). The resultant mixture was diluted with Et_2O (50 mL), dried ($MgSO_4$) and filtered. The filter cake was rinsed with Et_2O (50 mL) and the organic extracts were concentrated *in vacuo* to yield the title compound **83** (4.06 g, 0.019 mol, 92%) as a colourless oil. The product was used without further purification in the following step. **^{1}H NMR** δ 7.25 (d, 2H, *J* = 8.7 Hz, Ar*H*), 6.88 (d, 2H, *J* = 8.7 Hz, Ar*H*), 4.45 (s, 2H CH_2Ar), 3.81 (s, 3H, OCH_3), 3.64-3.57 (m, 2H, CH_2OTES), 3.53 (dd, 1H, *J* = 9.0, 3.3 Hz, CH_AH$_B$OH), 3.39 (dd, 1H, *J* = 9.0, 8.2 Hz, CH$_A$*H*$_B$OH), 2.16 (bs, 1H, O*H*), 2.15-2.00 (m, 1H, C*H*(CH$_3$)), 0.87 (d, 3H, *J* = 7.2 Hz, CH(CH_3)); **^{13}C NMR** δ 159.2, 130.1, 129.2, 113.8, 75.3, 73.0, 68.0, 55.2, 35.5, 13.4.

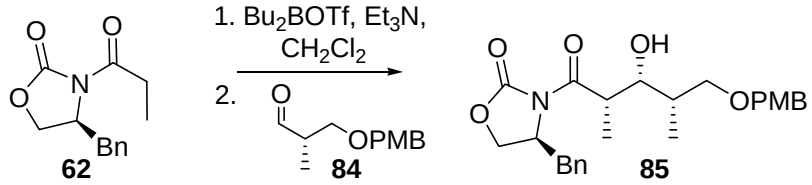
(*S*)-3-(4-Methoxybenzyloxy)-2-methylpropional (84)



To a stirred solution of DMSO (6.07 mL, 0.086 mol) in CH_2Cl_2 (125 mL) under N_2 at –78°C was added oxalyl chloride (2M in CH_2Cl_2, 21.40 mL, 0.043 mol) over 10 minutes

and the solution was stirred for 30 minutes at –78°C. A solution of alcohol **83** (6.00 g, 0.028 mol) in dry CH_2Cl_2 (10 mL) was added dropwise *via* cannula (5 mL rinse) down the side of the flask over 10 minutes. The resultant mixture was stirred for 45 minutes at –78°C, then Et_3N (23.86 mL, 0.171 mol) was added over 15 minutes and stirring was continued at –78°C for 30 minutes. The reaction was slowly warmed to 0°C and quenched by addition to a vigorously stirred solution of $NaHSO_4$ (1M, 170 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organic phases were concentrated *in vacuo*, diluted with Et_2O (100 mL) and washed successively with $NaHSO_4$ (1M, 3 x 30 mL), water (30 mL), $NaHCO_3$ (sat., 30 mL) and brine (30 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the title compound **84** (5.85 g, 0.028 mol, 98%) as a colourless oil with identical spectral data to those reported in the literature.[72] The aldehyde was used without further purification in the next step.

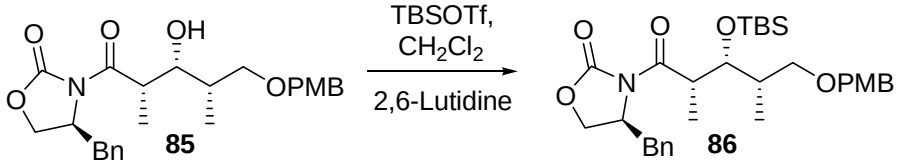
(*S*)-4-Benzyl-3-[(*2S*,3*R*,4*R*)-*3*-hydroxy-5-(4-methoxybenzyloxy)-2,4-dimethylpent-anoyl]-oxazolidin-2-one (85)



To a stirred solution of *N*-acyloxazolidinone **62** (10.71 g, 0.046 mol) in dry CH_2Cl_2 (65 mL) under N_2 at 0°C was added Bu_2BOTf (1M in CH_2Cl_2, 55.32 mL, 0.055 mol) and the deep red solution was stirred at 0°C for 30 minutes. To this solution was added Et_3N (8.35 mL, 0.060 mol) dropwise and the yellow mixture was stirred at 0°C for 30 minutes before being cooled to –78°C. A solution of aldehyde **84** (4.80 g, 0.023 mol) in dry CH_2Cl_2 (30 mL) was added *via* cannula (10 mL rinse) over a 15 minute period and the yellow solution was stirred at –78°C for 30 minutes and at 0°C for 2.5 hours. The reaction was quenched with pH 7 buffer (40 mL) and methanol (125 mL). To this cloudy solution was added *carefully* at 0°C a 2:1 mixture of methanol/30% H_2O_2 (126 mL) and the resulting solution was stirred at rt for 1 hour, affording a homogeneous solution. The volatile components were removed *in vacuo* and the resulting slurry was extracted with CH_2Cl_2 (3 x 200 mL). The organic extracts were washed with $NaHCO_3$ (sat., 200 mL) and brine (150 mL) and dried ($MgSO_4$). The dried organic extracts were filtered and concentrated *in vacuo* to yield a yellow oil which was purified by flash

chromatography on silica (5% Et_2O/CH_2Cl_2, R_f = 0.15) to give the title compound **85** (8.45 g, 0.019 mol, 83%, >95% ds) as a colourless oil, plus recovered auxiliary **62** (5.25 g). **[α]$_D$** = +44.0 (*c* 1.00, $CHCl_3$); **IR** (film) 3511 (br), 1780, 1695, 1613, 1514, 1456, 1384, 1354, 1248, 1211, 1110, 1034, 972 cm^{-1}; **^{1}H NMR** δ 7.36-7.19 (m, 7H, Ar*H*), 6.89-6.85 (m, 2H, Ar*H*), 4.70-4.62 (m, 1H, $PhCH_2CH$), 4.43 (s, 2H, OCH_2Ar), 4.23-4.16 (m, 2H, aux. ring CH_2), 4.04-3.92 (m, 2H, $COCH(CH_3)$, C*H*OH), 3.80 (s, 3H, $ArOCH_3$), 3.50-3.41 (m, 2H, CH_2OPMB), 3.25 (dd, 1H, *J* = 13.4, 3.2 Hz, aux. $PhCH_AH_B$), 2.77 (dd, 1H, *J* = 13.4, 9.4 Hz, aux. $PhCH_AH_B$), 2.30 (bs, 1H, O*H*), 1.94-1.83 (m, 1H, $CH(CH_3)CH_2$), 1.32 (d, 3H, *J* = 6.6 Hz, $COCH(CH_3)$), 1.02 (d, 3H, *J* = 6.9 Hz, $CH(CH_3)CH_2$); **^{13}C NMR** δ 177.0, 159.1, 152.7, 135.0, 130.3, 129.4, 129.2, 128.9, 127.4, 113.7, 74.0, 73.8, 72.9, 66.0, 55.2, 55.1, 40.6, 37.7, 36.2, 12.8, 12.4; **HRESIMS** calculated for $C_{25}H_{31}NO_6Na^+$ ($M+Na^+$): 464.2049; found: 464.2038; **EIMS** *m/z* (%): 441 (M^+, 1), 233 (9), 208 (5), 190 (15), 175 (9), 142 (13), 137 (45), 121 (100), 111 (7), 91 (18), 57 (48).

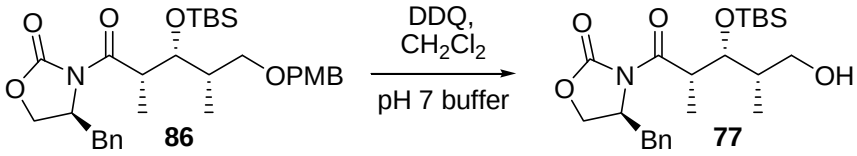
(*S*)-4-Benzyl-3-[(*2S*,3*R*,4*S*)-*3*-(*tert*-butyldimethylsilyloxy)-5-(4-methoxybenzyloxy)-2,4-dimethylpentanoyl]-oxazolidin-2-one (86)



To a stirred solution of aldol adduct **85** (8.29 g, 18.8 mmol) in dry CH_2Cl_2 (94 mL) under N_2 at –78°C was added 2,6-lutidine (4.37 mL, 37.6 mmol) dropwise, followed by TBSOTf (6.47 mL, 28.2 mmol) dropwise. The mixture was stirred at –78°C for 4 hours before being warmed to rt and quenched with $NaHCO_3$ (sat., 75 mL). The phases were separated, the aqueous phase was extracted with CH_2Cl_2 (3 x 100 mL) and the combined organic phases were washed with brine (50 mL) and dried ($MgSO_4$). The dried organic extracts were filtered and concentrated *in vacuo* to yield a pale yellow oil which was purified by flash chromatography on silica (10% hexanes/CH_2Cl_2, R_f = 0.22) to give the title compound **86** (10.10 g, 18.2 mmol, 97%) as a colourless oil. **[α]$_D$** = +36.0 (*c* 1.00, $CHCl_3$); **IR** (film) 1783, 1696, 1514, 1384, 1249, 1210, 1116, 1041, 838 cm^{-1}; **^{1}H NMR** δ 7.36-7.18 (m, 7H, Ar*H*), 6.87 (d, 2H, *J* = 8.4 Hz, Ar*H*), 4.66-4.57 (m, 1H, $PhCH_2CH$), 4.42 (s, 2H, OCH_2Ar), 4.17-4.08 (m, 3H, aux. ring CH_2, C*H*OTBS), 3.98 (app. qn, 1H, *J* = 7.0 Hz, $COCH(CH_3)$), 3.80 (s, 3H, $ArOCH_3$), 3.45 (dd, 1H, *J* =

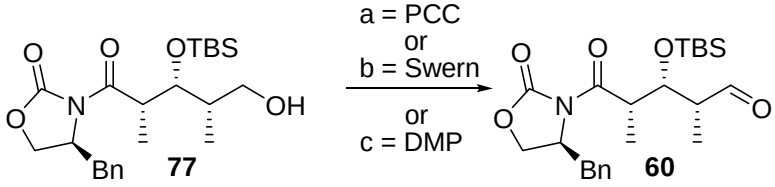
9.2, 6.2 Hz, CH_AH$_B$OPMB), 3.27-3.22 (m, 2H, CH$_A$$H_B$OPMB, aux. PhC$H_AH_B$), 2.75 (dd, 1H, *J* = 13.2, 9.9 Hz, aux. PhCH$_A$$H_B$), 1.91-1.83 (m, 1H, C$H$(CH$_3$)CH$_2$), 1.24 (d, 3H, *J* = 6.9 Hz, COCH(CH_3)), 0.92 (m, 12H, CH(CH_3)CH$_2$, SiC(CH_3)$_3$), 0.057 (s, 3H, SiCH_3), 0.041 (s, 3H, SiCH_3); **^{13}C NMR** δ 175.9, 159.0, 152.8, 135.3, 130.8, 129.4, 129.2, 128.9, 12734, 113.7, 73.5, 72.8, 72.5, 65.9, 55.4, 55.3, 41.9, 38.9, 37.6, 26.1, 18.4, 15.0, 11.9, -3.9, -4.1; **HRLSIMS** calculated for $C_{31}H_{46}NO_6Si^+$ (M+H$^+$): 556.3095; found: 556.3088; **EIMS** *m/z* (%): 540 (87), 498 (20), 376 (8), 290 (45), 199 (31), 121 (100).

(*S*)-4-Benzyl-3-[(*2S*,3*R*,4*S*)-*3*-(*tert*-butyldimethylsilyloxy)-5-hydroxy-2,4-dimethyl-pentanoyl]-oxazolidin-2-one (77)



To a stirred solution of PMB ether **86** (2.42 g, 4.35 mmol) in CH_2Cl_2 (85 mL) and pH 7 buffer (8.5 mL) at 0°C was added DDQ (1.28 g, 5.66 mmol) and the solution was stirred at 0°C for 4 hours. The reaction was diluted with CH_2Cl_2 (100 mL) and quenched with $NaHCO_3$ (sat., 200 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were washed with $NaHCO_3$ (sat., 2 x 30 mL) and brine (30 mL). The dried ($MgSO_4$) organic extracts were filtered and concentrated *in vacuo* to yield a colourless oil which was purified by flash chromatography on buffered silica (10% Et_2O/CH_2Cl_2, R_f = 0.27) to yield the title compound **77** (1.85 g, 4.25 mmol, 96%) as a colourless oil with identical spectral data to that synthesised previously.

(2*R*,3*S*,4*S*)-5-[(*S*)-4-Benzyl-2-oxo-oxazolidin-3-yl]-3-(*tert*-butyldimethylsilyloxy)-2,4-dimethyl-5-oxopentanal (60)



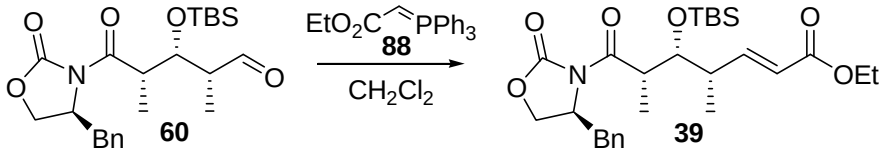
a) To a stirred suspension of PCC (0.735 g, 3.41 mmol) in dry CH_2Cl_2 (40 mL) under N_2 at rt was added alcohol **77** (0.495 g, 1.14 mmol) in dry CH_2Cl_2 (10 mL) *via* cannula

(10 mL rinse) and the mixture was stirred at rt for 3 hours. After this time the reaction mixture was triturated with dry Et_2O (*ca.* 200 mL), filtered (florisil) and concentrated *in vacuo* to yield a colourless oil (0.445 g, 1.03 mmol, 90%). A small amount of product was purified by flash chromatography on silica (10% Et_2O/CH_2Cl_2, R_f = 0.64) to give the title compound **60** as a colourless oil. The remainder of the product was used without further purification in the next step. **$[\alpha]_D$** = +18.7 (*c* 1.55, $CHCl_3$); **IR** (film) 1783, 1724, 1695, 1456, 1385, 1254, 1212, 1114, 1031, 972, 838, 777 cm^{-1}; **^{1}H NMR** δ 9.79 (d, 1H, *J* = 0.9 Hz), 7.36-7.18 (m, 5H, Ar*H*), 4.67-4.60 (m, 1H, aux. $PhCH_2CH$), 4.56 (dd, 1H, *J* = 6.8, 3.8 Hz, C*H*OTBS), 4.24-4.17 (m, 2H, aux. ring CH_2), 3.96 (app. qn, 1H, *J* = 6.9 Hz, $COCH(CH_3)$), 3.25 (dd, 1H, *J* = 13.3, 3.3 Hz, aux. $PhCH_AH_B$), 2.77 (dd, 1H, *J* = 13.3, 9.6 Hz, aux. $PhCH_AH_B$), 2.52-2.44 (m, 1H, $CH(CH_3)CHO$), 1.26 (d, 3H, *J* = 6.9 Hz, $COCH(CH_3)$), 1.10 (d, 3H, *J* = 6.9 Hz, $CH(CH_3)CHO$), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.073 (s, 3H, $SiCH_3$), 0.023 (s, 3H, $SiCH_3$); **^{13}C NMR** δ 204.0, 175.0, 152.8, 135.0, 129.4, 129.0, 127.4, 71.8, 66.1, 55.4, 51.7, 42.3, 37.6, 25.8, 18.2, 14.8, 8.2, -5.0, -4.4; **HRESIMS** calculated for $C_{23}H_{35}NO_5SiNa^+$ ($M+Na^+$): 456.2182; found: 456.2185; **EIMS** *m/z* (%): 433 (M^+, 1), 376 (24), 318 (74), 199 (100), 143 (51), 115 (63), 91 (83).

b) To a stirred solution of DMSO (1.65 mL, 23.2 mmol) in dry CH_2Cl_2 (35 mL) under N_2 at –78°C was added oxalyl chloride (2M in CH_2Cl_2, 5.80 mL, 11.6 mmol) dropwise and the solution was stirred for 30 minutes at –78°C. A solution of alcohol **77** (3.37 g, 7.74 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise *via* cannula (5 mL rinse) down the side of the flask. The resulting mixture was stirred for 45 minutes at –78°C, Et_3N (6.47 mL, 46.4 mmol) was added dropwise and stirring was continued at –78°C for 30 minutes. The solution was slowly warmed to 0°C and quenched by addition to a vigorously stirred solution of $NaHSO_4$ (1M, 50 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organic phases were concentrated *in vacuo*, diluted with Et_2O (100 mL) and washed successively with $NaHSO_4$ (1M, 20 mL), water (20 mL), $NaHCO_3$ (sat., 20 mL) and brine (20 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a colourless oil (3.33 g, 7.68 mmol, 99%). A small amount of product was purified by flash chromatography on silica (10% Et_2O/CH_2Cl_2, R_f = 0.64) to give aldehyde **60** as a colourless oil with identical spectral properties to those above. The remainder of the aldehyde was used without further purification.

c) To a stirred suspension of Dess-Martin periodinane[65] (1.14 g, 2.68 mmol) in dry CH_2Cl_2 (5 mL) under N_2 was added a solution of alcohol **77** (0.780 g, 1.79 mmol) in dry CH_2Cl_2 (2 mL) *via* cannula (2 mL rinse) and the reaction was stirred at rt for 2 hours. The reaction mixture was diluted with Et_2O (75 mL) and quenched with a solution of $NaHCO_3$ (sat., 25 mL) containing $Na_2S_2O_3.5H_2O$ (4.56 g, 18.4 mmol) and stirring was continued for 5 minutes. The phases were separated, and the organic phase was washed with $NaHCO_3$ (sat., 20 mL) and brine (20 mL). The dried ($MgSO_4$) organic extracts were filtered and concentrated *in vacuo* to yield aldehyde **60** as a colourless oil (0.775 g, 1.79 mmol, *ca.* 100%) with identical spectral properties to those above. The product was used without further purification.

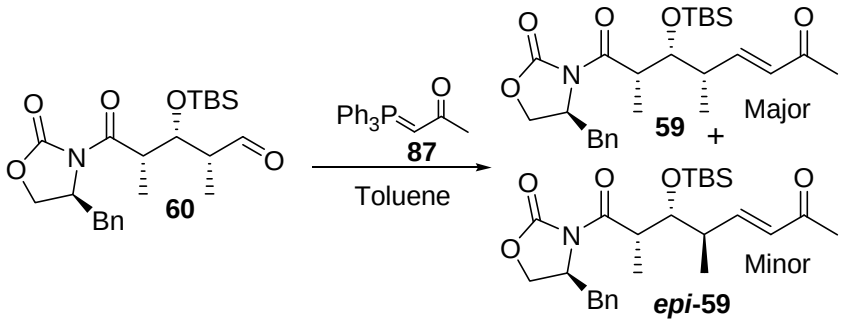
(2*E*,4*S*,5*R*,6*S*)-Ethyl 7-[(*S*)-4-benzyl-2-oxo-oxazolidin-3-yl]-5-(*tert*-butyldimethyl-silyloxy)-4,6-dimethyl-7-oxohept-2-enoate (39)



A solution of aldehyde **60** (0.440 g, 1.01 mmol) and (carbethoxymethylene)triphenyl-phosphorane (**88**) (0.530 g, 1.52 mmol) was stirred in dry CH_2Cl_2 (10 mL) under N_2 for 4.5 days. The solvent was removed *in vacuo* and the residue was triturated with hexanes (*ca.* 150 mL) and the triturate passed through a short plug of silica. Concentration *in vacuo* yielded a pale yellow oil which was purified by flash chromatography on silica (2.5% Et_2O/CH_2Cl_2, R_f = 0.43) to give the title compound **39** (0.457 g, 0.907 mmol, 89%) as a colourless oil, which crystallised upon standing for several days. A small portion was recrystallised from *n*-pentane to yield colourless crystals mp 74-77°C. $[\alpha]_D$ = +27.0 (*c* 1.00, $CHCl_3$); **IR** (film) 1784, 1716 (with shoulder), 1653, 1473, 1385, 1352, 1255, 1212, 1186, 1110, 1021, 971, 838, 776, 703 cm^{-1}; **^{1}H NMR** δ 7.36-7.18 (m, 5H, Ar*H*), 7.02 (dd, 1H, *J* = 15.6, 7.8 Hz, C*H*=CHCO), 5.80 (dd, 1H, *J* = 15.6, 1.2 Hz, CH=C*H*CO), 4.65-4.57 (m, 1H, aux. $PhCH_2CH$), 4.22-4.06 (m, 4H, aux. ring CH_2, OCH_2CH_3), 4.09 (dd, 1H, *J* = 6.9, 4.9 Hz C*H*OTBS), 3.86 (app. qn, 1H, *J* = 6.9 Hz, $COCH(CH_3)$), 3.24 (dd, 1H, *J* = 13.4, 3.2 Hz, aux. $PhCH_AH_B$), 2.73 (dd, 1H, *J* = 13.4, 9.9 Hz, aux. $PhCH_AH_B$), 2.51-2.40 (m, 1H, $CH(CH_3)CH$=), 1.27 (t, 3H, 7.0 Hz, OCH_2CH_3), 1.21 (d, 3H, *J* = 6.9 Hz, $COCH(CH_3)$), 1.06 (d, 3H, *J* = 6.9 Hz, $CH(CH_3)CH$=), 0.91 (s, 9H, $SiC(CH_3)_3$), 0.054 (s, 3H, $SiCH_3$), 0.034 (s, 3H, $SiCH_3$);

^{13}C NMR δ 175.3, 166.5, 152.8, 151.5, 135.2, 129.4, 128.9, 127.3, 121.0, 75.4, 66.0, 60.2, 55.5, 42.4 (2C), 37.6, 26.0, 18.3, 14.6, 14.2, 13.7, -3.8, -4.1; **HRESIMS** calculated for $C_{27}H_{41}NO_6SiNa^+$ ($M+Na^+$): 526.2601; found: 526.2607; **EIMS** *m/z* (%): 503 (M^+, 1), 446 (42), 376 (32), 290 (29), 199 (100), 85 (42), 83 (57), 73 (43); **Anal. Calcd.** for $C_{27}H_{41}NO_6Si$: C, 64.38; H, 8.20; N, 2.78; found: C, 64.52; H, 8.32; N, 2.59.

(2*S*,3*R*,4*S*,5*E*)-1-[(*S*)-4-Benzyl-2-oxo-oxazolidin-3-yl]-3-(*tert*-butyldimethylsilyloxy)-2,4-dimethyloct-5-ene-1,7-dione (59) and (2*S*,3*R*,4*R*,5*E*)-1-[(*S*)-4-benzyl-2-oxo-oxazolidin-3-yl]-3-(*tert*-butyldimethylsilyloxy)-2,4-dimethyloct-5-ene-1,7-dione (*epi*-59)



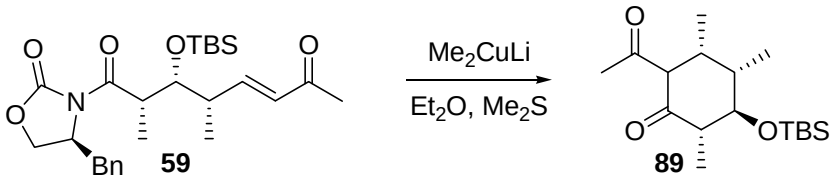
A solution of aldehyde **60** (0.700 g, 1.61 mmol) and 1-triphenylphosphoranylidene-2-propanone (**87**) (0.617 g, 1.94 mmol) was heated in dry toluene (15 mL) under N_2 at 80°C for 4.5 days. The solvent was removed *in vacuo* and the residue was triturated with hexanes (*ca.* 150 mL) and the triturate passed through a short plug of silica. Concentration *in vacuo* yielded a pale yellow oil which was purified by flash chromatography on silica (5% Et_2O/CH_2Cl_2, R_f = 0.36) to afford the enone (0.635 g, 1.34 mmol, 83%) as a colourless oil which was an inseparable 2:1 mixture of two epimers, **59** and ***epi*-59**. **IR** (film) 1782, 1697, 1677, 1456, 1386, 1361, 1255, 1211, 1110, 838, 776cm^{-1}; **HRLSIMS** calculated for $C_{26}H_{40}NO_5Si^+$ ($M+H^+$): 474.2676; found: 474.2672; **LSIMS** *m/z* (%): 474 ($M+H^+$, 7), 416 (40), 376 (73), 342 (44), 318 (10), 290 (13), 241 (15), 199 (100), 109 (14).

Major epimer **59**: **^{1}H NMR** δ 7.37-7.16 (m, 5H, Ar*H*), 6.88 (dd, 1H, *J* = 16.3, 8.2 Hz, C*H*=CHCO), 6.03 (dd, 1H, *J* = 16.3, 1.2 Hz, CH=C*H*CO), 4.64-4.56 (m, 1H, aux. $PhCH_2CH$), 4.18-4.16 (m, 2H, aux. ring CH_2), 4.06 (app. t, 1H, *J* = 5.6 Hz, C*H*OTBS), 3.86 (app. qn, 1H, *J* = 6.7 Hz, $COCH(CH_3)$), 3.26 (dd, 1H, *J* = 13.2, 3.3 Hz, aux. $PhCH_AH_B$), 2.74 (dd, 1H, *J* = 13.2, 9.9 Hz, aux. $PhCH_AH_B$), 2.56-2.45 (m, 1H,

C*H*(CH_3)CH=), 2.28 (s, 3H, C*H*$_3$CO), 1.20 (d, 3H, *J* = 6.9 Hz, COCH(C*H*$_3$)), 1.08 (d, 3H, *J* = 6.9 Hz, CH(C*H*$_3$)CH=), 0.92 (s, 9H, SiC(C*H*$_3$)$_3$), 0.055 (s, 3H, SiC*H*$_3$), 0.014 (s, 3H, SiC*H*$_3$); **^{13}C NMR** δ 199.0, 175.0, 153.0, 150.7, 135.2, 130.9, 129.4, 129.0, 127.4, 75.4, 66.1, 55.6, 42.8, 42.5, 37.6, 26.6, 26.0, 18.2, 15.6, 12.5, -3.6, -4.3.

Minor epimer ***epi*-59**: **^{1}H NMR** δ 7.37-7.16 (m, 5H, Ar*H*), 6.80 (dd, 1H, *J* = 16.2, 7.5 Hz, C*H*=CHCO), 5.95 (dd, 1H, *J* = 16.2, 1.5 Hz, CH=C*H*CO), 4.53-4.45 (m, 1H, aux. PhCH_2C*H*), 4.17-4.15 (m, 2H, aux. ring CH_2), 4.13 (app. t, 1H, *J* = 5.4 Hz, C*H*OTBS), 3.88 (app. qn, 1H, *J* = 6.7 Hz, COC*H*(CH_3)), 3.19 (dd, 1H, *J* = 13.2, 3.2 Hz, aux. PhC*H*$_A$H$_B$), 2.74 (dd, 1H, *J* = 13.2, 9.9 Hz, aux. PhCH$_A$*H*$_B$), 2.64-2.55 (m, 1H, C*H*(CH_3)CH=), 2.24 (s, 3H, C*H*$_3$CO), 1.23 (d, 3H, *J* = 6.9 Hz, COCH(C*H*$_3$)), 1.12 (d, 3H, *J* = 6.9 Hz, CH(C*H*$_3$)CH=), 0.93 (s, 9H, SiC(C*H*$_3$)$_3$), 0.092 (s, 3H, SiC*H*$_3$), 0.086 (s, 3H, SiC*H*$_3$); **^{13}C NMR** δ 198.8, 175.5, 152.8, 149.9, 135.1, 130.8, 129.4, 129.0, 127.4, 75.5, 66.1, 55.4, 42.6, 41.2, 37.6, 26.6, 26.0, 25.6, 14.73, 14.69, -3.9, -4.2.

(3*R*,4*S*,5*R*,6*S*)-2-Acetyl-5-(*tert*-butyldimethylsilyoxy)-3,4,6-trimethylcyclohexanone (89)



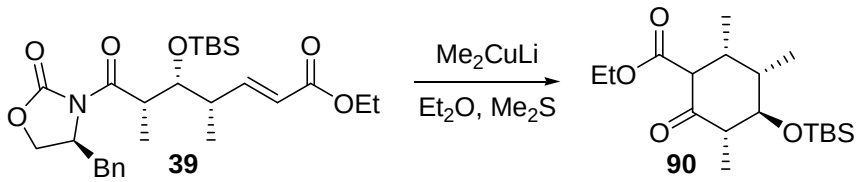
To a stirred suspension of CuI (0.362 g, 1.90 mmol) in dry Et_2O (2 mL) and dry Me_2S (4 mL) under N_2 at rt was added MeLi (1.4 M in Et_2O, 2.71 mL, 3.80 mmol) dropwise until the initially formed yellow precipitate just dissolved to form a pale yellow solution. To this solution was added the enone epimeric mixture **59** (0.450 g, 0.950 mmol) in dry Et_2O (2mL) dropwise *via* cannula (2 mL rinse), causing a yellow precipitate to form, and the mixture was stirred at rt for 1 hour. The reaction was diluted with Et_2O (10 mL) and quenched by the slow addition of a 90% NH_4Cl/10% NH_4OH solution (10 mL). The mixture was stirred for 5 minutes by which time a deep blue colour had developed. The mixture was extracted with Et_2O (3 x 20 mL) and the combined organic phases were washed with brine (20 mL) and dried ($MgSO_4$). The dried organic extracts were filtered through celite and concentrated *in vacuo* to yield a yellow oil which was purified by flash chromatography on silica (20% hexanes/CH_2Cl_2, R_f = 0.48) to give the title compound **89** (0.131 g, 0.419 mmol, 44%) as a colourless oil.

The product was determined to be a 6:1 mixture of *enol:keto* tautomers by ^{1}H NMR. **IR** (film) 1704, 1600, 1462, 1404, 1372, 1360, 1254, 1092, 1062, 1005, 854, 835, 774 cm^{-1}; **HRLSIMS** calculated for $C_{17}H_{33}O_3Si^+$ ($M+H^+$): 313.2200; found: 313.2202; **LSIMS** *m/z* (%): 313 ($M+H^+$, 30), 255 (13), 197 (42), 181 (100), 139 (16).

Enol: **^{1}H NMR** δ 16.43 (s, 1H, O*H*), 3.39 (dd, 1H, *J* = 11.0, 7.4 Hz, C*H*OTBS), 2.53 (qd, 1H, *J* = 7.0, 4.2 Hz, =C(CO)C*H*(CH_3)), 2.32 (app. qn, 1H, *J* = 7.4 Hz, =C(OH)C*H*(CH_3)), 2.15 (s, 3H, C*H*$_3$CO), 1.80-1.69 (m, 1H, C*H*(CH_3)CHOTBS), 1.27 (d, 3H, *J* = 7.2 Hz, =C(OH)CH(C*H*$_3$)), 1.02 (d, 3H, *J* = 6.9 Hz, CH(C*H*$_3$)CHOTBS), 0.94 (d, 3H, *J* = 7.0 Hz, =C(CO)CH(C*H*$_3$)), 0.89 (s, 9H, SiC(C*H*$_3$)$_3$), 0.091 (s, 3H, SiC*H*$_3$), 0.076 (s, 3H, SiC*H*$_3$); **^{13}C NMR** δ 196.8, 186.0, 113.2, 75.2, 46.3, 39.7, 34.0, 26.0, 23.8, 18.3, 16.8, 16.3, 16.2, -3.4, -3.5.

Keto: **^{1}H NMR** δ 3.30 (dd, 1H, *J* = 7.5, 6.0 Hz, C*H*OTBS), 3.28 (d, 1H, *J* = 6.3 Hz, COC*H*CH(CH_3)), 2.82-2.72 (m, 1H, COCHC*H*(CH_3)), 2.34 (app. qn, 1H, *J* = 7.2 Hz, COC*H*(CH_3)), 2.17 (s, 3H, C*H*$_3$CO), 2.00-1.92 (m, 1H, C*H*(CH_3)CHOTBS), 1.08 (d, 3H, *J* = 7.2 Hz, COCH(C*H*$_3$)), 0.92-0.90 (m, 3H, CH(C*H*$_3$)CHOTBS), 0.89 (s, 9H, SiC(C*H*$_3$)$_3$), 0.86 (d, 3H, *J* = 7.2 Hz, COCHCH(C*H*$_3$)), 0.051 (s, 6H, SiC*H*$_3$); **^{13}C NMR** δ 207.8, 203.1, 79.0, 70.1, 51.9, 40.0, 32.7, 29.6, 25.8, 18.0, 15.5, 14.7, 12.5, -3.8, -4.0.

(2*R*,3*S*,4R,5*S*)-Ethyl 4-(*tert*-butyldimethylsilyloxy)-2,3,5-trimethyl-6-oxocyclo-hexanecarboxylate (90)



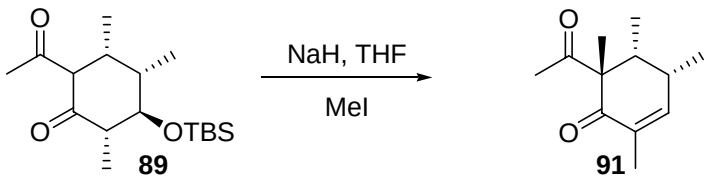
To a stirred suspension of CuI (0.378 g, 1.98 mmol) in dry Et_2O (1 mL) and dry Me_2S (2 mL) under N_2 at rt was added MeLi (1.4 M in Et_2O, 2.84 mL, 3.97 mmol) dropwise until the initially formed yellow precipitate just dissolved to form a pale yellow solution. To this solution was added enoate **39** (0.200 g, 0.397 mmol) in dry Et_2O (1mL) *via* cannula (1 mL rinse), causing a yellow precipitate to form, and the mixture was stirred at rt for 45 minutes. The reaction was diluted with Et_2O (5 mL) and quenched by the slow addition of a 90% NH_4Cl/10% NH_4OH solution (10 mL). The mixture was stirred for 5 minutes by which time a deep blue colour had developed. The mixture was

extracted with Et_2O (3 x 20 mL) and the combined organic phases were washed with brine (20 mL) and dried ($MgSO_4$). The dried organic extracts were filtered through celite and concentrated *in vacuo* to yield a pale yellow oil which was purified by flash chromatography on silica (20% Et_2O/hexanes, R_f = 0.57 and 0.36) to give the title compound **90** (0.093 g, 0.271 mmol, 68%) as a colourless oil. The product was determined to be a 3:2 mixture of *enol:keto* tautomers by ^{1}H NMR. **IR** (film) 1734, 1718, 1652, 1618, 1473, 1464, 1373, 1266, 1253, 1212, 1093, 1036, 861, 836, 774 cm^{-1}; **HRESIMS** calculated for $C_{18}H_{34}O_4SiNa^+$ ($M+Na^+$): 365.2124; found: 365.2115; **EIMS** *m/z* (%): 285 (36), 239 (24), 211 (29), 201 (24), 164 (72), 137 (24), 75 (100), 57 (37).

Enol: **^{1}H NMR** δ 12.34 (s, 1H, O*H*), 4.26-4.16 (m, 2H, OC*H*$_2$CH$_3$), 3.37 (dd, 1H, *J* = 11.0, 7.6 Hz, C*H*OTBS), 2.58 (qd, 1H, *J* = 6.8, 4.5 Hz, =C(CO)C*H*(CH$_3$)), 2.32 (app. qn, 1H, *J* = 7.2 Hz, =C(OH)C*H*(CH$_3$)), 1.77-1.65 (m, 1H,), 1.31 (t, 3H, *J* = 7.1 Hz, OCH$_2$C*H*$_3$), 1.26 (d, 3H, *J* = 7.2 Hz, =C(OH)CH(C*H*$_3$)), 1.00 (d, 3H, *J* = 6.9 Hz, CH(C*H*$_3$)CHOTBS), 0.914 (s, 9H, SiC(C*H*$_3$)$_3$), 0.909 (d, 3H, *J* = 6.8 Hz, =C(CO)CH(C*H*$_3$)), 0.11 (s, 3H, SiC*H*$_3$), 0.088 (s, 3H, SiC*H*$_3$); **^{13}C NMR** δ 173.5, 172.3, 103.4, 75.5, 60.2, 44.4, 39.2, 32.4, 26.1, 18.3, 16.4, 16.2, 15.5, 14.2, -3.3, -3.5.

Keto: **^{1}H NMR** δ 4.25-4.17 (m, 2H, OC*H*$_2$CH$_3$), 3.32 (app. t, 1H, *J* = 8.1 Hz, C*H*OTBS), 3.14 (d, 1H, *J* = 5.1 Hz, COC*H*CH(CH$_3$)), 2.72-2.63 (m, 2H, COCHC*H*(CH$_3$), COC*H*(CH$_3$)), 2.06-1.95 (m, 1H, C*H*(CH$_3$)CHOTBS), 1.26 (t, 3H, *J* = 6.9 Hz, OCH$_2$C*H*$_3$), 1.12 (d, 3H, *J* = 6.6 Hz, COCH(C*H*$_3$)), 0.98 (d, 3H, *J* = 7.2 Hz, CH(C*H*$_3$)CHOTBS), 0.91 (s, 9H, SiC(C*H*$_3$)$_3$), 0.88 (d, 3H, *J* = 7.2 Hz, COCHCH(C*H*$_3$)), 0.065 (s, 3H, SiC*H*$_3$), 0.060 (s, 3H, SiC*H*$_3$); **^{13}C NMR** δ 206.6, 169.5, 78.4, 61.5, 61.3, 52.0, 39.8, 34.8, 25.9, 18.1, 15.3, 14.5, 14.1, 12.4, -3.6, -3.8.

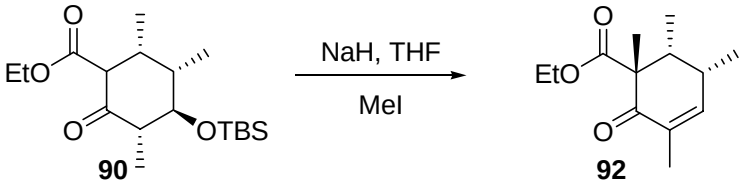
(4*R*,5*R*,6*S*)-6-Acetyl-2,4,5,6-tetramethylcyclohex-2-enone (91)



To a stirred suspension of NaH (60% dispersion in oil, 0.012 g, 0.288 mmol) in dry THF (1 mL) was added diketone **89** (0.045 g, 0.144 mmol) in dry THF (1 mL) *via* cannula (1 mL rinse) and the mixture was stirred at rt for 10 minutes. To this yellow

solution was added MeI (45 μL, 0.720 mmol) and the resulting pale yellow solution was stirred at rt for 3 days. The mixture was diluted with CH_2Cl_2 (5 mL), quenched with $NaHCO_3$ (sat., 5 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a yellow oil. The product was purified by flash chromatography on a silica (2.5% Et_2O/CH_2Cl_2, R_f = 0.28) to give the title compound **91** (0.017 g, 0.088 mmol, 61%) as a colourless oil. **[α]$_D$** = –96.4 (*c* 0.14, $CHCl_3$); **IR** (film) 1703, 1669, 1457, 1376, 1356, 1166, 1035 cm^{-1}; **^{1}H NMR** δ 6.37-6.34 (m, 1H, C*H*=C), 2.90-2.79 (m, 1H, C*H*(CH_3)CH=C), 2.24, (s, 3H, C*H*$_3$CO), 2.21-2.12 (m, 1H, C(CH_3)C*H*(CH_3)), 1.81 (dd, 3H, *J* = 2.6, 1.4 Hz, C(C*H*$_3$)=CH), 1.35 (s, 3H, C(C*H*$_3$)), 1.08 (d, 3H, *J* = 7.2 Hz, CH(C*H*$_3$)CH=C), 0.89 (d, 3H, *J* = 6.9 Hz, C(CH_3)CH(C*H*$_3$)); **^{13}C NMR** δ 210.3, 200.0, 147.4, 133.5, 62.0, 42.5, 31.9, 30.8, 21.0, 16.9, 16.0, 11.3; **HREIMS** calculated for $C_{12}H_{18}O_2$: 194.1307; found: 194.1313; **EIMS** *m/z* (%):194 (M^+, 13), 151 (86), 137 (26), 125 (53), 112 (12), 99 (37), 83 (34), 69 (22), 55 (50), 43 (100).

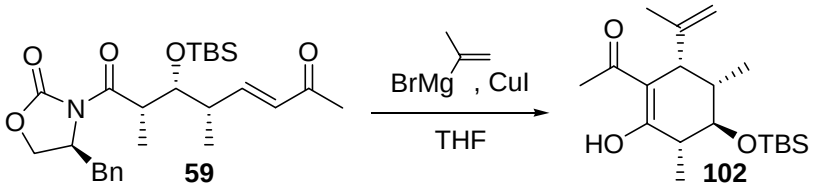
(1*S*,5*S*,6*R*)-Ethyl 1,3,5,6-Tetramethyl-2-oxocyclohex-3-enecarboxylate (92)



To a stirred suspension of NaH (60% dispersion in oil, 0.012 g, 0.292 mmol) in dry THF (1 mL) was added ketoester **90** (0.050 g, 0.146 mmol) in dry THF (1 mL) *via* cannula (1 mL rinse) and the mixture was stirred at rt for 10 minutes. To this pale pink solution was added MeI (45 μL, 0.730 mmol) and the resulting colourless solution was stirred at rt for 2 hours. The mixture was diluted with CH_2Cl_2 (5 mL), quenched with $NaHCO_3$ (sat., 5 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a yellow oil. The product was purified by flash chromatography on silica (2.5% Et_2O/CH_2Cl_2, R_f = 0.34) to give the title compound **92** (0.021 g, 0.094 mmol, 64%) as a colourless oil. **[α]$_D$** = –132 (*c* 0.46, $CHCl_3$); **IR** (film) 1730, 1678, 1452, 1376, 1255, 1226, 1172, 1137, 1102 cm^{-1}; **^{1}H NMR** δ 6.50-6.46 (m, 1H, C*H*=C), 4.11 (q, 2H, *J* = 7.1 Hz, OC*H*$_2$CH$_3$), 2.64-2.56 (m, 1H, C*H*(CH_3)CH=C), 2.17 (qd, 1H, *J* = 7.0, 5.3 Hz, C(CH_3)C*H*(CH_3)), 1.82-1.79 (m, 3H, C(C*H*$_3$)=CH), 1.42 (s, 3H, C(C*H*$_3$)),

1.22 (t, 3H, 7.1 Hz, OCH_2CH_3), 1.09 (d, 3H, *J* = 7.0 Hz, $C(CH_3)CH(CH_3)$), 1.03 (d, 3H, *J* = 7.2 Hz, $CH(CH_3)CH=C$); **^{13}C NMR** δ 197.4, 173.4, 147.6, 133.5, 60.8, 55.6, 41.8, 33.6, 20.3, 16.4, 14.7, 13.9, 13.0; **HRLSIMS** calculated for $C_{13}H_{19}O_3^+$ ($M-H^-$): 223.1334; found: 223.1328; **LSIMS** *m/z* (%): 223 ($M-H^-$, 65), 154 (97), 137 (100), 107 (56).

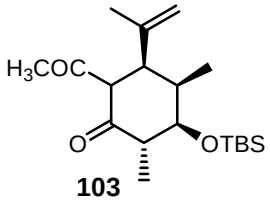
(3*S*,4*S*,5*R*,6*S*)-2-Acetyl-5-(*tert*-butyldimethylsilyoxy)-3-isopropenyl-4,6-dimethylcyclohexanone (102)



To a stirred suspension of CuI (0.028 g, 0.148 mmol) in dry THF (2 mL) under N_2 at –78°C was added isopropenylmagnesium bromide (0.591 mL, 0.296 mmol) and the resulting orange solution was stirred at *ca.* –20°C for 30 minutes. To this solution was slowly added the enone epimeric mixture **59** (0.035 g, 0.074 mmol) in dry THF (0.5 mL) *via* cannula (0.5 mL rinse) at -78°C and the solution was gradually warmed to rt (whereby a black ppt formed) and stirred for 16 hours. The yellow solution was diluted with ether (10 mL), quenched with 90% NH_4Cl/10% NH_4OH (10 mL) and stirred for 10 minutes by which time a deep blue colour had developed. The reaction mixture was extracted with Et_2O (3 x 15 mL) and the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a pale yellow oil. The product was purified by flash chromatography on silica (20% hexanes/ CH_2Cl_2, R_f = 0.51) to yield the title compound **102** (0.015 g, 0.044 mmol, 60%) as a colourless oil which existed almost exclusively as the *enol* tautomer as determined by ^{1}H NMR. **IR** (film) 1705, 1607, 1473, 1463, 1259, 1090, 1058, 860, 837, 774 cm^{-1}; **^{1}H NMR** δ 16.36 (s, 1H, O*H*), 5.06-5.05 (m, 1H, $=CH_AH_B$), 4.65 (app. s, 1H, $=CH_AH_B$), 3.45 (dd, 1H, *J* = 11.0, 8.0 Hz, C*H*OTBS), 3.13 (d, 1H, *J* = 4.8 Hz, $CHC(CH_3)=CH_2$), 2.37 (app. qn, 1H, *J* = 7.4 Hz, $=C(OH)CH(CH_3)$), 2.09 (s, 3H, CH_3CO), 1.90-1.81 (m, 1H, $CH(CH_3)CHOTBS$), 1.78-1.76 (m, 3H, $C(CH_3)=CH_2$), 1.30 (d, 3H, *J* = 7.2 Hz, $=C(OH)CH(CH_3)$), 1.02 (d, 3H, 7.2 Hz, $CH(CH_3)CHOTBS$), 0.92 (s, 9H $SiC(CH_3)_3$), 0.087 (s, 3H, $SiCH_3$), 0.060 (s, 3H, $SiCH_3$); **^{13}C NMR** δ 200.0, 183.3, 145.0, 116.2, 110.2, 74.8, 47.4, 45.5, 39.7, 26.1, 25.2, 24.4, 18.3, 17.3, 15.5, -3.2, -3.5; **HRLSIMS**

calculated for $C_{19}H_{34}O_3SiNa^+$ ($M+Na^+$): 361.2175; found: 361.2177; **EIMS** *m/z* (%): 338 (M^+, 3), 281 (9), 239 (11), 199 (15), 183 (13), 169 (14), 155 (16), 141 (25), 111 (42), 85 (56), 71 (78), 57 (100).

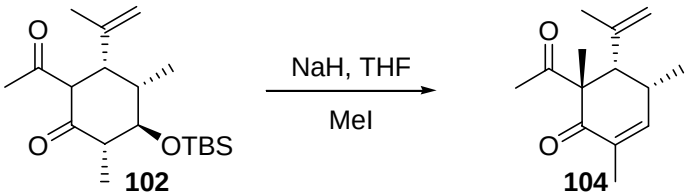
(3*R*,4*R*,5*R*,6*S*)-2-Acetyl-5-(*tert*-butyldimethylsilyoxy)-3-isopropenyl-4,6-dimethyl-cyclohexanone (103)



103

On occasions the cyclic product from the minor enone diastereomer ***epi*-59** was isolated as a colourless oil which existed almost exclusively as the *keto* tautomer as determined by ^{1}H NMR. **^{1}H NMR** δ 4.96-4.93 (m, 1H, =C*H*$_A$H$_B$), 4.55 (app. s, 1H, =CH$_A$*H*$_B$), 3.71 (d, 1H, *J* = 13.2 Hz, CH$_3$COC*H*), 3.58 (dd, 1H, *J* = 11.1, 4.5 Hz, C*H*OTBS), 2.72 (dd, 1H, *J* = 13.2, 3.8 Hz, C*H*C(CH$_3$)=CH$_2$), 2.62 (dq, 1H, *J* = 11.8, 6.0 Hz, COC*H*(CH$_3$)), 2.31-2.22 (m, 1H, C*H*(CH$_3$)CHOTBS), 2.14 (s, 3H, C*H*$_3$CO), 1.78-1.76 (m, 3H, C(C*H*$_3$)=CH$_2$), 1.05 (d, 3H, *J* = 6.3 Hz, COCH(C*H*$_3$)), 0.98 (d, 3H, 7.2 Hz, CH(C*H*$_3$)CHOTBS), 0.92 (s, 9H, SiC(C*H*$_3$)$_3$), 0.079 (s, 3H, SiC*H*$_3$), 0.075 (s, 3H, SiC*H*$_3$); **^{13}C NMR** δ 208.0, 206.0, 143.4, 111.8, 77.6, 61.6, 48.4, 45.3, 36.7, 30.4, 25.8, 23.0, 18..0, 10.7, 7.1, -4.4, -4.9.

(4*R*,5*R*,6*S*)-6-Acetyl-5-isopropenyl-2,4,6-trimethylcyclohex-2-enone (104)



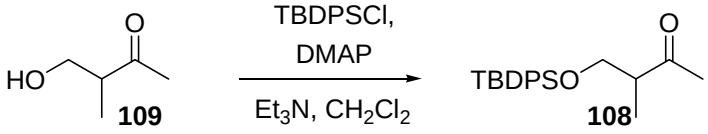
102 **104**

To a stirred suspension of NaH (60% dispersion in oil, 0.004 g, 0.089 mmol) in dry THF (2 mL) was added diketone **102** (0.015 g, 0.044 mmol) in dry THF (1 mL) *via* cannula (1 mL rinse) and the mixture was stirred at rt for 10 minutes. To this yellow solution was added MeI (28 μL, 0.444 mmol) and the resulting pale yellow solution was stirred at rt for 3 days. The mixture was diluted with CH_2Cl_2 (5 mL), quenched with $NaHCO_3$ (sat., 5 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic

phases were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a yellow oil. The product was purified by flash chromatography on a silica (2.5% Et_2O/CH_2Cl_2, R_f = 0.29) to give the title compound **104** (0.006 g, 0.027 mmol, 60%) as a colourless oil. $[\alpha]_D$ = –69.0 (*c* 0.33, $CHCl_3$); **IR** (film) 1704, 1666, 1455, 1376, 1356, 1220, 1198, 1152, 1031 cm^{-1}; **^{1}H NMR** δ 6.41-6.39 (m, 1H, C*H*=C), 4.86-4.84 (m, 1H, =CH_AH$_B$), 4.72-4.70 (m, 1H, =CH$_A$$H_B$), 3.08-2.97 (m, 1H, C*H*(CH_3)CH=C), 2.70 (dd, 1H, *J* = 5.7, 1.2 Hz, C*H*C(CH_3)=CH_2), 2.19, (s, 3H, CH_3CO), 1.84-1.82 (m, 3H, C(CH_3)=CH), 1.57-1.56 (m, 3H, C(CH_3)=CH_2), 1.42 (s, 3H, C(CH_3)), 1.08 (d, 3H, *J* = 7.5 Hz, CH(CH_3)CH=C); **^{13}C NMR** δ 209.0, 199.1, 147.4, 143.0, 134.5, 118.4, 61.6, 57.8, 29.7, 29.6, 24.6, 22.6, 17.4, 16.0; **HRESIMS** calculated for $C_{14}H_{20}O_2Na^+$ ($M+Na^+$): 243.1361; found: 243.1352; **EIMS** *m/z* (%): 220 (M^+, 1), 192 (61), 177 (10), 163 (55), 149 (100), 137 (63), 121 (42), 110 (55), 105 (16), 96 (57), 91 (25), 77 (18), 67 (27), 53 (18).

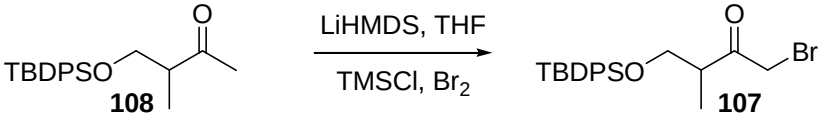
6.3 Experimental Procedures for Chapter Three

4-(*tert*-Butyldiphenylsilyloxy)-3-methylbutan-2-one (108)



To a stirred solution of 4-hydroxy-3-methylbutan-2-one (**109**) (1.55 g, 15.18 mmol) in dry CH_2Cl_2 (18 mL) under N_2 at 0°C was added DMAP (0.185 g, 1.52 mmol) in dry CH_2Cl_2 (2 mL), followed by Et_3N (4.23 mL, 30.35 mmol) dropwise and TBDPSCl (4.74 mL, 18.21 mmol) dropwise. After 5 minutes a white precipitate formed and the solution was stirred at rt for 46 hours. The reaction was quenched with $NaHCO_3$ (sat., 15 mL), the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a colourless oil. The product was purified by Kugelrohr distillation (oven temp. 150°C, 0.2 mmHg) to afford the title compound **108** (5.05 g, 14.83 mmol, 98%) as a colourless oil. **IR** (film) 1720, 1590, 1473, 1429, 1390, 1359, 1260, 1187, 1123, 1112, 1084 cm^{-1}; **^{1}H NMR** δ 7.66-7.62 (m, 4H, Ar*H*), 7.44-7.35 (m, 6H, Ar*H*), 3.80 (dd, 1H, *J* = 9.9, 7.2 Hz, CH_AH$_B$OTBDPS), 3.69 (dd, 1H, *J* = 9.9, 5.4 Hz, CH$_A$$H_B$OTBDPS), 2.84-2.72 (m, 1H, C*H*(CH$_3$)), 2.19 (s, 3H, CH_3CO), 1.04 (d, 3H, *J* = 6.6 Hz, CH(CH_3)), 1.03 (s, 9H, SiC(CH_3)); **^{13}C NMR** δ 190.6, 135.6, 135.5, 133.3, 133.2, 129.7, 127.7, 66.0, 49.3, 29.3, 26.8, 19.2, 12.9; **HRLSIMS** calculated for $C_{21}H_{28}O_2SiNa^+$ (M+Na^+): 363.1756; found: 363.1752; **EIMS** *m/z* (%): 283 (100), 239 (41), 205 (87), 199 (44), 183 (55), 123 (20), 105 (13), 77 (12), 57 (12).

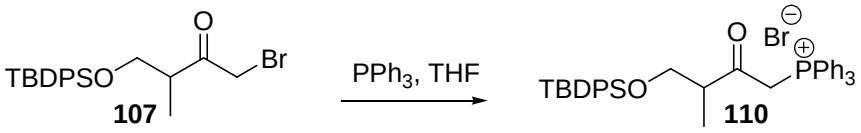
1-Bromo-4-(*tert*-butyldiphenylsilyloxy)-3-methylbutan-2-one (107)



To a stirred solution of ketone **108** (2.00 g, 5.87 mmol) in dry THF (20 mL) under N_2 at -78°C was added LiHMDS (1 M in THF, 8.81 mL, 8.81 mmol) dropwise and the resulting yellow solution was stirred at -78°C for 1 hour. To this solution was added TMSCl (2.24 mL, 17.62 mmol) dropwise at -78°C and the mixture was warmed slowly

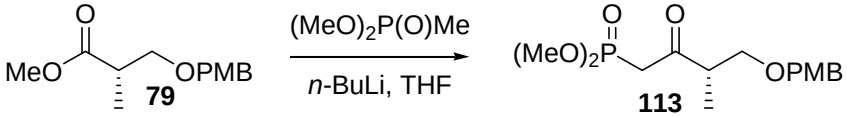
to 0°C and recooled to -78°C. Bromine (0.602 mL, 11.75 mmol) was added dropwise and the reaction was stirred at -78°C for 30 minutes before being quenched with $NaHCO_3$ (sat., 5 mL), warmed to rt and extracted with Et_2O (3 x 75 mL). The combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4), filtered and concentrated in *vacuo to* yield a pale yellow oil which was purified by flash chromatography on silica (CH_2Cl_2, R_f = 0.64) to afford the bromoketone **107** (2.30 g, 5.48 mmol, 93%) as a colourless oil. **IR** (film) 1718, 1472, 1428, 1389, 1112, 1088, 824, 740, 702 cm^{-1}; **^{1}H NMR** δ 7.66-7.59 (m, 4H, Ar*H*), 7.45-7.36 (m, 6H, Ar*H*), 4.10 (d, 1H, *J* = 13.2 Hz, C*H*$_A$H$_B$Br), 4.05 (d, 1H, *J* = 13.2 Hz, CH$_A$*H*$_B$Br), 3.76 (dd, 1H, *J* = 9.9, 8.2 Hz, C*H*$_A$H$_B$OTBDPS), 3.68 (dd, 1H, *J* = 9.9, 5.4 Hz, CH$_A$*H*$_B$OTBDPS), 3.23-3.12 (m, 1H, C*H*(CH$_3$)), 1.05 (d, 3H, *J* = 6.9 Hz, CH(C*H*$_3$)), 1.03 (s, 9H, SiC(C*H*$_3$)); **^{13}C NMR** δ 204.3, 135.6, 135.5, 133.0, 132.8, 129.9, 127.8, 66.6, 45.9, 35.5, 26.8, 19.1, 13.1; **HRESIMS** calculated for $C_{21}H_{27}BrO_2SiNa^+$ ($M+Na^+$): 441.0861; found: 441.0849; **EIMS** *m/z* (%): 363 (82), 331 (28), 283 (24), 251 (68), 203 (100), 181 (45), 131 (79), 91 (59), 77 (31), 57 (13).

[4-(*tert*-Butyldiphenylsilyloxy)-3-methyl-2-oxobutyl]triphenylphosphonium bromide (110)



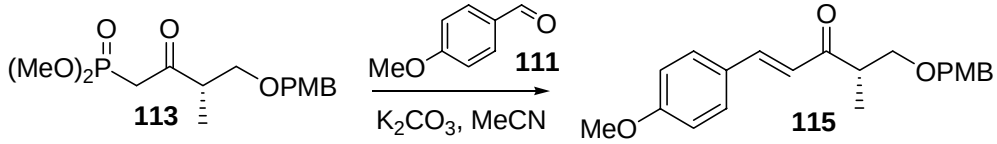
A solution of bromoketone **107** (2.28 g, 5.44 mmol) and PPh_3 (1.43 g, 5.44 mmol) in dry THF (10 mL) under N_2 was stirred under reflux for 43 hours and the solvent was removed *in vacuo*, yielding an orange solid. The solid was triturated with toluene (30 mL), filtered and washed with hexane (20 mL), yielding the title compound **110** (2.54 g, 3.76 mmol, 68%) as an off-white solid. A portion of the material was recrystallised from CH_2Cl_2/EtOAc (1:3) to afford colourless crystals mp 158-161°C. **^{1}H NMR** δ 7.82-7.23 (m, 25 H, Ar*H*), 7.14 (dd, 1H, *J* = 18.6, 11.1 Hz, COC*H*$_A$H$_B$P), 4.89 (dd, 1H, *J* = 18.6, 11.1 Hz, COCH$_A$*H*$_B$P), 4.08 (dd, 1H, *J* = 10.2, 4.2 Hz, C*H*$_A$H$_B$OTBDPS), 3.83 (dd, 1H, *J* = 10.2, 7.2 Hz, CH$_A$*H*$_B$OTBDPS), 3.68-3.58 (m, 1H, C*H*CH$_3$), 1.09 (d, 3H, *J* = 6.6 Hz, CHC*H*$_3$), 0.94 (s, 9H, Si(C*H*$_3$)$_3$); **^{13}C NMR** δ 206.0 (d, *J* = 7.5 Hz), 135.40, 135.36, 134.5 (d, *J* = 2.9 Hz), 133.8 (d, *J* = 10.9 Hz), 133.0, 132.7, 130.0 (d, *J* = 13.1 Hz), 129.84, 129.79, 127.8, 127.7, 118.7 (d, *J* = 88.8 Hz), 66.6, 49.6 (d, *J* = 5.7 Hz), 40.3 (d, *J* = 58.4 Hz), 26.9, 19.2, 12.3 (d, *J* = 1.1 Hz).

(3*S*)-Dimethyl [4-(4-methoxybenzyloxy)-3-methyl-2-oxobutyl]phosphonate (113)



To a stirred solution of dimethyl methylphosphonate (9.09 mL, 0.084 mol) in dry THF (130 mL) under N_2 at –78°C was added *n*-BuLi (1.6 M in hexanes, 52.46 mL, 0.084 mol) dropwise and the resulting white suspension was stirred at –78°C for 1 hour. To this suspension was added ester **79** (5.00g, 0.021 mol) in dry THF (15 mL) dropwise *via* cannula (5 mL rinse) and the cloudy yellow mixture was stirred at –78°C for 15 minutes before being quenched with 10% AcOH (50 mL). The mixture was warmed to rt and extracted with Et_2O (3 x 100 mL). The combined organic extracts were washed successively with $NaHCO_3$ (sat., 50 mL), water (30 mL) and brine (30 mL). The organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a pale yellow oil which was purified by flash chromatography on silica (2.5% MeOH/CH_2Cl_2, R_f = 0.22) to afford the title compound **113** (6.27 g, 0.019 mol, 90%) as a colourless oil. **[α]$_D$** = +51.1 (*c* 1.08, $CHCl_3$); **IR** (film) 1715, 1613, 1515, 1463, 1249, 1180, 1032, 814 cm^{-1}; **^{1}H NMR** δ 7.21 (d, 2H, *J* = 8.9 Hz, Ar*H*), 6.86 (d, 2H, *J* = 8.9 Hz, Ar*H*), 4.41 (s, 2H, OCH_2Ar), 3.80 (s, 3H, ArOCH_3), 3.78 (d, 3H, *J* = 3.9 Hz, POCH_3), 3.74 (d, 3H, *J* = 3.9 Hz, POCH_3), 3.54 (dd, 1H, *J* = 9.0, 7.8 Hz, CH_AH$_B$OPMB), 3.49 (dd, 1H, *J* = 9.0, 5.3 Hz, CH$_A$$H_B$OPMB), 3.29 (dd, 1H, *J* = 22.5, 14.1 Hz, PCH_AH$_B$), 3.11 (dd, 1H, *J* = 21.9, 14.1 Hz, PCH$_A$$H_B$), 3.17-3.05 (m, 1H, COC*H*(CH$_3$)), 1.08 (d, 3H, *J* = 6.9 Hz, COCH(CH_3)); **^{13}C NMR** δ 204.8 (d, *J* = 6.9 Hz), 159.2, 129.9, 129.2, 113.8, 72.9, 72.0, 55.2, 53.0 (d, *J* = 4.0 Hz), 52.9 (d, *J* = 4.0 Hz), 47.2 (d, *J* = 1.7 Hz), 40.9 (d, *J* = 129.5 Hz), 13.0; **HRESIMS** calculated for $C_{15}H_{23}O_6NaP^+$ (M+Na^+): 353.1130; found: 353.1113; **EIMS** *m/z* (%): 312 (16), 297 (5), 203 (16), 179 (19), 166 (21), 151 (62), 135 (10), 124 (100), 109 (34), 94 (33), 77 (23).

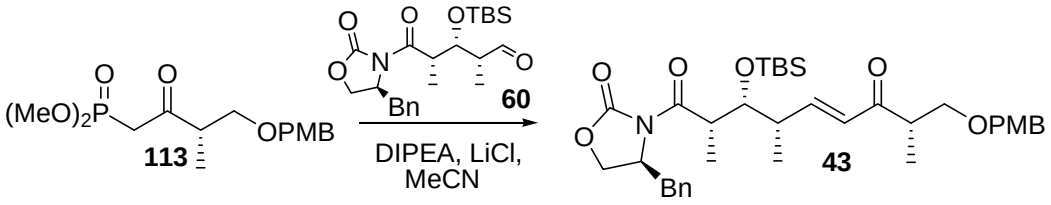
(1*E*,4*S*)-5-(4-Methoxybenzyloxy)-1-(4-methoxyphenyl)-4-methylpent-1-en-3-one (115)



To a stirred solution of β-ketophosphonate **113** (0.090g, 0.272 mmol) and anhydrous potassium carbonate (0.038 g, 0.272 mmol) in dry MeCN (2 mL) under N_2 at rt was

added *p*-anisaldehyde (**111**) (0.037 g, 0.272 mmol) in dry MeCN (1 mL) and the mixture was stirred at rt for 21 hours. The reaction mixture was filtered and acidified with AcOH (10 drops). The solvent was removed *in vacuo* and the residue was dissolved in Et_2O (50 mL) and washed with $NaHCO_3$ (sat., 10 mL) and brine (10 mL). The organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a colourless oil which was purified by flash chromatography on silica (2% Et_2O/CH_2Cl_2, R_f = 0.35) to give the title compound **115** (0.046 g, 0.135 mmol, 65% based on recovery of 0.021 g of phosphonate) as a colourless oil. **$[\alpha]_D$** = –14.1 (*c* 0.92, $CHCl_3$); **IR** (film) 1684, 1654, 1599, 1574, 1510, 1464, 1423, 1304, 1249, 1174, 1098, 1034, 827 cm^{-1}; **^{1}H NMR** δ 7.58 (d, 1H, *J* = 16.0 Hz, C*H*=CHCO)), 7.49 (d, 2H, *J* = 8.7 Hz, Ar*H*), 7.23 (d, 2H, *J* = 8.7 Hz, Ar*H*), 6.90 (d, 2H, *J* = 8.7 Hz, Ar*H*), 6.84 (d, 2H, *J* = 8.7 Hz, Ar*H*), 6.70 (d, 1H, *J* = 16.0 Hz, CH=C*H*CO), 4.47 (d, 1H, *J* = 11.7 Hz, OCH_AH_BAr), 4.42 (d, 1H, *J* = 11.7 Hz, OCH_AH_BAr), 3.84 (s, 3H, $ArOCH_3$), 3.78 (s, 3H, $ArOCH_3$), 3.72 (dd, 1H, *J* = 9.3, 7.4 Hz, CH_AH_BOPMB), 3.48 (dd, 1H, *J* = 9.3, 6.0 Hz, CH_AH_BOPMB), 3.25-3.12 (m, 1H, $COCH(CH_3)$), 1.16 (d, 3H, *J* = 6.9 Hz, $CH(CH_3)$); **^{13}C NMR** δ 202.0, 161.5, 159.1, 142.6, 130.3, 130.1, 129.2, 127.3, 123.1, 114.3, 113.7, 72.9, 72.0, 55.4, 55.2, 44.8, 14.1.

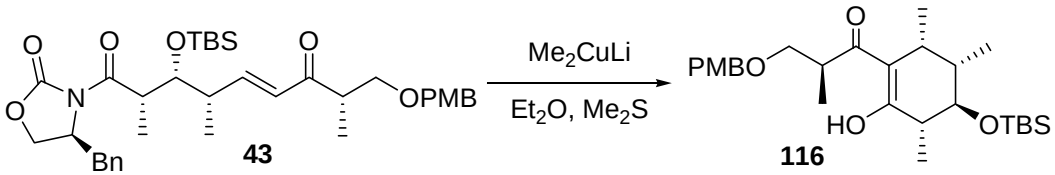
(2*S*,3*R*,4*S*,5*E*,8*S*)-1-(4-Benzyl-2-oxo-oxazolidin-3-yl)-3-(*tert*-butyldimethylsilyloxy)-9-(4-methoxybenzyloxy)-2,4,8-trimethylnon-5-ene-1,7-dinone (43)



To a stirred suspension of LiCl (0.389 g, 9.19 mmol) in dry MeCN (45 mL) under N_2 at rt was added phosphonate **113** (3.03 g, 9.19 mmol), DIPEA (1.40 mL, 8.04 mmol) and finally aldehyde **60** (3.32 g, 7.66 mmol) in dry MeCN (5 mL) *via* cannula (5 mL rinse). Stirring was continued at rt for 4.5 days, the reaction was diluted with ether (30 mL) and quenched with $NaHCO_3$ (sat., 50 mL). The phases were separated, the aqueous phase was extracted with ether (3 x 100 mL) and the combined organic extracts were washed with brine (20 mL). The organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a pale yellow oil which was purified by flash chromatography on silica (2.5% Et_2O/CH_2Cl_2, R_f = 0.27) to give enone **43** (3.14 g, 4.92

mmol, 64%) as a colourless oil. **[α]$_D$** = +19.0 (*c* 1.06, $CHCl_3$); **IR** (film) 1782, 1695, 1669, 1624, 1615, 1514, 1462, 1384, 1362, 1249, 1210, 1108, 1037, 1016, 972, 838, 777 cm^{-1}; **^{1}H NMR** δ 7.36-7.19 (m, 5H, aux. Ar*H*), 7.23 (d, 2H, *J* = 8.6 Hz, Ar*H*), 6.94 (dd, 1H, *J* = 15.9, 8.1 Hz, C*H*=CHCO), 6.86 (d, 2H, *J* = 8.7 Hz, Ar*H*), 6.16 (dd, 1H, *J* = 15.9, 0.9 Hz, CH=C*H*CO), 4.66-4.58 (m, 1H, aux. $PhCH_2CH$), 4.45 (d, 1H, *J* = 11.7 Hz, $ArCH_AH_BOCH_2$), 4.39 (d, 1H, *J* = 11.7 Hz, $ArCH_AH_BOCH_2$), 4.21-4.12 (m, 2H, aux. ring CH_2), 4.09 (app. t, 1H, *J* = 5.7 Hz, C*H*OTBS), 3.85 (app. qn, 1H, *J* = 6.9 Hz, $COCH(CH_3)CHOTBS$), 3.80 (s, 3H, $ArOCH_3$), 3.67 (dd, 1H, *J* = 9.2, 7.4 Hz, CH_AH_BOPMB), 3.42 (dd, 1H, *J* = 9.2, 5.8 Hz, CH_AH_BOPMB), 3.24-3.11 (m, 1H, $CH(CH_3)CH_2OPMB$), 3.23 (dd, 1H, *J* = 13.2, 3.2 Hz, aux. $PhCH_AH_B$), 2.75 (dd, 1H, *J* = 13.2, 9.6 Hz, aux. $PhCH_AH_B$), 2.54-2.43 (m, 1H, $CH(CH_3)CH=CH$), 1.21 (d, 3H, *J* = 6.9 Hz, $COCH(CH_3)CHOTBS$), 1.10 (d, 3H, *J* = 7.2 Hz, $CH(CH_3)CH_2OPMB$), 1.08 (d, 3H, *J* = 7.2 Hz, $CH(CH_3)CH=CH$), 0.93 (s, 9H, $Si(CH_3)_3$), 0.059 (s, 3 H, $SiCH_3$), 0.033 (s, 3H, $SiCH_3$); **^{13}C NMR** δ 202.3, 175.1, 159.1, 152.8, 149.7, 135.2, 130.3, 129.4, 129.1, 128.9, 128.8, 127.3, 113.6, 75.4, 72.8, 71.8, 66.0, 55.4, 55.2, 43.7, 43.0, 42.6, 37.5, 26.0, 18.2, 15.4, 14.1, 13.0, -3.7, -4.2; **HRESIMS** calculated for $C_{36}H_{51}NO_7NaSi^+$ ($M+Na^+$): 660.3332; found: 660.3325; **EIMS** *m/z* (%): 442 (6), 376 (25), 290 (21), 199 (65), 137 (11), 121 (100), 91 (13), 73 (27).

(2*S*,3*R*,4*S*,5*R*)-3-(*tert*-Butyldimethylsilyloxy)-6-[(2*S*)-3-(4-methoxybenzyloxy)-2-methylpropionyl]-2,4,5-trimethylcyclohexanone (116)



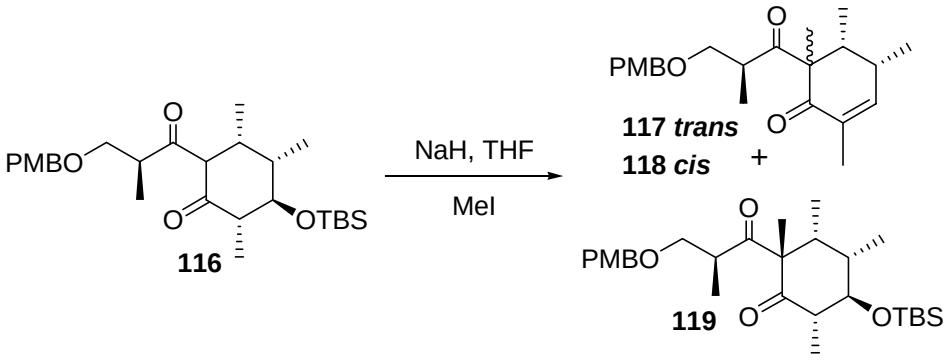
To a stirred suspension of CuI (0.676 g, 3.55 mmol) in dry Et_2O (10 mL) and dry Me_2S (10 mL) under N_2 at rt was added MeLi (1.4 M in Et_2O, 5.07 mL, 7.10 mmol) dropwise until the initially formed yellow precipitate just dissolved to form a pale yellow solution. To this solution was added enone **43** (1.51 g, 2.37 mmol) in dry Et_2O (10mL) dropwise *via* cannula (3 mL rinse), causing a yellow precipitate to form, and the mixture was stirred at rt for 1 hour. The reaction was diluted with Et_2O (30 mL) and quenched by the slow addition of a 90% NH_4Cl/10% NH_4OH solution (50 mL). The mixture was stirred for 10 minutes by which time a deep blue colour had developed. The mixture was extracted with Et_2O (3 x 75 mL) and the combined organic phases were washed

with brine (20 mL) and dried ($MgSO_4$). The dried organic extracts were filtered through celite and concentrated *in vacuo* to yield a yellow oil which was purified by flash chromatography on silica (CH_2Cl_2, R_f = 0.25) to give cyclohexanone **116** (0.865 g, 1.81 mmol, 76%) as a colourless oil. The product was determined to be a 2:1 mixture of *enol:keto* tautomers by ^{1}H NMR. **IR** (film) 3402 (br), 1719, 1699, 1614, 1588, 1515, 1463, 1373, 1361, 1303, 1250, 1174, 1093, 1039, 1006, 863, 836, 775 cm^{-1}; **HRESIMS** calculated for $C_{27}H_{44}O_5NaSi^+$ ($M+Na^+$): 499.2856; found: 499.2849; **EIMS** *m/z* (%): 326 (3), 206 (16), 137 (24), 121 (100), 91 (3), 77 (5), 69 (6).

Enol: **^{1}H NMR** δ 16.82 (s, 1H, O*H*), 7.18 (d, 2H, *J* = 8.4 Hz, Ar*H*), 6.85 (d, 2H, *J* = 8.4 Hz, Ar*H*), 4.40 (s, 2H, ArCH_2O), 3.79 (s, 3H, CH_3OAr), 3.63-3.54 (m, 1H, CH_AH$_B$OPMB), 3.48-3.37 (m, 2H, CH$_A$$H_B$OPMB, C*H*OTBS), 3.18-3.05 (m 1H, CH$_2$C*H*(CH$_3$)CO), 2.78-2.71 (m, 1H, =C(CO)C*H*(CH$_3$)), 2.36 (app. qn, 1H, *J* = 7. 2 Hz, =C(OH)C*H*(CH$_3$)), 1.78-1.67 (m, 1H, C*H*(CH$_3$)CHOTBS), 1.30 (d, 3H, *J* = 6.9 Hz, =C(OH)CH(CH_3)), 1.12 (d, 3H, *J* = 6.6 Hz, CH$_2$CH(CH_3)CO), 1.01 (d, 3H, *J* = 6.6 Hz, CH(CH_3)CHOTBS), 0.94-0.91 (m, 12H, =C(CO)CH(CH_3), SiC(CH_3)), 0.11 (s, 3H, SiCH_3), 0.096 (s, 3H, SiCH_3); **^{13}C NMR** δ 200.6, 187.7, 159.1, 130.3, 128.9, 113.7, 113.4, 75.2, 73.3, 72.9, 55.2, 46.7, 39.6, 38.6, 33.1, 26.0, 18.2, 16.8 (2C), 16.4, 14.5, -3.4, -3.5.

Keto: **^{1}H NMR** δ 7.21 (d, 2H, *J* = 8.4 Hz, Ar*H*), 6.85 (d, 2H, *J* = 8.4 Hz, Ar*H*), 4.39 (s, 2H, ArCH_2O), 3.79 (s, 3H, CH_3OAr), 3.63-3.54 (m, 1H, CH_AH$_B$OPMB), 3.50 (d, 1H, *J* = 5.7 Hz, COC*H*CH(CH$_3$)), 3.48-3.42 (m, 1H, CH$_A$$H_B$OPMB), 3.26 (dd, 1H, *J* = 7.8, 6.3 Hz C*H*OTBS), 3.18-3.05 (m, 1H, CH$_2$C*H*(CH$_3$)CO), 2.78-2.71 (m, 1H, COCHC*H*(CH$_3$)), 2.64 (app. qn, 1H, *J* = 7.0 Hz, COC*H*(CH$_3$)), 2.05-1.95 (m, 1H, CH(CH_3)CHOTBS), 1.07 (d, 3H, *J* = 6.6 Hz, COCH(CH_3)), 0.99 (d, 3H, *J* = 6.6 Hz, CH$_2$CH(CH_3)CO), 0.91 (s, 9H, SiC(CH_3)$_3$), 0.83 (d, 3H, 6.9 Hz, CH(CH_3)CHOTBS), 0.82 (d, 3H, *J* = 7.2 Hz COCHCH(CH_3)), 0.057 (s, 6H, SiCH_3); **^{13}C NMR** δ 207.9, 207.8, 159.1, 130.0, 129.3, 113.7, 79.1, 72.9, 72.2, 69.7, 55.2, 52.0, 46.0, 39.7, 32.8, 25.9, 18.1, 15.4, 14.8, 13.2, 12.1, -3.7, -3.9.

(4*S*,5*R*,6*S*)-6-[(2*S*)-3-(4-Methoxybenzyloxy)-2-methylpropionyl]-2,4,5,6-tetramethylcyclohex-2-enone (117), (4*S*,5*R*,6*R*)-6-[(2*S*)-3-(4-methoxybenzyloxy)-2-methylpropionyl]-2,4,5,6-tetramethylcyclohex-2-enone (118) and (2*R*,3*R*,4*S*,5*R*,6*S*)-5-(*tert*-butyldimethylsilyloxy)-2-[(2*S*)-3-(4-methoxybenzyloxy)-2-methylpropionyl]-2,3,4,6-tetramethylcyclohexanone (119)



To a stirred suspension of NaH (60% dispersion in oil, 0.006 g, 0.147 mmol) in dry THF (1 mL) was added diketone **116** (0.035 g, 0.073 mmol) in dry THF (2 x 0.5 mL) and the mixture was stirred at rt for 10 minutes. To this yellow solution was added MeI (23 μL, 0.367 mmol) and the resulting pale yellow solution was stirred at rt for 42 hours. The yellow reaction mixture was diluted with CH_2Cl_2 (5 mL), quenched with $NaHCO_3$ (sat., 5 mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a yellow oil. The product was purified by flash chromatography on silica (CH_2Cl_2, R_f = 0.26, 0.25) to give firstly the methylated product **119** (0.007 g, 0.0014 mmol, 19%) as a colourless oil, followed by an inseparable 3:1 mixture of *trans*:*cis* methylated and eliminated products **117** and **118** (0.010 g, 0.0028 mmol, 38%) as a colourless oil.

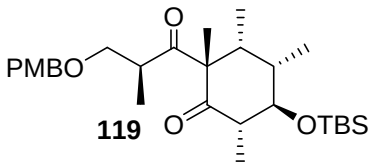
Methylated product **119**: $[\alpha]_D$ = –2.5 (*c* 0.40, $CHCl_3$); **IR** (film) 1734, 1707, 1614, 1514, 1463, 1372, 1250, 1090, 1038, 1006, 836, 775 cm^{-1}; **^{1}H NMR** δ 7.27 (d, 2H, *J* = 8.4 Hz, Ar*H*), 6.86 (d, 2H, *J* = 8.4 Hz, Ar*H*), 4.52 (d, 1H, *J* = 11.4 Hz, ArCH_AH_BO), 4.41 (d, 1H, *J* = 11.4 Hz, ArCH_AH_BO), 3.93-3.86 (m, 1H, PMBOCH_AH_B), 3.80 (s, 3H, CH_3OAr), 3.37-3.30 (m, 2H, PMBOCH_AH_B, $CH_2CH(CH_3)CO$), 3.25 (app. t, 1H, *J* = 9.6 Hz, C*H*OTBS), 2.79 (qd, 1H, *J* = 6.4, 2.7 Hz, COC*H*(CH_3)), 2.32-2.23 (m, 1H, C*H*(CH_3)CHOTBS), 2.17 (qd, 1H, *J* = 7.2, 3.6 Hz, C(CH_3)C*H*(CH_3)), 1.56 (s, 3H, C(CH_3)), 1.18 (d, 3H, *J* = 6.0 Hz, $CH_2CH(CH_3)CO$), 1.09 (d, 3H, *J* = 6.4 Hz,

COCH(CH_3)), 1.04 (d, 3H, *J* = 6.9 Hz, CH(CH_3)CHOTBS),0.92 (s, 9H, SiC(CH_3)$_3$), 0.67 (d, 3H, *J* = 7.2 Hz, C(CH_3)CH(CH_3)), 0.076 (s, 3H, SiCH_3), 0.073 (s, 3H, SiCH_3); **^{13}C NMR** δ 213.6, 211.3, 159.0, 130.7, 129.2, 113.7, 79.5, 72.6, 71.7, 66.7, 55.2, 49.6, 44.8, 41.0, 37.4, 26.1, 22.1, 18.3, 16.81, 16.77, 12.3, 10.5, -3.2, -3.3; **HRESIMS** calculated for $C_{28}H_{46}O_5NaSi^+$ (M+Na^+): 513.3012; found: 513.3003; **EIMS** *m/z* (%): 472 (2), 433 (3), 354 (9), 297 (12), 222 (8), 199 (13), 159 (10), 151 (21), 137 (13), 121 (100), 91 (5), 75 (25), 69 (6), 55(9).

Trans eliminated isomer **117**: **IR** (film) 1699, 1669, 1614, 1514, 1457, 1362, 1248, 1174, 1097, 1035, 988, 820 cm^{-1}; **^{1}H NMR** δ 7.20 (d, 2H, *J* = 8.7 Hz, Ar*H*), 6.85 (d, 2H, *J* = 8.7 Hz, Ar*H*), 6.36-6.33 (m, 1H, C*H*=C), 4.41 (d, 1H, *J* = 11.7 Hz, ArCH_AH$_B$O), 4.34 (d, 1H, *J* = 11.7 Hz, ArCH$_A$$H_B$O), 3.79 (s, 3H, C$H_3$OAr), 3.66 (dd, 1H, *J* = 8.7, 6.6 Hz, PMBOCH_AH$_B$), 3.36 (app. sex, 1H, *J* = 6.6 Hz, CH$_2$C*H*(CH$_3$)), 3.28 (dd, 1H, *J* = 8.7, 6.3 Hz, PMBOCH$_A$$H_B$), 2.78-2.69 (m, 1H, C*H*(CH$_3$)CH=C), 2.23-2.19 (m, 1H, C(CH$_3$)C*H*(CH$_3$)), 1.77 (dd, 3H, *J* = 2.1, 1.5 Hz, C(CH_3)=CH), 1.40 (s, 3H, C(CH_3)), 1.13 (d, 3H, *J* = 6.6 Hz, CH$_2$CH(CH_3)), 1.07 (d, 3H, *J* = 7.5 Hz, CH(CH_3)CH=C), 0.96 (d, 3H, *J* = 7.2 Hz, C(CH$_3$)CH(CH_3)); **^{13}C NMR** δ 214.4, 199.8, 159.0, 147.5, 133.5, 130.4, 129.2, 113.6, 72.7, 72.2, 62.6, 55.2, 44.1, 42.2, 32.7, 21.6, 16.5, 16.3, 16.0, 11.7; **HRESIMS** calculated for $C_{22}H_{30}O_4Na^+$ (M+Na^+): 381.2042; found: 381.2035; **EIMS** *m/z* (%): 222 (11), 151 (23), 137 (21), 121 (100), 96 (8), 77 (6), 69 (5), 55 (4).

Cis eliminated isomer **118**: **IR** (film) see *trans* data; **^{1}H NMR** δ 7.20 (d, 2H, *J* = 8.7 Hz, Ar*H*), 6.84 (d, 2H, *J* = 8.7 Hz, Ar*H*), 6.33-6.30 (m, 1H, C*H*=C), 4.41 (d, 1H, *J* = 11.7 Hz, ArCH_AH$_B$O), 4.36 (d, 1H, *J* = 11.7 Hz, ArCH$_A$$H_B$O), 3.80 (s, 3H, C$H_3$OAr), 3.71 (dd, 1H, *J* = 9.9, 6.9 Hz, PMBOCH_AH$_B$), 3.57-3.46 (m, 1H, CH$_2$C*H*(CH$_3$)), 3.35 (dd, 1H, *J* = 9.9, 8.7 Hz, PMBOCH$_A$$H_B$), 2.89-2.82 (m, 1H, C*H*(CH$_3$)CH=C), 2.37-2.28 (m, 1H, C(CH$_3$)C*H*(CH$_3$)), 1.79 (dd, 3H, *J* = 2.4, 0.9 Hz, C(CH_3)=CH), 1.40 (s, 3H, C(CH_3)), 1.08 (d, 3H, *J* = 7.2 Hz, CH(CH_3)CH=C), 1.02 (d, 3H, *J* = 6.9 Hz, CH$_2$CH(CH_3)), 0.86 (d, 3H, *J* = 6.9 Hz, C(CH$_3$)CH(CH_3)); **^{13}C NMR** δ 213.2, 200.0, 159.0, 147.0, 133.2, 130.5, 128.6, 113.9, 72.8, 72.7, 62.5, 55.2, 43.8, 40.9, 32.4, 20.4, 17.0, 16.2, 14.4, 11.4; **HRESIMS** and **EIMS** see *trans* data.

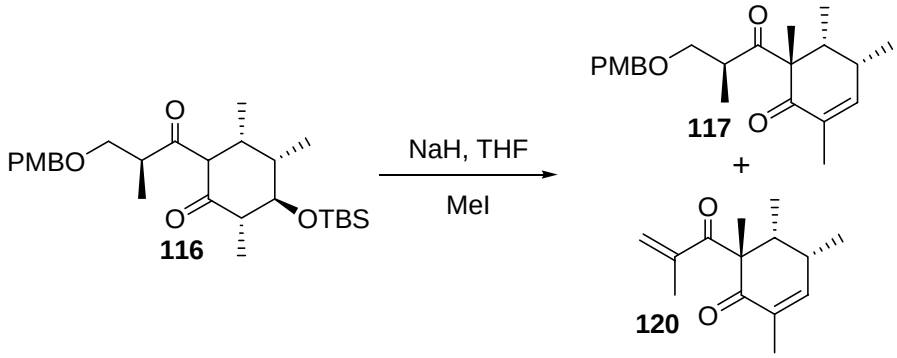
(2*R*,3*R*,4*S*,5*R*,6*S*)-5-(*tert*-Butyldimethylsilyloxy)-2-[(2*S*)-3-(4-methoxybenzyloxy)-2-methylpropionyl]-2,3,4,6-tetramethylcyclohexanone (119)



119

To a stirred suspension of NaH (60% dispersion in oil, 0.0305 g, 0.763 mmol) in dry THF (5 mL) under N_2 at rt was added diketone **116** (0.360 g, 0.755 mmol) in dry THF (3 mL) *via* cannula (2 mL rinse) and the mixture was stirred at rt for 10 minutes. To this yellow solution was added MeI (470 μL, 7.55 mmol) and the resulting pale yellow solution was stirred at rt for 18 hours. The yellow reaction mixture was diluted with CH_2Cl_2 (10 mL), quenched with $NaHCO_3$ (sat., 5 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a yellow oil. The product was purified by flash chromatography on silica (20% Et_2O/hexanes, R_f = 0.30) to give the title compound **119** (0.320 g, 0.652 mmol, 86%) as a colourless oil with identical spectral properties to those given above.

(4*S*,5*R*,6*S*)-6-[(2*S*)-3-(4-Methoxybenzyloxy)-2-methylpropionyl]-2,4,5,6-tetra-methylcyclohex-2-enone (117) and (4*S*,5*R*,6*S*)-2,4,5,6-tetramethyl-6-(2-methyl-acryloyl)cyclohex-2-enone (120)



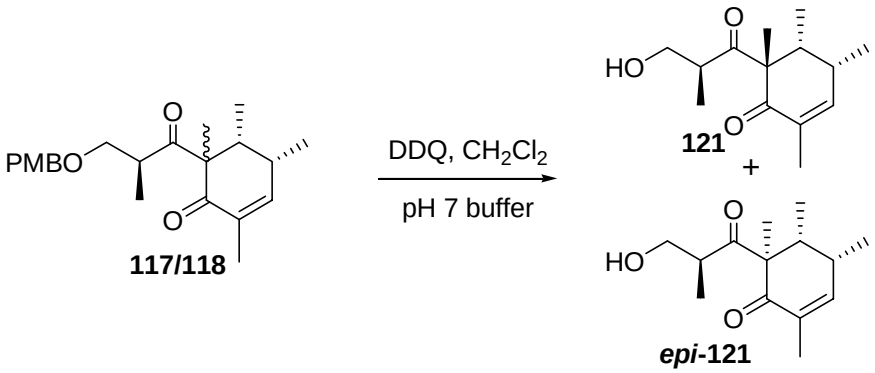
116 **117** **120**

To a stirred suspension of NaH (60% dispersion in oil, 0.0713 g, 1.78 mmol) in dry THF (15 mL) was added diketone **116** (0.850 g, 1.78 mmol) in dry THF (4 mL) *via* cannula (4 mL rinse) and the mixture was stirred at rt for 10 minutes. To this yellow solution was added MeI (1.11 mL, 17.8 mmol) and the resulting pale yellow solution was stirred at rt for 17 hours. The yellow reaction mixture was cannulated into NaH

(0.040g, 1.00 mmol) and stirred for a further 15 minutes to promote β-elimination. The reaction was quenched with $NaHCO_3$ (sat., 10 mL) and the volatiles were removed *in vacuo*. The aqueous residue was extracted with CH_2Cl_2 (3 x 50 mL), the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a yellow oil. The product was purified by flash chromatography on silica (2% Et_2O/CH_2Cl_2, R_f = 0.28, 0.26) to give firstly the terminal alkene **120** (0.037 g, 0.168 mmol, 9%) as a colourless oil, followed by an inseparable 9:1 mixture (as determined by GCMS) of *trans*:*cis* **117** and **118** (0.531 g, 1.48 mmol, 83%) as a colourless oil with identical spectral data to those reported above. $[\alpha]_D$ = – 84.0 (*c* 0.17, $CHCl_3$)

Terminal alkene **120**: **IR** (film) 1666 (with shoulder), 1453, 1376, 1295, 1251, 1156, 1033, 989, 932 cm^{-1}, **^{1}H NMR** δ 6.36-6.30 (m, 1H, C*H*=C), 5.50-5.45 (m, 1H, C*H*$_A$H$_B$=), 5.19-5.13 (m, 1H, CH$_A$*H*$_B$=), 2.89-2.78 (m, 1H, C*H*(CH$_3$)CH=C), 2.24-2.15 (m, 1H, C(CH$_3$)C*H*(CH$_3$)), 1.87 (app. s, 3H, C(C*H*$_3$)=CH), 1.82-1.77 (m, 3H, CH$_2$=C(C*H*$_3$)), 1.44 (s, 3H, C(C*H*$_3$)), 1.09 (d, 3H, *J* = 7.2 Hz, CH(C*H*$_3$)CH=C), 0.96 (d, 3H, *J* = 7.2 Hz, C(CH$_3$)CH(C*H*$_3$)); **^{13}C NMR** δ 205.9, 199.9, 147.2, 144.8, 134.2, 121.4, 61.4, 43.0, 32.0, 22.7, 20.1, 16.8, 16.3, 12.7; **EIMS** *m/z* (%): 221 (M^+, 1), 205 (2), 192 (3), 177 (3), 150 (6), 135 (3), 123 (7), 107 (4), 96 (12), 81 (11), 69 (67), 53 (10), 41 (100).

(4*S*,5*R*,6*S*)-6-[(2*S*)-3-Hydroxy-2-methylpropionyl]-2,4,5,6-tetramethylcyclohex-2-enone (121) and (4*S*,5*R*,6*R*)-6-[(2*S*)-3-hydroxy-2-methylpropionyl]-2,4,5,6-tetramethylcyclohex-2-enone (*epi*-121)



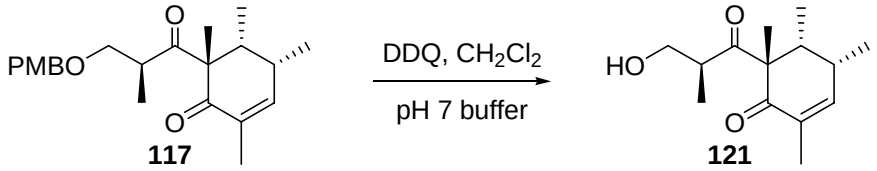
To a stirred solution of the 3:1 PMB ether **117**:**118** (0.115 g, 0.321 mmol) in CH_2Cl_2 (8 mL) and pH 7 buffer (0.8 mL) at 0°C was added DDQ (0.109 g, 0.481 mmol) and the

solution was stirred at 0°C for 3.5 hours. The reaction was diluted with CH_2Cl_2 (15 mL) and quenched with $NaHCO_3$ (sat., 20 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were washed with $NaHCO_3$ (sat., 2 x 10 mL) and brine (10 mL). The dried ($MgSO_4$) organic extracts were filtered and concentrated *in vacuo* to yield a colourless oil which was purified by flash chromatography on buffered silica (20% Et_2O/CH_2Cl_2, R_f = 0.26) to yield the inseparable primary alcohols **121** and ***epi*-121** (0.054 g, 0.226 mmol, 71%) as a colourless oil.

Trans enone isomer **121**: **^{1}H NMR** δ 6.34-6.32 (m, 1H, C*H*=C), 3.78-3.64 (m, 2H, HOCH_2), 3.46-3.38 (m, 1H, $CH_2CH(CH_3)$), 2.88-2.77 (m, 1H, C$H(CH_3)$CH=C), 2.63 (bs, 1H, O*H*), 2.38-2.31 (m, 1H, $C(CH_3)CH(CH_3)$), 1.80 (dd, 3H, *J* = 2.4, 0.9 Hz, $C(CH_3)$=CH), 1.44 (s, 3H, $C(CH_3)$), 1.15 (d, 3H, *J* = 6.9 Hz, $CH_2CH(CH_3)$), 1.10 (d, 3H, *J* = 7.5 Hz, $CH(CH_3)$CH=C), 0.89 (d, 3H, *J* = 6.9 Hz, $C(CH_3)CH(CH_3)$); **^{13}C NMR** δ 216.2, 201.2, 147.4, 133.2, 65.7, 62.9, 45.8, 41.7, 32.4, 21.1, 17.0, 16.1, 15.7, 11.2.

Cis enone isomer ***epi*-121**: **^{1}H NMR** δ 6.38-6.36 (m, 1H, C*H*=C), 3.78-3.64 (m 2H, HOCH_2), 3.48-3.40 (m, 1H, $CH_2CH(CH_3)$), 2.92-2.81 (m, 1H, C$H(CH_3)$CH=C), 2.63 (bs, 1H, O*H*), 2.32-2.26 (m, 1H, $C(CH_3)CH(CH_3)$), 1.82 (dd, 3H, *J* = 2.4, 0.9 Hz, $C(CH_3)$=CH), 1.40 (s, 3H, $C(CH_3)$), 1.11 (d, 3H, *J* = 7.5 Hz, $CH(CH_3)$CH=C), 1.03 (d, 3H, *J* = 6.6 Hz, $CH_2CH(CH_3)$), 0.86 (d, 3H, *J* = 6.9 Hz, $C(CH_3)CH(CH_3)$); **^{13}C NMR** δ 216.5, 201.1, 147.9, 133.5, 66.4, 62.7, 45.8, 42.3, 31.9, 21.2, 17.2, 16.1, 13.8, 11.2.

(4*S*,5*R*,6*S*)-6-[(2*S*)-3-Hydroxy-2-methylpropionyl]-2,4,5,6-tetramethylcyclohex-2-enone (121)

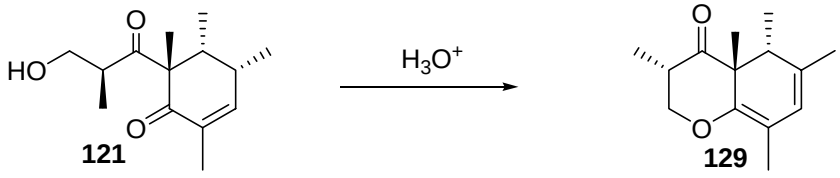


117 **121**

To a stirred solution of PMB ether **117** (0.230 g, 0.642 mmol) in CH_2Cl_2 (16 mL) and pH 7 buffer (1.6 mL) at 0°C was added DDQ (0.175 g, 0.770 mmol) and the solution was stirred at 0°C for 3 hours. The reaction was diluted with CH_2Cl_2 (50 mL) and quenched with $NaHCO_3$ (sat., 50 mL). The phases were separated and the aqueous

phase was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were washed with $NaHCO_3$ (sat., 20 mL) and brine (20 mL). The dried ($MgSO_4$) organic extracts were filtered and concentrated *in vacuo* to yield a colourless oil which was purified by flash chromatography on silica (20% Et_2O/CH_2Cl_2, R_f = 0.26) to yield the title compound **121** (0.147 g, 0.617 mmol, 96%) as a colourless oil with identical spectral data to those reported above. **$[\alpha]_D$** = –102 (*c* 1.07, $CHCl_3$); **IR** (film) 3460 (br), 1699, 1669, 1456, 1378, 1032, 989 cm^{-1}; **^{1}H NMR** (C_6D_6) δ 5.74-5.70 (m, 1H, C*H*=C), 3.88-3.74 (m 1H, HOCH_AH_B), 3.60-3.51 (m 1H, HOCH_AH_B), 3.39-3.23 (m, 1H, $CH_2CH(CH_3)$), 2.28-2.03 (m, 3H, $C(CH_3)CH(CH_3)$, $CH(CH_3)CH$=C, O*H*), 1.72 (dd, 3H, J = 2.1, 1.5 Hz, $C(CH_3)$=CH), 1.16 (s, 3H, $C(CH_3)$), 1.07 (d, 3H, *J* = 6.8 Hz, $CH_2CH(CH_3)$), 0.86 (d, 3H, *J* = 6.8 Hz, $C(CH_3)CH(CH_3)$), 0.71 (d, 3H, *J* = 7.2 Hz $CH(CH_3)$CH=C); **HRESIMS** calculated for $C_{14}H_{22}O_3Na^+$ ($M+Na^+$): 261.1467; found: 261.1459; **EIMS** *m/z* (%): 220 (9), 205 (3), 152 (43), 137 (100), 122 (15), 107 (14), 96 (15), 77 (8), 59 (20), 55 (16).

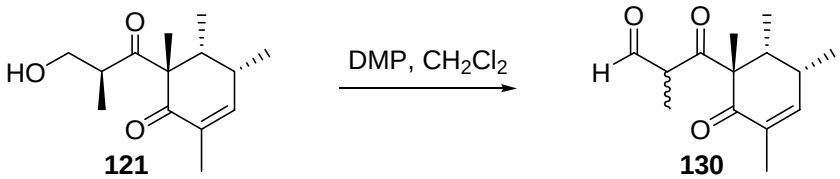
(3*S*,4a*R*,5*R*)-3,4a,5,6,8-Pentamethyl-2,3,4a,5-tetrahydro-4H-1-benzopyran-4-one (129)



There was a tendency for the alcohol **121** to cyclise to the bicyclic diene **129** in $CDCl_3$, depending on the acidity of the solvent. Furthermore, treatment of an NMR sample (non-acidic $CDCl_3$) with a small crystal of *p*-TsOH resulted in cyclisation after several minutes. Purification by flash chromatography on silica (20% Et_2O/CH_2Cl_2, R_f = 0.72) afforded the title compound **129** as a colourless oil. **$[\alpha]_D$** = –290 (*c* 0.40, $CHCl_3$); **IR** (film) 1716, 1672, 1616, 1451, 1380, 1362, 1327, 1284, 1265, 1220, 1171, 1143 cm^{-1}; **^{1}H NMR** δ 5.36 (q, 1H, *J* = 1.8 Hz, $(CH_3)C$=C*H*), 4.25 (dd, 1H, *J* = 11.1, 5.7 Hz, OCH_AH_B), 3.55 (dd, 1H, *J* = 11.1, 10.5 Hz, OCH_AH_B), 2.88-2.77 (m, 1H, COC*H*(CH_3)), 2.29 (q, 1H, *J* = 6.9 Hz, $C(CH_3)CH(CH_3)$), 1.75 (d, 3H, *J* = 1.8 Hz, (CH_3)C=CH), 1.67 (s, 3H, OC=C(CH_3)), 1.27 (s, 3H, $C(CH_3)$), 1.04 (d, 3H, *J* = 6.9 Hz, COCH(CH_3)), 0.83 (d, 3H, *J* = 6.9 Hz, $C(CH_3)CH(CH_3)$); **^{13}C NMR** δ 211.9, 148.0,

134.4, 121.3, 108.8, 69.7, 52.0, 42.3, 42.2, 24.0, 21.6, 13.5, 12.3, 9.8; **HRESIMS** calculated for $C_{14}H_{20}O_2Na^+$ ($M+Na^+$): 243.1361; found: 243.1358; **EIMS** *m/z* (%): 220 (M^+, 51), 205 (16), 177 (14), 150 (58), 135 (49), 107 (60), 84 (100), 77 (15), 69 (9), 51 (36).

2-Methyl-3-oxo-3-[(1*S*,5*S*,6*R*)-1,3,5,6-tetramethyl-2-oxocyclohex-3-enyl]propionaldehyde (130)



121 **130**

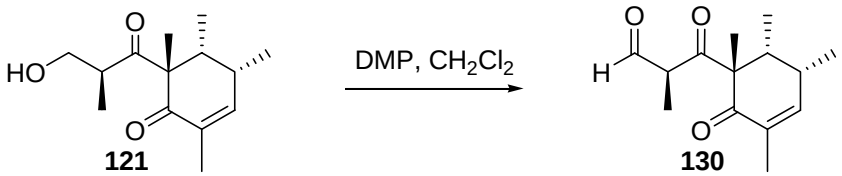
To a stirred suspension of Dess-Martin periodinane[65] (0.053 g, 0.126 mmol) in dry CH_2Cl_2 (1mL) under N_2 was added a solution of alcohol **121** (0.020 g, 0.0839 mmol) in dry CH_2Cl_2 (1 mL) *via* cannula (1 mL rinse) and the reaction was stirred at rt for 2.5 hours. The reaction mixture was diluted with Et_2O (10 mL) and quenched with a solution of $NaHCO_3$ (sat., 5 mL) containing $Na_2S_2O_3.5H_2O$ (0.212 g, 0.854 mmol) and stirring was continued for 5 minutes. The phases were separated, and the organic phase was washed with $NaHCO_3$ (sat., 5 mL) and brine (5 mL). The dried ($MgSO_4$) organic extracts were filtered and concentrated *in vacuo* to yield a colourless oil which was purified by flash chromatography on buffered silica (5% Et_2O/CH_2Cl_2, R_f = 0.44) to give the title compound **130** (0.014 g, 0.0592 mmol, 71%) as a colourless oil, which was determined to be a 1:1 mixture of 2 epimers by ^{1}H NMR. **IR** (film) 1731, 1699, 1666, 1458, 1382, 1359, 1196, 1160, 1083, 1033, 1004, 987 cm^{-1}.

Epimer 1: **^{1}H NMR** δ 9.70 (d, 1H, *J* = 2.4 Hz, C*H*O), 6.35-6.30 (m, 1H, C*H*=C), 4.01 (qd, 1H, *J* = 6.9, 2.4 Hz, COC*H*(CH_3)CO), 2.98-2.83 (m, 1H, C*H*(CH_3)CH=C), 2.31-2.21 (m, 1H, C(CH_3)C*H*(CH_3)), 1.80-1.78 (m, 3H, C(C*H*$_3$)=CH), 1.38 (s, 3H, C(C*H*$_3$)), 1.27 (d, 3H, *J* = 6.9 Hz, COCH(C*H*$_3$)CO), 1.10 (d, 3H, *J* = 7.2 Hz, CH(C*H*$_3$)CH=C), 0.80 (d, 3H, *J* = 7.2 Hz, C(CH_3)CH(C*H*$_3$)); **^{13}C NMR** δ 208.9, 200.6, 197.3, 147.6, 133.1, 62.3, 59.4, 42.8, 31.5, 21.0, 17.4, 15.9, 12.1, 10.8.

Epimer 2: **^{1}H NMR** δ 9.68 (d, 1H, *J* = 2.4 Hz, C*H*O), 6.35-6.30 (m, 1H, C*H*=C), 4.22 (qd, 1H, *J* = 7.0, 2.4 Hz, COC*H*(CH_3)CO), 2.98-2.83 (m, 1H, C*H*(CH_3)CH=C), 2.40-2.31 (m, 1H, C(CH_3)C*H*(CH_3)), 1.80-1.78 (m, 3H, C(C*H*$_3$)=CH), 1.39 (s, 3H, C(C*H*$_3$)),

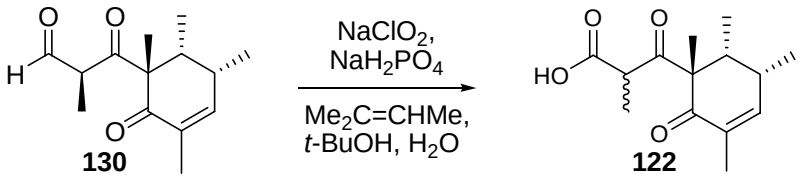
1.35 (d, 3H, *J* = 7.0 Hz, COCH(C*H*$_3$)CO), 1.10 (d, 3H, *J* = 7.2 Hz, CH(C*H*$_3$)CH=C), 0.83 (d, 3H, *J* = 7.2 Hz, C(CH$_3$)CH(C*H*$_3$)); **^{13}C NMR** δ 209.3, 200.5, 198.5, 147.4, 133.1, 62.5, 57.8, 41.7, 31.9, 21.2, 17.3, 15.9, 13.7, 10.9.

(2*R*)-2-Methyl-3-oxo-3-[(1*S*,5*S*,6*R*)-1,3,5,6-tetramethyl-2-oxocyclohex-3-enyl]-propionaldehyde (130)



To a stirred suspension of the Dess-Martin periodinane[65] (0.747 g, 1.76 mmol) in dry CH_2Cl_2 (10 mL) under N_2 was added a solution of alcohol **121** (0.280 g, 1.17 mmol) in dry CH_2Cl_2 (3 mL) *via* cannula (3 mL rinse) and the reaction was stirred at rt for 1 hour. The reaction mixture was diluted with Et_2O (80 mL) and quenched with a solution of $NaHCO_3$ (sat., 40 mL) containing $Na_2S_2O_3.5H_2O$ (2.99 g, 12.0 mmol) and stirring was continued for 5 minutes. The phases were separated, and the organic phase was washed with $NaHCO_3$ (sat., 10 mL) and brine (10 mL). The dried ($MgSO_4$) organic extracts were filtered and concentrated *in vacuo* to yield the title compound **130** (0.280 g, 1.18 mmol, *ca.* 100%) as a colourless oil with identical spectral data to epimer 2 above. The product was used without further purification.

2-Methyl-3-oxo-3-[(1*S*,5*S*,6*R*)-1,3,5,6-tetramethyl-2-oxocyclohex-3-enyl]propionic acid (122)



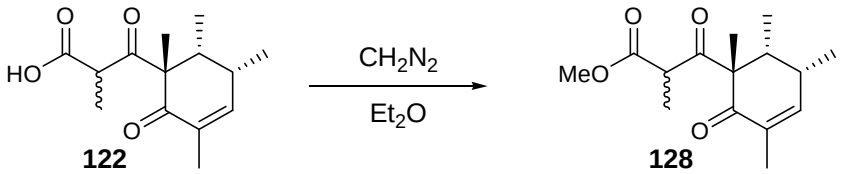
To a stirred solution of crude ketoaldehyde **130** (0.140 g, 0.592 mmol) in *t*-BuOH (12 mL) and Me_2C=CHMe (3 mL) at rt was added a solution of $NaClO_2$ (0.670 g, 7.40 mmol) and $NaH_2PO_4.2H_2O$ (0.924 g, 5.92 mmol) in water (5 mL) dropwise. The resulting pale yellow solution was stirred at rt for 1 hour and the volatiles were removed *in vacuo*. Water (20 mL) was added and the aqueous residue was washed with hexane (2 x 10 mL). The aqueous phase was acidified to pH 3 with HCl (1M) and extracted with

Et_2O (3 x 30 mL). The combined organic phases were washed with cold water (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a colourless oil. Purification by flash chromatography on silica (40% Et_2O/CH_2Cl_2 + 0.5% AcOH, R_f = 0.31) yielded the title compound **122** (0.095 g, 0.376 mmol, 64%) as a colourless oil which was a 1:1 mixture of 2 epimers as determined by ^{1}H NMR. **IR** (film) 3263 (br), 1727, 1703, 1668, 1456, 1378, 1358, 1295, 1192, 1083, 1034, 985 cm^{-1}. **HRESIMS** calculated for $C_{14}H_{20}O_4Na^+$ (M+Na$^+$): 275.1259; found: 275.1254; **EIMS** *m/z* (%): 209 ([M-CO_2]$^+$, 28), 180 (1), 152 (29), 137 (100), 122 (11), 109 (12), 96 (16), 81 (12), 67 (19), 57 (20), 41 (22).

Epimer 1: **^{1}H NMR** δ 6.36-6.28 (m, 1H, C*H*=C), 4.06 (q, 1H, *J* = 7.0 Hz, COC*H*(CH_3)CO), 2.98-2.81 (m, 1H, C*H*(CH_3)CH=C), 2.35-2.26 (m, 1H, C(CH_3)C*H*(CH_3)), 1.82-1.77 (m, 3H, C(C*H*$_3$)=CH), 1.38 (s, 3H, C(C*H*$_3$)), 1.37 (d, 3H, *J* = 7.0 Hz, COCH(C*H*$_3$)CO), 1.10 (d, 3H, *J* = 7.5 Hz, CH(C*H*$_3$)CH=C), 0.77 (d, 3H, *J* = 6.9 Hz, C(CH_3)CH(C*H*$_3$)); **^{13}C NMR** δ 207.9, 200.6, 175.4, 147.7, 133.1, 62.7, 51.4, 42.8, 31.6, 21.7, 17.4, 16.0, 14.0, 10.8.

Epimer 2: **^{1}H NMR** δ 6.36-6.28 (m, 1H, C*H*=C), 4.33 (q, 1H, *J* = 7.0 Hz, COC*H*(CH_3)CO), 2.98-2.81 (m, 1H, C*H*(CH_3)CH=C), 2.47-2.38 (m, 1H, C(CH_3)C*H*(CH_3)), 1.82-1.77 (m, 3H, C(C*H*$_3$)=CH), 1.46 (s, 3H, C(C*H*$_3$)), 1.44 (d, 3H, *J* = 7.0 Hz, COCH(C*H*$_3$)CO), 1.11 (d, 3H, *J* = 7.2 Hz, CH(C*H*$_3$)CH=C), 0.86 (d, 3H, *J* = 6.6 Hz, C(CH_3)CH(C*H*$_3$)); **^{13}C NMR** δ 207.5, 200.3, 175.0, 147.6, 133.1, 62.6, 49.9, 41.3, 32.0, 21.6, 17.3, 16.1, 15.5, 10.7.

Methyl 2-methyl-3-oxo-3-[(1*S*,5*S*,6*R*)-1,3,5,6-tetramethyl-2-oxocyclohex-3-enyl]-propionate (128)



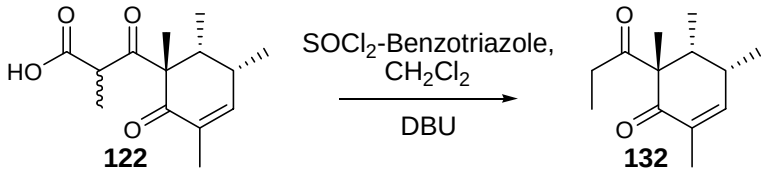
To crude acid **122** (*ca.* 0.029 g, 0.114 mmol) in Et_2O (2 mL) at rt was added CH_2N_2/Et_2O (excess) until the yellow colour persisted. The mixture was stirred at rt for a further 10 minutes and N_2 was bubbled through the solution to remove excess diazomethane. The solvent was removed *in vacuo* to yield a colourless oil which was

purified by flash chromatography on silica (20% Et_2O/CH_2Cl_2, R_f = 0.65) to afford the title compound **128** (0.014 g, 0.0526 mmol, 47%) as a colourless oil which was a 3:2 mixture of epimers as determined by ^{1}H NMR. **IR** (film) 1746, 1708, 1670, 1455, 1435, 1375, 1359, 1326, 1299, 1245, 1204, 1171, 1154, 1088, 1035, 988 cm^{-1}. **HRESIMS** calculated for $C_{15}H_{22}O_4Na^+$ ($M+Na^+$): 289.1416; found: 289.1415; **EIMS** *m/z* (%): 266 (M^+, 1), 235 (1), 179 (1), 152 (2), 137 (6), 118 (2), 85 (64), 83 (100), 59 (2), 49 (29), 35 (8).

Major epimer: **^{1}H NMR** δ 6.34-6.30 (m, 1H, C*H*=C), 3.96 (q, 1H, *J* = 7.1 Hz, COC*H*(CH_3)CO), 3.74 (s, 3H, CO_2CH_3), 2.96-2.86 (m, 1H, C*H*(CH_3)CH=C), 2.35-2.25 (m, 1H, C(CH_3)C*H*(CH_3)), 1.83 (dd, 3H, *J* = 2.4, 1.2 Hz, C(CH_3)=CH), 1.45 (s, 3H, C(CH_3)), 1.33 (d, 3H, *J* = 7.1 Hz, COCH(CH_3)CO), 1.09 (d, 3H, *J* = 7.5 Hz, CH(CH_3)CH=C), 0.77 (d, 3H, *J* = 6.9 Hz, C(CH_3)CH(CH_3)); **^{13}C NMR** δ 208.2, 200.0, 171.5, 147.2, 133.1, 62.3, 52.3, 51.8, 42.9, 31.6, 21.6, 17.2, 16.1, 13.8, 10.8.

Minor epimer: **^{1}H NMR** δ 6.34-6.30 (m, 1H, C*H*=C), 4.34 (q, 1H, *J* = 7.0 Hz, COC*H*(CH_3)CO), 3.66 (s, 3H, CO_2CH_3), 2.89-2.80 (m, 1H, C*H*(CH_3)CH=C), 2.49-2.40 (m, 1H, C(CH_3)C*H*(CH_3)), 1.78 (dd, 3H, *J* = 2.4, 1.5 Hz, C(CH_3)=CH), 1.40 (d, 3H, *J* = 7.0 Hz, COCH(CH_3)CO), 1.35 (s, 3H, C(CH_3)), 1.12 (d, 3H, *J* = 7.2 Hz, CH(CH_3)CH=C), 0.88 (d, 3H, *J* = 6.9 Hz, C(CH_3)CH(CH_3)); **^{13}C NMR** δ 207.0, 199.6, 171.4, 147.2, 133.1, 62.1, 52.0, 49.6, 41.0, 32.0, 21.9, 17.2, 16.2, 14.8, 10.8.

(4*S*,5*R*,6*S*)-2,4,5,6-Tetramethyl-6-propionylcyclohex-2-enone (132)



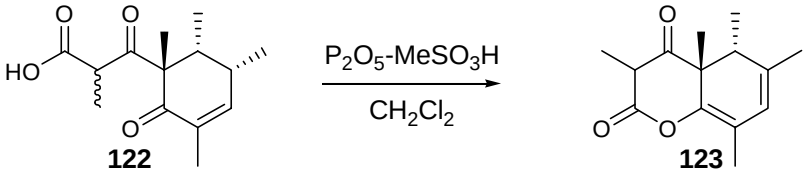
122 **132**

A 0.1 M stock solution of $SOCl_2$-Benzotriazole in CH_2Cl_2 was prepared according to the procedure of Chaudhari and Akamanchi[90] for the formation of the acid chloride.

To a stirred solution of acid **122** (0.018 g, 0.0713 mmol) in dry CH_2Cl_2 (1.5 mL) under N_2 at rt was added the $SOCl_2$-Benzotriazole stock solution (1.07 mL, 0.107 mmol) dropwise and stirring was continued at rt for 10 minutes. The solution was filtered and

the filtrate was stirred with $MgSO_4.7H_2O$ (0.035 g, 0.143 mmol) to destroy excess reagent. The solids were filtered off and the filtrate was treated with DBU (21 μL, 0.143 mmol) under N_2 at rt and stirring was continued for 3 hours. The reaction was quenched with $NaHSO_4$ (1 M, 2 mL) and the volatiles were removed *in vacuo*. The residue was taken up in Et_2O (20 mL), the phases were separated and the organic phase was washed with $NaHCO_3$ (sat., 5 mL) and brine (5 mL) The organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a colourless oil which was purified by flash chromatography on silica (5% Et_2O/CH_2Cl_2, R_f = 0.51) to afford the title compound **132** (0.005 g, 0.024 mmol, 34%) as a colourless oil. **^{1}H NMR** δ 6.41-6.37 (m, 1H, C*H*=C), 2.87-2.77 (m, 1H, C*H*(CH_3)CH=C), 2.76 (dq, 1H, *J* = 18.6, 7.2 Hz, $CH_3CH_AH_BCO$), 2.37 (dq, 1H, *J* = 18.6, 7.2 Hz, $CH_3CH_AH_BCO$), 2.21-2.13 (m, 1H, C(CH_3)C*H*(CH_3)), 1.83-1.81 (m, 3H, C(C*H*$_3$)=CH), 1.35 (s, 3H, C(C*H*$_3$)), 1.06 (d, 3H, *J* = 7.5 Hz, CH(C*H*$_3$)CH=C), 1.02 (t, 3H, *J* = 7.2 Hz, *C*H_3CH_2), 0.90 (d, 3H, *J* = 7.2 Hz, C(CH_3)CH(C*H*$_3$)); **^{13}C NMR** δ 212.9, 200.3, 147.6, 133.7, 61.8, 42.8, 35.9, 32.1, 21.1, 16.7, 16.2, 11.6, 7.8; **EIMS** *m/z* (%): 209 (M^+, 48), 180 (1), 152 (31), 137 (100), 122 (13), 109 (13), 96 (19), 81 (11), 67 (19), 57 (20), 41 (20).

(4a*R*,5*R*)-3,4a,5,6,8-Pentamethyl-3,4,4a,5-tetrahydro-2H-1-benzopyran-2,4-dione (123)



Eaton's reagent[91] was freshly prepared by heating a 1:10 mixture (w/w) of P_2O_5 and freshly distilled $MeSO_3H$ with stirring under N_2 at 40°C until homogeneous (approx. 40 minutes).

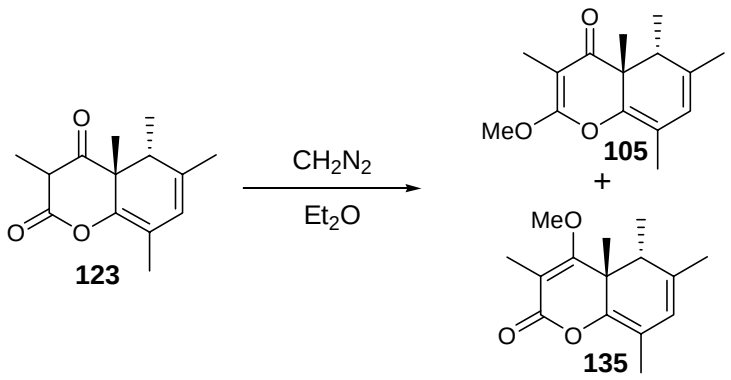
To a stirred, colourless solution of acid **122** (0.120 g, 0.476 mmol) in dry CH_2Cl_2 (5 mL) under N_2 at rt was added Eaton's reagent (300 μL) dropwise whereby the colour of the solution changed immediately to yellow and then brown. The reaction was stirred at rt for 1 hour (a dense, brown oil separated from the reaction mixture after several minutes), diluted with hexanes (20 mL) and quenched by the *slow* addition of $NaHCO_3$ (sat., 10 mL). The phases were separated and the aqueous phase was extracted with

hexanes (3 x 30 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a yellow oil. Purification by flash chromatography on silica (1:1 Et_2O/hexanes, R_f = 0.25) afforded title compound **123** (0.058 g, 0.248 mmol, 52%) as a colourless oil which crystallised upon standing. The product existed predominantly in the *keto* form as determined by ^{1}H NMR. **IR** (film) 3276 (br), 1729, 1699, 1671, 1634, 1456, 1363, 1258, 1201, 1174, 1116 cm^{-1}; **HRESIMS** calculated for $C_{14}H_{18}O_3Na^+$: 257.1154; found: 257.1148; EIMS *m/z* (%): 234 (M^+, 40), 219 (17), 206 (6), 191 (3), 163 (5), 151 (83), 135 (44), 122 (71), 107 (100), 91 (67), 79 (41), 65 (20), 55 (22), 41 (31).

Keto: **^{1}H NMR** δ 5.52-5.48 (m, 1H, $(CH_3)C=CH$), 3.43 (q, 1H, *J* = 6.6 Hz, $COCH(CH_3)$), 2.22 (q, 1H, *J* = 6.9 Hz, $C(CH_3)CH(CH_3)$), 1.82 (app. s, 6H, $(CH_3)C=CH$, $OC=C(CH_3)$), 1.35 (d, 3H, *J* = 7.5 Hz, $COCH(CH_3)$), 1.19 (s, 3H, $C(CH_3)$), 0.90 (d, 3H, *J* = 7.2 Hz, $C(CH_3)CH(CH_3)$); **^{13}C NMR** δ 205.3, 167.5, 141.4, 136.9, 120.9, 115.6, 54.2, 50.9, 45.0, 21.4, 20.2, 14.0, 13.1, 7.3.

Enol: **^{1}H NMR** δ 5.67 (bs, 1H, O*H*), 5.43-5.39 (m, 1H, $(CH_3)C=CH$), 2.23 (q, 1H, *J* = 7.0 Hz, $C(CH_3)CH(CH_3)$), 1.86 (s, 3H, $(CH_3)C=C(OH)$), 1.79 (d, 3H, *J* = 1.8 Hz, $(CH_3)C=CH$), 1.74 (s, 3H, $OC=C(CH_3)$), 1.25 (s, 3H, $C(CH_3)$), 0.93 (d, 3H, *J* = 6.6 Hz, $C(CH_3)CH(CH_3)$).

(4a*R*,5*R*)-2-Methoxy-3,4a,5,6,8-pentamethyl-4a,5-dihydro-4H-1-benzopyran-4-one (105) and (4a*R*,5*R*)-4-methoxy-3,4a,5,6,8-pentamethyl-4a,5-dihydro-2H-1-benzopyran-2-one (135)



To a stirred solution of pyrone **123** (0.030 g, 0.128 mmol) in Et_2O (2 mL) at rt was added CH_2N_2/Et_2O (excess) until the yellow colour persisted. The mixture was stirred at

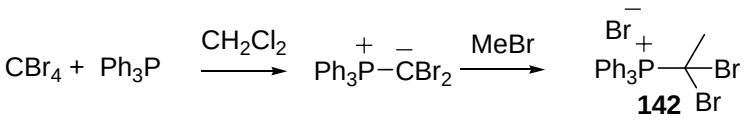
rt for a further 10 minutes and N_2 was bubbled through the solution to remove excess diazomethane. The solvent was removed *in vacuo* to yield a colourless oil which was purified by flash chromatography on silica (2% Et_2O/CH_2Cl_2, R_f = 0.41, 0.16) to afford firstly α-pyrone **135** (0.013 g, 0.0524 mmol, 41%) as a colourless oil and secondly γ-pyrone **105** (0.011 g, 0.0443 mmol, 34%) as a colourless oil. Both isomers crystallised upon standing.

α-pyrone **135**: **mp** 95-99°C (*n*-pentane); **$[\alpha]_D$** = –806 (*c* 0.75, $CHCl_3$); **IR** (film) 1724, 1681, 1647, 1449, 1345, 1305, 1296, 1247, 1226, 1181, 1104 cm^{-1}; **UV/Vis (MeOH)** λ_{max} 241 (ε 1457) nm; **^{1}H NMR** δ 5.40-5.36 (m, 1H, $(CH_3)C=CH$), 3.93 (s, 3H, OCH_3), 2.17 (q, 1H, *J* = 6.9 Hz, $C(CH_3)CH(CH_3)$), 1.96 (s, 3H, $(CH_3)C=C(OCH_3)$), 1.76 (d, 3H, *J* = 1.5 Hz, $(CH_3)C=CH$), 1.72 (s, 3H, $OC=C(CH_3)$), 1.26 (s, 3H, $C(CH_3)$), 0.86 (d, 3H, *J* = 6.9 Hz, $C(CH_3)CH(CH_3)$); **^{13}C NMR** δ 172.2, 165.8, 142.4, 135.6, 121.0, 110.6, 105.4, 61.8, 44.0, 42.7, 21.6, 21.4, 13.5, 12.6, 11.6; **HRESIMS** calculated for $C_{15}H_{20}O_3Na^+$: 271.1310; found: 271.1309; **EIMS** *m/z* (%): 248 (M^+, 79), 233 (100), 218 (8), 205 (54), 189 (10), 173 (27), 159 (17), 145 (28), 129 (15), 119 (22), 105 (23), 97 (10), 91 (54), 79 (32), 65 (28), 53 (31), 41 (50).

γ-pyrone **105**: **mp** 106-111°C (*n*-pentane); **$[\alpha]_D$** = –780 (*c* 0.69, $CHCl_3$); **IR** (film) 1642, 1603, 1464, 1393, 1381, 1373, 1354, 1290, 1204, 1164 cm^{-1}; **UV/Vis** (MeOH) λ_{max} 245 (ε 6059) nm; **^{1}H NMR** δ 5.37-5.33 (m, 1H, $(CH_3)C=CH$), 3.96 (s, 3H, OCH_3), 2.38 (q, 1H, *J* = 6.8 Hz, $C(CH_3)CH(CH_3)$), 1.78 (d, 3H, *J* = 1.5 Hz, $(CH_3)C=CH$), 1.75 (s, 3H, $OC=C(CH_3)$), 1.65 (s, 3H, $(CH_3)C=C(OCH_3)$) 1.26 (s, 3H, $C(CH_3)$), 0.90 (d, 3H, *J* = 6.8 Hz, $C(CH_3)CH(CH_3)$); **^{13}C NMR** δ 193.8, 165.2, 144.7, 137.6, 119.8, 112.6, 89.3, 54.8, 46.9, 43.0, 22.8, 21.6, 13.4, 12.3, 6.4; **HRESIMS** calculated for $C_{15}H_{20}O_3Na^+$: 271.1310; found: 271.1308; **EIMS** *m/z* (%): 248 (M^+, 27), 233 (44), 215 (2), 201 (2), 187 (1), 177 (2), 161 (10), 145 (4), 134 (27), 119 (100), 105 (5), 91 (35), 83 (24), 77 (12), 65 (5), 53 (6), 41 (16).

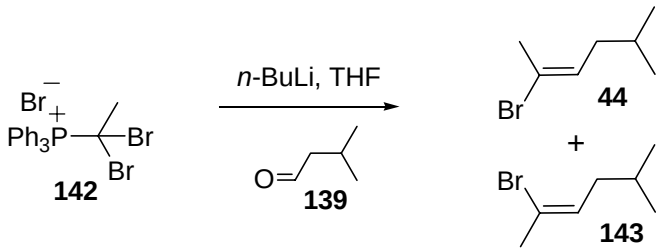
6.4 Experimental Procedures for Chapter Four

(1,1-Dibromoethyl)triphenylphosphonium bromide (142)



To a rapidly stirred solution of CBr_4 (20.0 g, 0.060 mol) in dry CH_2Cl_2 (60 mL) under N_2 at 0°C was added Ph_3P (31.63 g, 0.121 mol) in dry CH_2Cl_2 (60 mL) dropwise and the solution was stirred for a further 15 minutes, by which time the solution had changed from colourless to orange. Into this orange solution was slowly vapourised MeBr (excess) at 0°C with slow stirring and the solution decolourised within 1.5 hours. The reaction was quenched with $NaHCO_3$ (sat., 100 mL) with vigorous stirring, the phases were separated and the organic phase was dried ($MgSO_4$). The solvent was removed *in vacuo*, yielding a white solid which was triturated with benzene (100 mL), to remove soluble $Ph_3P{=}O$, and the remaining off-white solid was air dried. Recrystallisation of the salt from $CH_2Cl_2/(CH_3)_2CO$ (3:1) afforded the title compound **142** (18.32 g, 0.035 mol, 57%) as colourless crystals mp 197-199°C (lit.[94] mp 198-201°C). Spectral data were identical to those reported in the literature.[94]

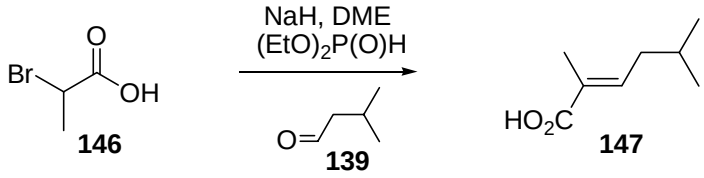
(*E*)-2-Bromo-5-methylhex-2-ene (44) and (*Z*)-2-bromo-5-methylhex-2-ene (143)



A suspension of phosphonium salt **142** (0.500 g, 0.945 mmol) in dry THF (3 mL) under N_2 was stirred for 20 minutes to pulverise the salt. The mixture was then cooled to -40°C internal temp. and *n*-BuLi (1.6M in hexanes, 0.591 mL, 0.945 mmol) was added dropwise with stirring, maintaining the internal temp. between -40°C and -45°C. After complete addition of the organolithium solution the mixture was stirred for a further 10 minutes at -40°C and to the resulting deep orange solution was added isovaleraldehyde (**139**) (0.152 mL, 1.42 mmol) in dry THF (1 mL) at -60°C, whereupon the colour was

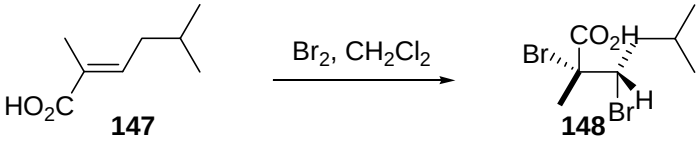
discharged to a cloudy yellow. After stirring for another 10 minutes at -60°C the solution was allowed to warm to rt, filtered and concentrated in vacuo to yield a yellow oil. The residue was triturated with hexane (50 mL), filtered and the filtrate was *carefully* concentrated *in vacuo* to give a colourless oil which was purified by flash chromatography on silica (hexanes, R_f = 0.67) to yield a volatile, colourless oil (0.045 g, 0.254 mmol, 27%) as a 5.7:1 mixture of *Z:E* isomers **143** and **44**. Spectral data of the 2 isomers was identical to those stated below.

(*E*)-2,5-Dimethylhex-2-enoic acid (147)



Acid **147** was prepared by the method of Villa and Warren[96] from 2-bromopropionic acid (**146**) (20.00 g, 0.131 mol), with the exception that the additions and quenching were carried out *slowly* at 0°C. The product was distilled under reduced pressure to yield the title compound **147** (15.20 g, 0.107 mol, 82%) as a colourless oil bp 114-118°C at 18 mmHg (lit.[96] bp 135-140°C at 30 mmHg), with identical spectral properties to those reported in the literature.[96]

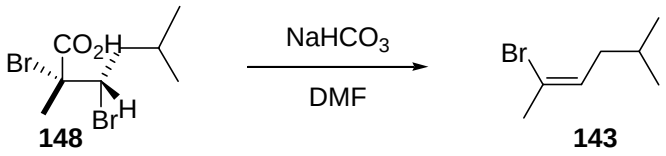
***erythro*-2,3-Dibromo-2,5-dimethylhexanoic acid (148)**



To a stirred solution of acid **147** (14.90 g, 0.105 mol) in dry CH_2Cl_2 (140 mL) under N_2 at –78°C was added bromine (8.05 mL, 0.157 mol) dropwise over 15 minutes and the mixture was stirred for 1 hour at –78°C. The reaction mixture was quenched with $Na_2S_2O_3$ (1M, 100 mL), warmed to rt and the phases were separated and the organic phase dried ($MgSO_4$). The dried organic extracts were concentrated *in vacuo* to yield the title compound **148** (23.51 g, 0.078 mol, 74%) as a pale yellow solid, a portion of which was recrystallised from hexanes to afford colourless crystals mp 106-110°C. The remainder of the product was used without further purification. **IR** (film) 3100 (br),

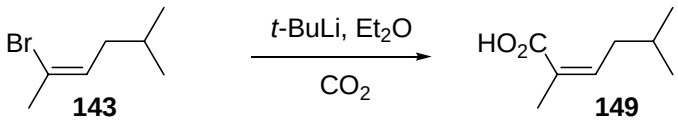
1713, 1469, 1409, 1384, 1294, 1258, 1201, 1046 cm^{-1}; **^{1}H NMR** δ 11.30 (bs, 1H, CO_2H), 4.68 (dd, 1H, *J* = 11.6, 1.4 Hz, C*H*Br), 2.06-1.91 (m, 2H, C*H*$(CH_3)_2$, CH_AH_BCH$(CH_3)_2$), 1.97 (s, 3H, CH_3CBr), 1.85-1.76 (m, 1H, CH_AH_BCH$(CH_3)_2$), 1.03 (d, 3H, *J* = 6.3 Hz, CH_2CH(CH_3)), 0.96 (d, 3H, *J* = 6.3 Hz, CH_2CH(CH_3)); **^{13}C NMR** δ 175.3, 61.7, 56.5, 41.8, 26.0, 23.6, 21.6, 20.3; **Anal. Calcd.** for $C_8H_{14}Br_2O_2$: C, 31.82; H, 4.67; found: C, 31.98; H, 4.58.

(*Z*)-2-Bromo-5-methylhex-2-ene (143)



To a stirred suspension of $NaHCO_3$ (6.52 g, 0.078 mol) in dry DMF (30 mL) under N_2 at 65°C was added dibromide **148** (23.45 g, 0.078 mol) in dry DMF (30 mL) slowly over 30 minutes. Heating was continued at 65°C for an additional 30 minutes (until CO_2 evolution ceased), the reaction was cooled to rt and water (20 mL) was added. The mixture was extracted with *n*-pentane (8 x 60 mL) and the combined organic extracts were washed with water (10 x 10 mL) and dried (Na_2SO_4). The dried organic extracts were *carefully* concentrated *in vacuo*, yielding a pale yellow oil. The product was distilled under reduced pressure to afford the title compound **143** (9.87 g, 0.056 mol, 72%) as a volatile, colourless oil bp 70-75°C at 20 mmHg. **IR** (film) 1664, 1429, 1368, 1261, 1228, 1144, 1056 cm^{-1}; **^{1}H NMR** δ 5.61 (tq, 1H, *J* = 6.9, 1.4 Hz, =C*H*), 2.29 (q, 3H, *J* = 1.4 Hz, CH_3CBr), 2.03 (tq, 2H, *J* = 6.9, 1.4 Hz, =CHCH_2), 1.69 (n, 1H, *J* = 6.7 Hz, C*H*$(CH_3)_2$), 0.91 (d, 6H, *J* = 6.7 Hz, CH(CH_3)$_2$); **^{13}C NMR** δ 127.9, 122.7, 40.5, 28.9, 28.0, 22.3 (2C); **HREIMS** calculated for $C_7H_{13}Br$: 176.0201; found: 176.0203; **EIMS** *m/z* (%): 176 (M, 13), 134 (24), 97 (35), 84 (100), 69 (25), 55 (66).

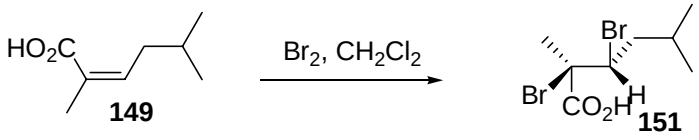
(*Z*)-2,5-Dimethylhex-2-enoic acid (149)



To a stirred solution of alkene **143** (9.65 g, 0.054 mol) in dry Et_2O (150 mL) under N_2 at –78°C was added *t*-BuLi (1.62 M in pentane, 67.3 mL, 0.109 mol) dropwise and the

mixture was stirred at -78°C for 40 minutes. The mixture was transferred *via* cannula to a flask containing dry ice (excess) and the reaction mixture was warmed slowly to *ca.* -20°C and quenched with HCl (1M, 70 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 x 75 mL) and the combined organic extracts were washed with brine (50 mL) and dried ($MgSO_4$), The dried organic extracts were filtered and concentrated *in vacuo* to yield a pale yellow oil. The product was purified by Kugelrohr distillation (70-80°C oven, 0.6 mmHg) to yield the title compound **149** (7.25 g, 0.051 mol, 94%) as a colourless oil bp 144-148°C at 17 mmHg. **IR** (film) 3100 (br), 1694, 1638, 1459, 1419, 1298, 1282, 1255 cm^{-1}; **^{1}H NMR** δ 9.56 (bs, 1H, CO_2H), 6.11 (tq, 1H, *J* = 7.3, 1.4 Hz, =C*H*), 2.43 (tq, 2H, *J* = 7.3, 1.4 Hz, =CHCH_2), 1.97 (q, 3H, *J* = 1.4 Hz, C(CH_3)CO_2H), 1.69 (n, 1H, *J* = 6.7 Hz, C*H*$(CH_3)_2$), 0.92 (d, 6H, *J* = 6.7 Hz, CH(CH_3)$_2$); **^{13}C NMR** δ 173.5, 145.8, 126.6, 38.6, 28.8, 22.4 (2C), 20.6; **HRESIMS** calculated for $C_8H_{14}O_2Na^+$ ($M+Na^+$): 165.0891; found: 165.0892; **EIMS** *m/z* (%): 142 (M^+, 19), 125 (8), 100 (54), 84 (100), 56 (30).

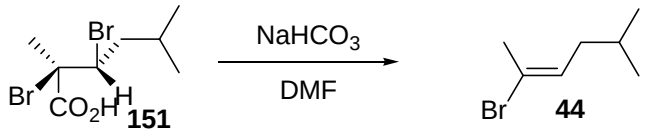
***threo*-2,3-Dibromo-2,5-dimethylhexanoic acid (151)**



149 **151**

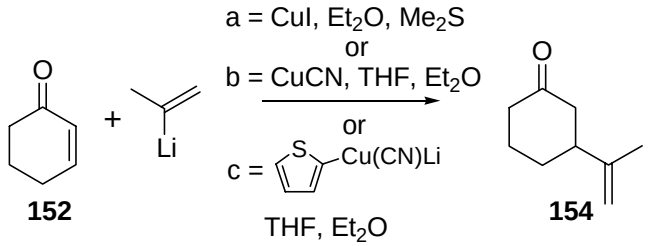
To a stirred solution of acid **149** (7.24 g, 0.051 mol) in dry CH_2Cl_2 (100 mL) under N_2 at –78°C was added bromine (3.13 mL, 0.061 mol) dropwise and the mixture was stirred for 1 hour at –78°C. The reaction mixture was diluted with CH_2Cl_2 (30 mL), quenched with $Na_2S_2O_3$ (1M, 100 mL), warmed to rt and the phases were separated and the organic phase dried ($MgSO_4$). The dried organic extracts were concentrated *in vacuo* to yield the title compound **151** (13.68 g, 0.045 mol, 89%) as a yellow solid, a portion of which was recrystallised from hexane to afford colourless crystals mp 68-72°C. The remainder of the product was used without further purification in the subsequent step. **IR** (film) 3100 (br), 1718, 1454, 1384, 1288, 1269, 1172, 1053 cm^{-1}; **^{1}H NMR** δ 10.39 (bs, 1H, CO_2H), 4.48 (dd, 1H, *J* = 11.2, 1.6 Hz, C*H*Br), 2.05 (s, 3H, CH_3CBr), 2.03-1.89 (m, 2H, C*H*$(CH_3)_2$, CH_AH$_B$CH$(CH_3)_2$), 1.57-1.47 (m, 1H, CH$_A$*H*$_B$CH$(CH_3)_2$), 0.98 (d, 3H, *J* = 6.6 Hz, CH_2CH(CH_3)), 0.93 (d, 3H, *J* = 6.6 Hz, CH_2CH(CH_3)); **^{13}C NMR** δ 174.7, 63.4, 59.8, 44.1, 26.7, 25.7, 23.5, 20.3; **Anal. Calcd.** for $C_8H_{14}Br_2O_2$: C, 31.82; H, 4.67; found: C, 32.08; H, 4.59.

(*E*)-2-Bromo-5-methylhex-2-ene (44)



To a stirred suspension of $NaHCO_3$ (4.15 g, 0.049 mol) in dry DMF (15 mL) under N_2 at 65°C was added dibromide **151** (13.57 g, 0.045 mol) in dry DMF (15 mL) slowly over 30 minutes. Heating was continued at 65°C for an additional 30 minutes (until CO_2 evolution ceased), the reaction was cooled to rt and water (10 mL) was added. The mixture was extracted with *n*-pentane (8 x 40 mL), the combined organic extracts were washed with water (10 x 10 mL) and dried (Na_2SO_4). The dried organic extracts were *carefully* concentrated *in vacuo*, yielding a pale yellow oil which was purified by vacuum distillation to afford the title compound **44** (5.82 g, 0.033 mol, 73%) as a volatile, colourless oil bp 72-76°C at 12 mmHg. **IR** (film) 1653, 1431, 1368, 1145, 1061 cm^{-1}; **^{1}H NMR** δ 5.86 (tq, 1H, *J* = 7.8, 1.4 Hz, =C*H*), 2.21-2.19 (m, 3H, CH_3CBr), 1.92-1.87 (m, 2H, =CHCH_2), 1.65 (n, 1H, *J* = 6.7 Hz, C*H*(CH_3)$_2$), 0.90 (d, 6H, *J* = 6.7 Hz, CH(CH_3)$_2$); **^{13}C NMR** δ 131.3, 119.5, 38.6, 28.4, 23.2, 22.2 (2C); **HREIMS** calculated for $C_7H_{13}Br$: 176.0201; found: 176.0207; **EIMS** *m/z* (%): 176 (M^+, 57), 135 (63), 97 (23), 81 (13), 56 (100), 53 (73).

3-Isopropenylcyclohexanone (154)



a) To a stirred solution of 2-bromopropene (0.252 g, 2.08 mmol) in dry THF (5 mL) under N_2 at –78°C was added *t*-BuLi (1.44 M in pentane, 2.89 mL, 4.16 mmol) dropwise and the yellow solution was stirred at -78°C for 1 hour. The resultant organolithium solution was transferred *via* cannula to a stirred suspension of CuI (0.198 g, 1.04 mmol) in dry Et_2O (2 mL) and dry Me_2S (2 mL) under N_2 at -78°C and the resulting deep orange solution was warmed to –20°C and stirred for 30 minutes. The solution was recooled to –78°C and 2-cyclohexenone (**152**) (50 μL, 0.52 mmol) was

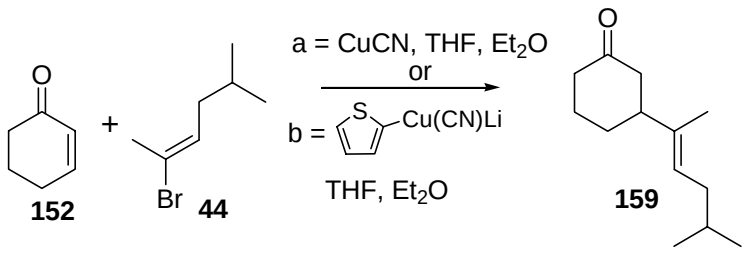
added neat dropwise. The orange/brown solution was stirred at -40°C for 30 minutes before being quenched with 90% NH_4Cl/10% NH_4OH (10 mL) and stirred at rt for 10 minutes. The mixture was filtered through celite and the layers were separated. The aqueous residue was extracted with Et_2O (3 x 20 mL) and the combined organic extracts were washed with brine (10 mL) and dried ($MgSO_4$). The dried organic extracts were filtered and concentrated *in vacuo* to yield a pale yellow oil which was purified by flash chromatography on silica (2.5% Et_2O/CH_2Cl_2, R_f = 0.34) to afford the title compound **154** (0.055 g, 0.398 mmol, 76%) as a colourless oil, with spectral data identical to the literature.[100]

b) To a stirred solution of 2-bromopropene (0.252 g, 2.08 mmol) in dry THF (5 mL) under N_2 at –78°C was added *t*-BuLi (1.50 M in pentane, 2.77 mL, 4.16 mmol) dropwise and the yellow solution was stirred at -78°C for 1 hour. The resultant organolithium solution was transferred *via* cannula to a stirred suspension of CuCN (0.093 g, 1.04 mmol) in dry Et_2O (5 mL) under N_2 at -78°C and the resulting pale yellow, homogeneous solution was stirred at –78°C for 30 minutes. To this solution was added 2-cyclohexenone (**152**) (50 μL, 0.52 mmol) neat dropwise. The bright yellow solution was allowed to warm slowly to rt (bright yellow discharged to colourless) before being quenched with 90% NH_4Cl/10% NH_4OH (10 mL) and stirred at rt for 10 minutes. The mixture was filtered through celite and the layers were separated. The aqueous residue was extracted with Et_2O (3 x 20 mL) and the combined organic extracts were washed with brine (10 mL) and dried ($MgSO_4$). The dried organic extracts were filtered and concentrated *in vacuo* to yield a colourless oil which was purified by flash chromatography on silica (2.5% Et_2O/CH_2Cl_2, R_f = 0.33) to afford product **154** (0.060 g, 0.43 mmol, 83%) as a colourless oil, with spectral data identical to those above.

c) The lower order cuprate was prepared according to the method of Lipshutz *et al.*[102] To a stirred solution of thiophene (0.087 g, 1.04 mmol) in dry THF (2 mL) under N_2 at -78°C was added n-BuLi (1.52 M in hexanes, 670 μL, 1.02 mmol) and the mixture was stirred at –78 °C for 15 minutes and –20°C for 30 minutes. The solution was transferred *via* cannula into a stirred suspension of CuCN (0.093g, 1.04 mmol) in dry THF (2 mL) under N_2 at -78°C (1 mL rinse). The reaction was warmed to -40°C to give a brown, homogeneous solution.

Separately, to a stirred solution of 2-bromopropene (0.126 g, 1.04 mmol) in dry THF (5 mL) under N_2 at –78°C was added *t*-BuLi (1.50 M in pentane, 1.39 mL, 2.08 mmol) dropwise and the yellow solution was stirred at -78°C for 30 minutes. The resultant organolithium solution was transferred *via* cannula to the lower order cuprate from above at -78°C and the homogeneous tan solution was warmed to -40°C and stirred for 30 minutes. The solution was recooled to -78°C and 2-cyclohexenone (**152**) (50 μL, 0.52 mmol) was added neat dropwise. The resulting yellow solution was stirred at -78°C for 10 minutes and allowed to warm slowly to 0°C before being quenched with 90% NH_4Cl/10% NH_4OH (10 mL) and stirred at rt for 10 minutes. The mixture was filtered through celite and the layers were separated. The aqueous residue was extracted with Et_2O (3 x 20 mL) and the combined organic extracts were washed with brine (10 mL) and dried ($MgSO_4$). The dried organic extracts were filtered and concentrated *in vacuo* to yield a yellow oil which was purified by flash chromatography on silica (2.5% Et_2O/CH_2Cl_2, R_f = 0.33) to afford product **154** (0.047 g, 0.34 mmol, 65%) as a colourless oil, with spectral data identical to those above.

3-[(*E*)-1,4-Dimethylpent-1-enyl]cyclohexanone (159)



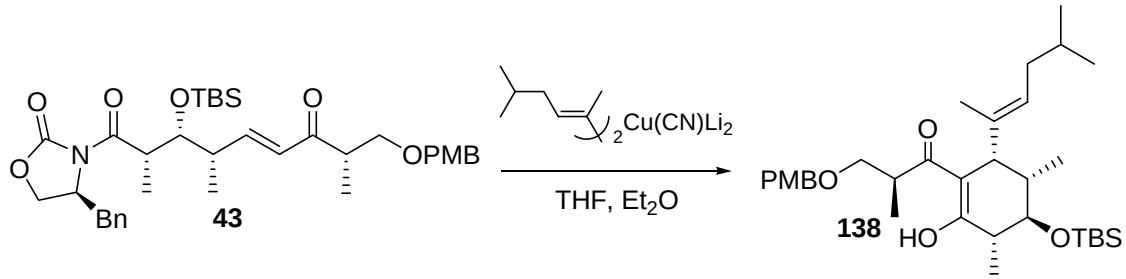
a) To a stirred solution of vinyl bromide **44** (0.276 g, 1.56 mmol) in dry THF (4 mL) under N_2 at –78°C was added *t*-BuLi (1.50 M in pentane, 2.08 mL, 3.12 mmol) dropwise and the yellow solution was stirred at -78°C for 1 hour. The resultant organolithium solution was transferred *via* cannula to a stirred suspension of CuCN (0.070 g, 0.78 mmol) in dry Et_2O (4 mL) under N_2 at -78°C and the resulting pale yellow, homogeneous solution was stirred at –78°C for 30 minutes. To this solution was added 2-cyclohexenone (**152**) (50 μL, 0.52 mmol) neat dropwise. The orange solution was allowed to warm slowly to rt (orange discharged to yellow then olive green) before being quenched with 90% NH_4Cl/10% NH_4OH (10 mL) and stirred at rt for 10 minutes. The mixture was filtered through celite and the layers were separated. The aqueous residue was extracted with Et_2O (3 x 20 mL) and the combined organic extracts were

washed with brine (10 mL) and dried ($MgSO_4$). The dried organic extracts were filtered and concentrated *in vacuo* to yield a colourless oil which was purified by flash chromatography on silica (CH_2Cl_2, R_f = 0.23) to afford the title compound **159** (0.088g, 0.45 mmol, 87%) as a colourless oil. **^{1}H NMR** δ 5.17 (t, 1H, *J* = 7.0 Hz, C=C*H*CH_2), 2.38-2.18 (m, 5H, CH_2C*H*$_2$CO, COC*H*$_2$CH, $COCH_2C$*H*), 2.07-1.97 (m, 1H, CH_2C*H*$_A$H$_B$CH), 1.84 (t, 2H, *J* = 7.0 Hz, C*H*$_2$CH(C*H*$_3$)$_2$), 1.66-1.51 (m, 7H, CH_2CH_A*H*$_B$CH, C*H*$(CH_3)_2$, C(C*H*$_3$)=CH, C*H*$_2CH_2$CO), 0.83 (d, 6H, *J* = 6.6 Hz, CH(C*H*$_3$)$_2$); **^{13}C NMR** δ 211.8, 137.3, 123.6, 47.7, 46.9, 41.2, 36.8, 30.1, 28.7, 25.2, 22.24, 22.22, 14.0; **EIMS** *m/z* (%): 194 (M^+, 20), 177 (27), 151 (18), 137 (30), 133 (12), 123 (24), 109 (24), 105 (16), 95 (42), 81 (76), 67 (30), 55 (44), 41 (100).

b) The lower order cuprate was prepared according to the method of Lipshutz *et al.*[102] To a stirred solution of thiophene (0.089 g, 1.06 mmol) in dry THF (2 mL) under N_2 at -78°C was added n-BuLi (1.52 M in hexanes, 670 μL, 1.04 mmol) and the mixture was stirred at –78 °C for 15 minutes and –20°C for 30 minutes. The solution was transferred *via* cannula into a stirred suspension of CuCN (0.093g, 1.04 mmol) in dry THF (2 mL) under N_2 at -78°C (1 mL rinse). The reaction was warmed to -40°C to give a brown, homogeneous solution.

Separately, to a stirred solution of vinyl bromide **44** (0.184 g, 1.04 mmol) in dry THF (5 mL) under N_2 at –78°C was added *t*-BuLi (1.50 M in pentane, 1.39 mL, 2.08 mmol) dropwise and the yellow solution was stirred at -78°C for 30 minutes. The resultant organolithium solution was transferred *via* cannula to the lower order cuprate from above at -78°C and the homogeneous tan solution was warmed to -40°C and stirred for 30 minutes. The solution was recooled to -78°C and 2-cyclohexenone (**152**) (50 μL, 0.52 mmol) was added neat dropwise. The resulting olive green solution was stirred at -78°C for 30 minutes and allowed to warm slowly to 0°C before being quenched with 90% NH_4Cl/10% NH_4OH (10 mL) and stirred at rt for 10 minutes. The mixture was filtered through celite and the layers were separated. The aqueous residue was extracted with Et_2O (3 x 20 mL) and the combined organic extracts were washed with brine (10 mL) and dried ($MgSO_4$). The dried organic extracts were filtered and concentrated *in vacuo* to yield an orange oil which was purified by flash chromatography on silica (CH_2Cl_2, R_f = 0.24) to afford compound **159** (0.095 g, 0.49 mmol, 94%) as a colourless oil, with identical spectral properties to those above.

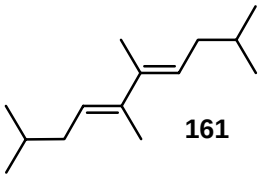
(2*S*,3*R*,4*S*,5*R*)-3-(*tert*-Butyldimethylsilyloxy)-5-[(*E*)-1,4-dimethylpent-1-enyl]-6-[(2*S*)-3-(4-methoxybenzyloxy)-2-methylpropionyl]-2,4-dimethylcyclohexanone (138)



To a stirred solution of vinyl bromide **44** (0.415 g, 2.34 mmol) in dry THF (10 mL) under Ar at –100°C was added *t*-BuLi (1.61 M in pentane, 2.91 mL, 4.69 mmol) dropwise and the yellow solution was stirred at -100°C for 15 minutes. The resultant organolithium solution was transferred *via* a pre-cooled cannula (pre-cooled by adding –78 °C Et_2O to the CuCN) to a stirred suspension of CuCN (0.105 g, 1.17 mmol) in dry Et_2O (10 mL) under Ar at -78°C and the resulting pale yellow, homogeneous solution was stirred at –50°C for 15 minutes. To this solution was added enone **43** (0.374 g, 0.586 mmol) in dry Et_2O (3 mL) *via* cannula (3 mL rinse) and the resulting bright yellow solution was stirred at –50°C for 90 minutes. The reaction was warmed to 0°C and the resulting green mixture was stirred at 0°C for 90 minutes before being quenched with 90% NH_4Cl/10% NH_4OH (20 mL) and stirred at rt for 10 minutes. The mixture was filtered through celite and the phases were separated. The aqueous residue was extracted with Et_2O (3 x 40 mL) and the combined organic extracts were washed with brine (20 mL) and dried ($MgSO_4$). The dried organic extracts were filtered and concentrated *in vacuo* to yield a pale yellow oil. Purification by flash chromatography on silica (CH_2Cl_2, R_f = 0.42) afforded the title compound **138** (0.196 g, 0.351 mmol, 60%) as a colourless oil, which existed exclusively as the *enol* tautomer, as determined by ^{1}H NMR. **$[\alpha]_D$** = +86.6 (*c* 0.48, $CHCl_3$); **IR** (film) 1701, 1612, 1587, 1514, 1462, 1367, 1303, 1249, 1208, 1173, 1081, 1037, 878, 835, 773 cm^{-1}; **^{1}H NMR** δ 16.76 (s, 1H, O*H*), 7.19 (d, 2H, *J* = 8.7 Hz, Ar*H*), 6.86 (d, 2H, *J* = 8.7 Hz, Ar*H*), 5.11 (t, 1H, *J* = 7.2 Hz, C=C*H*CH_2), 4.40 (s, 2H, ArCH_2O), 3.80 (s, 3H, ArOCH_3), 3.62 (app. t, 1H, *J* = 9.0 Hz, PMBOC$H_A$$H_B$), 3.41 (dd, 1H, *J* = 11.1, 8.1 Hz, C*H*OTBS), 3.37 (dd, 1H, *J* = 9.0, 5.7 Hz, PMBOC$H_A$$H_B$), 3.31 (d, 1H, *J* = 4.8 Hz, C*H*C(CH_3)=CH), 3.08-2.96 (m, 1H, CH_2C*H*(CH_3)CO), 2.36 (app. qn, 1H, *J* = 7.3 Hz, =C(OH)C*H*(CH_3)), 2.00-1.73 (m, 3H, C=CHCH_2, C*H*(CH_3)CHOTBS), 1.63 (s, 3H, C(CH_3)=CHCH_2), 1.61-1.56 (m, 1H,

C*H*(CH_3)$_2$), 1.32 (d, 3H, *J* = 6.9 Hz, =C(OH)CH(C*H*$_3$)), 0.97 (d, 3H, *J* = 6.9 Hz, CH(C*H*$_3$)CHOTBS), 0.92-0.87 (m, 18H, $CH_2CH(CH_3)CO$, CH(C*H*$_3$)$_2$, SiC(C*H*$_3$)$_3$), 0.073 (s, 3H, SiC*H*$_3$), 0.038 (s, 3H, SiC*H*$_3$); **^{13}C NMR** δ 204.0, 184.8, 159.1, 135.2, 130.4, 130.2, 128.9, 113.7, 110.4, 74.9, 73.1, 72.8, 55.2, 48.0, 45.9, 40.1, 39.4, 37.5, 28.8, 26.1, 22.6, 22.4, 18.8, 18.3, 17.3, 15.6, 14.2, -3.2, -3.6; **HRESIMS** calculated for $C_{33}H_{54}O_5SiNa^+$: 581.3638; found: 581.3622; **ESIMS/MS** *m/z* (%): 559 ($M+H^+$, 100), 541 (3), 427 (6), 121 (66).

(*E*,*E*)-2,5,6,9-Tetramethyldeca-4,6-diene (161)

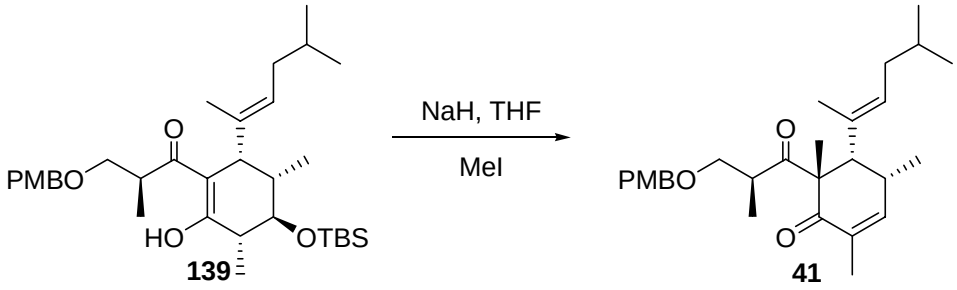


161

A small amount of dimer **161** was also obtained from the above reaction.

IR (film) 1466, 1383, 1375, 1367, 1168 cm^{-1}; **^{1}H NMR** δ 5.53 (t, 2H, *J* = 7.1 Hz, C=C*H*CH_2), 2.02 (t, 4H, *J* = 7.1 Hz, C=CHC*H*$_2$), 1.78 (s, 6H, C(C*H*$_3$)=$CHCH_2$), 1.66 (sept, 2H, *J* = 6.7 Hz, C*H*(CH_3)$_2$), 0.92 (d, 12H, *J* = 6.7 Hz, CH(C*H*$_3$)$_2$); **^{13}C NMR** δ 136.8, 124.7, 37.8, 29.1, 22.5 (2C), 14.2; **EIMS** *m/z* (%): 194 (M^+, 4), 137 (5), 123 (23), 109 (9), 95 (100), 91 (10), 81 (13), 67 (24), 55 (6), 41 (43).

(4*S*,5*R*,6*S*)-5-[(*E*)-1,4-Dimethylpent-1-enyl]-6-[(2*S*)-3-(4-methoxybenzyloxy)-2-methylpropionyl]-2,4,6-trimethylcyclohex-2-enone (41)

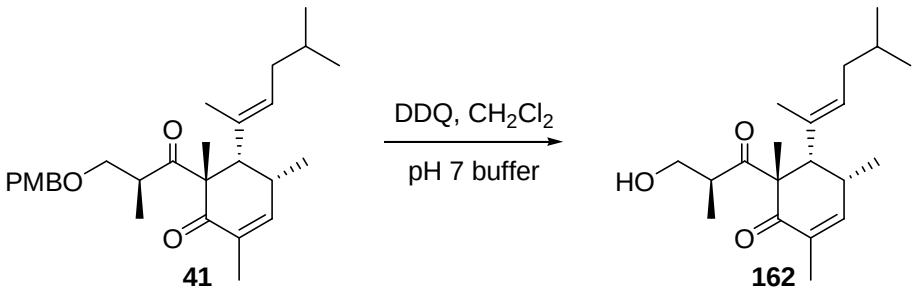


139 **41**

To a stirred suspension of NaH (60% dispersion in oil, 0.0214 g, 0.535 mmol) in dry THF (4 mL) was added diketone **138** (0.230 g, 0.412 mmol) in dry THF (3 mL) *via* cannula (3 mL rinse) and the mixture was stirred at rt for 10 minutes. To this yellow solution was added MeI (256 μL, 4.12 mmol) and the resulting pale yellow solution was

stirred at rt for 16 hours. The yellow/orange reaction mixture was quenched with $NaHCO_3$ (sat., 10 mL), the volatiles were removed *in vacuo* and the aqueous residue was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a yellow oil. Purification by flash chromatography on silica (5% Et_2O/CH_2Cl_2, R_f = 0.42) gave the title compound **41** (0.140 g, 0.318 mmol, 77%) as a colourless oil. **$[\alpha]_D$** = –113 (*c* 0.84, $CHCl_3$); **IR** (film) 1719, 1695, 1664, 1613, 1514, 1458, 1363, 1248, 1172, 1095, 1037 cm^{-1}; **^{1}H NMR** δ 7.20 (d, 2H, *J* = 8.7 Hz, Ar*H*), 6.83 (d, 2H, *J* = 8.7 Hz, Ar*H*), 6.32 (s, 1H, C*H*=C(CH_3)CO), 5.09 (t, 1H, *J* = 7.1 Hz, C=C*H*CH_2), 4.36 (s, 2H, ArCH_2O), 3.76 (s, 3H, ArOCH_3), 3.37 (dd, 1H, *J* = 9.0, 4.2 Hz, PMBOCH_AH_B), 3.27 (app. t, 1H, *J* = 9.0 Hz, PMBOCH_AH_B), 3.19-3.09 (m, 1H, CH_2C*H*(CH_3)CO), 3.01-2.90 (m, 1H, C*H*(CH_3)CH=C), 2.64 (d, 1H, *J* = 6.0 Hz, C*H*C(CH_3)=CH), 1.81-1.79 (m, 3H, CH=C(CH_3)CO), 1.75-1.60 (m, 2H, C=CHCH_2), 1.56-1.45 (m, 1H, C*H*(CH_3)$_2$), 1.43 (s, 3H, C(CH_3)), 1.37 (s, 3H, C(CH_3)=CHCH_2), 1.26 (d, 3H, *J* = 6.6 Hz, CH_2CH(CH_3)CO), 1.01 (d, 3H, *J* = 7.5 Hz, CH(CH_3)CH=C), 0.79 (app. t, 6H, *J* = 6.6 Hz, CH(CH_3)$_2$); **^{13}C NMR** δ 213.7, 199.2, 159.0, 147.3, 134.3, 133.2, 131.6, 130.5, 129.0, 113.6, 72.6, 71.6, 62.2, 59.5, 55.1, 44.4, 36.8, 30.1, 28.5, 23.6, 22.4, 22.2, 17.8, 17.6, 16.6, 15.9; **HRESIMS** calculated for $C_{28}H_{40}O_4Na^+$ ($M+Na^+$): 463.2824; found: 463.2824; **ESIMS/MS** *m/z* (%): 441 ($M+H^+$, 100), 423 (19), 303 (4), 121 (67).

(4*S*,5*R*,6*S*)-5-[(*E*)-1,4-Dimethylpent-1-enyl]-6-[(2*S*)-3-hydroxy-2-methylpropionyl]-2,4,6-trimethylcyclohex-2-enone (162)

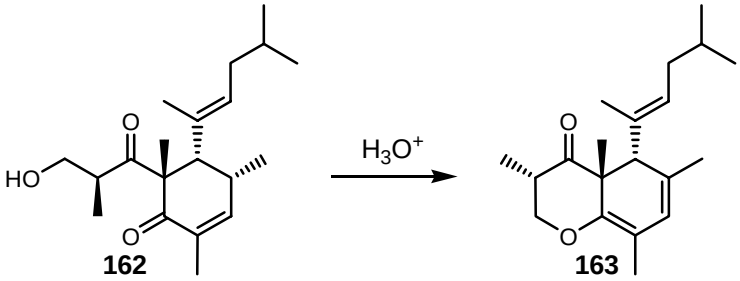


To a stirred solution of PMB ether **41** (0.137 g, 0.311 mmol) in CH_2Cl_2 (6 mL) and pH 7 buffer (1 mL) at 0°C was added DDQ (0.085 g, 0.373 mmol) and the solution was stirred at 0°C for 4 hours. The reaction was diluted with CH_2Cl_2 (15 mL) and quenched with $NaHCO_3$ (sat., 20 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were washed with

$NaHCO_3$ (sat., 10 mL) and brine (10 mL). The dried ($MgSO_4$) organic extracts were filtered and concentrated *in vacuo* to yield a colourless oil which was purified by flash chromatography on silica (20% Et_2O/CH_2Cl_2, R_f = 0.32) to yield the title compound **162** (0.093 g, 0.290 mmol, 93%) as a colourless oil which crystallised upon standing. A portion of the product was recrystallised from *n*-pentane mp 83-86°C. **$[\alpha]_D$** = –198 (*c* 0.21, CH_2Cl_2); **IR** (film) 3452 (br), 1713, 1663 (with shoulder), 1456, 1367, 1328, 1149, 1052, 1021, 991 cm^{-1}; **^{1}H NMR** (C_6D_6) δ 5.78-5.73 (m, 1H, C*H*=C(CH_3)CO), 5.08 (t, 1H, *J* = 6.9 Hz, C(CH_3)=C*H*CH_2), 3.70 (dd, 1H, *J* = 10.6, 5.2 Hz, CH_AH_BOH), 3.63 (dd, 1H, *J* = 10.6, 5.2 Hz, CH_AH_BOH), 3.23-3.12 (m, 1H, CH_2C*H*(CH_3)CO), 2.52 (dd, 1H, *J* = 6.0, 1.5 Hz, C*H*C(CH_3)=CH), 2.47-2.30 (m, 1H, C*H*(CH_3)CH=C), 2.23 (bs, 1H, O*H*), 1.79-1.73 (m, 5H, CH=C(CH_3)CO, C(CH_3)=CHCH_2), 1.53-1.42 (m, 1H, C*H*(CH_3)$_2$), 1.40 (d, 3H, *J* = 6.6 Hz, CH_2CH(CH_3)CO), 1.37 (s, 3H, C(CH_3)=CHCH_2), 1.30 (s, 3H, C(CH_3)), 0.83 (d, 3H, *J* = 6.9 Hz, CH_2CH(CH_3)), 0.80 (d, 3H, *J* = 6.6 Hz, CH_2CH(CH_3)), 0.69 (d, 3H, *J* = 7.5 Hz, CH(CH_3)CH=C); **^{13}C NMR** (C_6D_6) δ 215.9, 199.2, 147.1, 134.4, 134.2, 131.5, 65.1, 62.2, 59.7, 46.4, 37.1, 30.1, 28.9, 23.8, 22.6, 22.4, 18.1, 17.6, 16.1, 16.0; **ESIMS/MS** *m/z* (%): 343 ($M+Na^+$, 100); **Anal. Calcd.** for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06; found: C, 74.78; H, 9.92.

^{1}H NMR ($CDCl_3$) δ 6.38 (s, 1H, C*H*=C(CH_3)CO), 5.16 (t, 1H, *J* = 7.1 Hz, C(CH_3)=C*H*CH_2), 3.65-3.51 (m, 2H, CH_2OH), 3.14-3.06 (m, 1H, CH_2C*H*(CH_3)CO), 3.06-2.95 (m, 1H, C*H*(CH_3)CH=C), 2.74 (d, 1H, *J* = 4.8 Hz, C*H*C(CH_3)=CH), 2.00 (bs, 1H, OH), 1.87-1.78 (m, 5H, CH=C(CH_3)CO, C=CHCH_2), 1.60-1.49 (m, 1H, C*H*(CH_3)$_2$), 1.47 (s, 3H, C(CH_3)), 1.42 (s, 3H, C(CH_3)=CHCH_2), 1.30 (d, 3H, *J* = 6.9 Hz, CH_2CH(CH_3)CO), 1.03 (d, 3H, *J* = 7.5 Hz, CH(CH_3)CH=C), 0.85 (d, 3H, *J* = 6.9 Hz, CH_2CH(CH_3)), 0.82 (d, 3H, *J* = 6.6 Hz, CH_2CH(CH_3)).

(3*S*,4a*R*,5*R*)-5-[(*E*)-1,4-Dimethylpent-1-enyl]-3,4a,6,8-tetramethyl-2,3,4a,5-tetrahydro-4H-1-benzopyran-4-one (163)

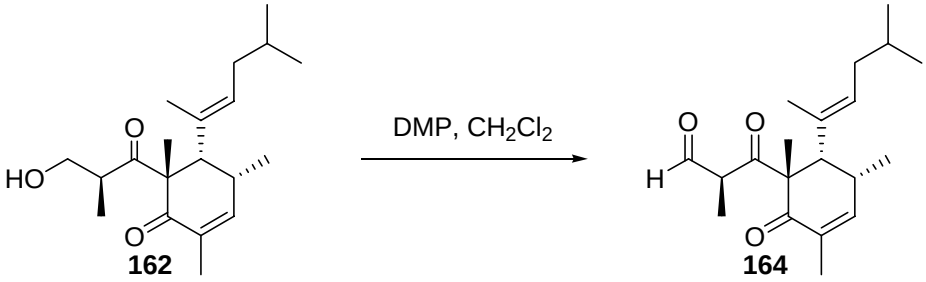


162 **163**

There was a tendency for alcohol **163** to cyclise to the bicyclic diene above in $CDCl_3$, depending on the acidity of the solvent.

$[\alpha]_D$ = –472 (*c* 0.37, $CHCl_3$); **IR** (film) 1719, 1676, 1618, 1451, 1379, 1255, 1223, 1168, 1134, 1050, 1025 cm^{-1}; **^{1}H NMR** δ 5.47 (q, 1H, J = 1.5 Hz, $C(CH_3)=CHC(CH_3)$), 5.42 (tq, 1H, *J* = 7.5, 1.5 Hz, $C=CHCH_2$), 4.24 (dd, 1H, *J* = 11.1, 6.2 Hz, CH_AH_BOC), 3.61 (app. t, 1H, *J* = 11.1 Hz, CH_AH_BOC), 2.83-2.71 (m, 1H, $CH_2CH(CH_3)CO$), 2.82 (s, 1H, $CHC(CH_3)=CH$), 1.81 (app. t, 2H, *J* = 6.9 Hz, $C(CH_3)=CHCH_2$), 1.71 (d, 3H, *J* = 1.5 Hz, $CHC(CH_3)=CH$), 1.67 (s, 3H, $OC=C(CH_3)$), 1.65-1.53 (m, 1H, $CH(CH_3)_2$), 1.49-1.47 (m, 3H, $C(CH_3)=CHC(CH_3)$), 1.36 (s, 3H, $C(CH_3)$), 0.98 (d, 3H, *J* = 7.2 Hz, $CH_2CH(CH_3)CO$), 0.85 (d, 3H, *J* = 6.6 Hz, $CH_2CH(CH_3)$), 0.84 (d, 3H, *J* = 6.6 Hz, $CH_2CH(CH_3)$); **^{13}C NMR** δ 210.6, 148.9, 132.8, 130.9, 128.2, 122.8, 109.2, 69.7, 58.3, 51.2, 42.0, 37.0, 28.9, 27.0, 22.42, 22.38, 21.7, 15.0, 13.5, 10.1; **EIMS** *m/z* (%): 302 (M^+, 29), 287 (8), 259 (10), 231 (5), 217 (26), 205 (4), 189 (13), 175 (48), 161 (24), 147 (14), 133 (14), 119 (20), 105 (14), 91 (25), 79 (16), 65 (10), 55 (16), 41 (100).

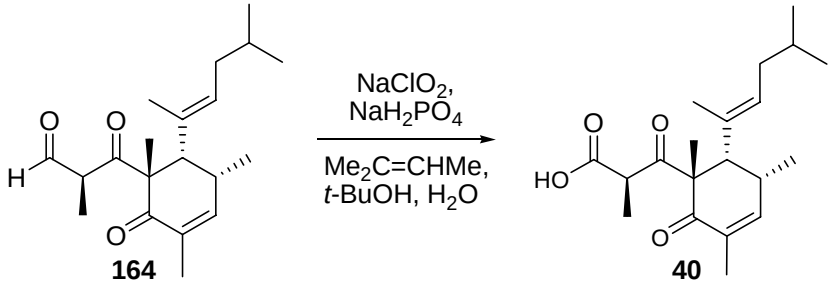
(2*R*)-3-[(1*S*,5*S*,6*R*)-6-[(*E*)-1,4-Dimethylpent-1-enyl]-1,3,5-trimethyl-2-oxocyclohex-3-enyl]-2-methyl-3-oxo-propionaldehyde (164)



To a stirred suspension of Dess-Martin periodinane[65] (0.198 g, 0.468 mmol) in dry CH_2Cl_2 (6 mL) under N_2 was added a solution of alcohol **162** (0.100 g, 0.312 mmol) in dry CH_2Cl_2 (2 mL) *via* cannula (2 mL rinse) and the reaction was stirred at rt for 1.5 hours. The reaction mixture was diluted with Et_2O (30 mL) and quenched with a solution of $NaHCO_3$ (sat., 10 mL) containing $Na_2S_2O_3.5H_2O$ (0.792 g, 3.19 mmol) and stirring was continued for 10 minutes. The phases were separated and the organic phase was washed with $NaHCO_3$ (sat., 10 mL) and brine (10 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the title compound **164** (0.099 g, 0.312 mmol, 100%) as a colourless solid, a portion of which was recrystallised from *n*-pentane to give colourless needles mp 98-103°C. **$[\alpha]_D$** = –20.6 (*c* 0.68, $CHCl_3$);

IR (film) 1726, 1695, 1659, 1453, 1363, 1317, 1153, 1132, 1068 cm^{-1}; **^{1}H NMR** δ 9.28 (d, 1H, *J* = 4.2 Hz, C*H*O), 6.43 (app. s, 1H, C*H*=C(CH_3)CO)), 5.16 (t, 1H, *J* = 6.9 Hz, C(CH_3)=C*H*CH_2), 3.57-3.46 (m, 1H, COC*H*(CH_3)CO), 3.08-2.97 (m, 1H, C*H*(CH_3)CH=C), 2.65 (dd, 1H, *J* = 5.7, 1.2 Hz, C*H*C(CH_3)=CH), 1.81 (dd, 3H, *J* = 2.7, 1.2 Hz, CH=C(C*H*$_3$)CO)), 1.75-1.61 (m, 2H, C(CH_3)=CHC*H*$_2$), 1.54-1.42 (m, 1H, C*H*(CH_3)$_2$), 1.42 (s, 3H, C(C*H*$_3$)), 1.37 (d, 3H, *J* = 6.9 Hz, COCH(C*H*$_3$)CO), 1.34 (s, 3H, C(C*H*$_3$)=CHCH$_2$), 0.99 (d, 3H, *J* = 7.5 Hz, CH(C*H*$_3$)CH=C), 0.82 (d, 3H, *J* = 6.6 Hz, CH_2CH(C*H*$_3$)), 0.77 (d, 3H, *J* = 6.6 Hz, CH_2CH(C*H*$_3$)); **^{13}C NMR** δ 211.0, 200.0, 199.7, 148.7, 134.0, 133.6, 132.1, 61.5, 61.0, 58.1, 36.8, 30.3, 28.4, 22.8, 22.5, 22.1, 17.1, 16.4, 15.8, (1 carbon unsighted); **ESIMS/MS** *m/z* (%): 341 (M+Na^+, 100); **Anal. Calcd.** for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50; found: C, 75.14; H, 9.63.

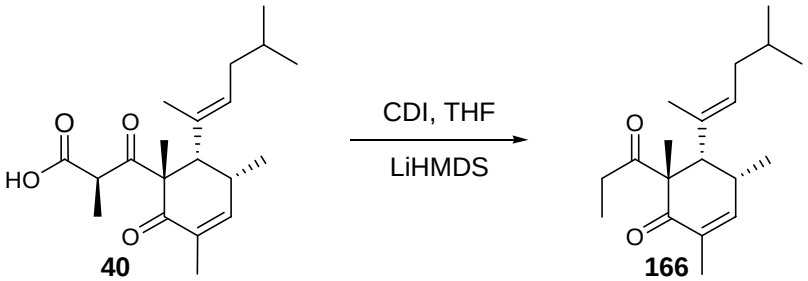
(2*R*)-3-[(1*S*,5*S*,6*R*)-6-[(*E*)-1,4-Dimethylpent-1-enyl]-1,3,5-trimethyl-2-oxocyclohex-3-enyl]-2-methyl-3-oxo-propionic acid (40)



To a stirred solution of crude ketoaldehyde **164** (0.095 g, 0.298 mmol) in *t*-BuOH (6.6 mL) and Me_2C=CHMe (6.6 mL) at rt was added a solution of $NaClO_2$ (0.135 g, 1.49 mmol) and $NaH_2PO_4.2H_2O$ (0.177 g, 1.13 mmol) in water (1.5 mL) dropwise. The resulting colourless solution was stirred at rt for 1.5 hours before being diluted with CH_2Cl_2/H_2O (2:1, 75 mL) and slightly acidified with TFA (10 drops, pH 3). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a colourless oil. Purification by flash chromatography on silica (40% Et_2O/CH_2Cl_2 + 0.5% AcOH, R_f = 0.21) yielded the title compound **40** (0.088 g, 0.263 mmol, 88%) as a colourless oil. **[α]$_D$** = –134 (*c* 1.00, $CHCl_3$); **IR** (film) 3270 (br), 1733, 1720, 1702, 1664, 1457, 1368, 1327, 1288, 1196, 1149, 1029, 990, 979 cm^{-1}; **^{1}H NMR** δ 8.64 (bs, 1H, CO_2*H*), 6.44 (s, 1H, C*H*=C(CH_3)CO), 5.13 (t, 1H, *J* = 6.9 Hz, C(CH_3)=C*H*CH_2), 3.85-3.73 (m, 1H, COC*H*(CH_3)CO), 3.06-2.97 (m, 1H, C*H*(CH_3)CH=C), 2.68 (d, 1H, *J*

= 6.0 Hz, C*H*C(CH$_3$)=CH), 1.83-1.81 (m, 3H, CH=C(C*H*$_3$)CO), 1.82-1.69 (m, 2H, C(CH$_3$)=CHC*H*$_2$), 1.55 (d, 3H, *J* = 6.9 Hz, COCH(C*H*$_3$)CO), 1.50-1.45 (m, 1H, C*H*(CH$_3$)$_2$), 1.46 (s, 3H, C(C*H*$_3$)), 1.42 (s, 3H, CHC(C*H*$_3$)=CH), 1.03 (d, 3H, *J* = 7.5 Hz, CH(C*H*$_3$)CH=C), 0.83 (d, 3H, *J* = 6.6 Hz, CH$_2$CH(C*H*$_3$)), 0.78 (d, 3H, *J* = 6.6 Hz, CH$_2$CH(C*H*$_3$)); **^{13}C NMR** δ 211.3, 199.1, 173.3, 148.5, 134.0, 133.5, 132.0, 62.5, 60.2, 50.3, 36.8, 30.3, 28.4, 22.9, 22.5, 22.1, 17.8, 17.5, 17.3, 15.8; **HRESIMS** calculated for $C_{19}H_{31}O_2^+$ (M-CO_2+H^+): 291.2324; found: 291.2321; **EIMS/MS** *m/z* (%): 313 ([M-CO_2+Na]$^+$, 100).

(4*S*,5*R*,6*S*)-5-[(*E*)-1,4-Dimethylpent-1-enyl]-2,4,6-trimethyl-6-propionylcyclohex-2-enone (165)

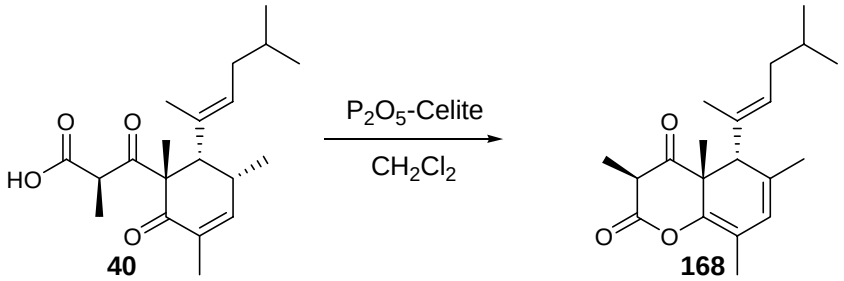


40 **166**

To a stirred solution of CDI (0.0032 g, 0.0194 mmol) in dry THF (0.5 mL) under N_2 at rt was added acid **40** (0.0065 g, 0.0194 mmol) in dry THF (0.5 mL) *via* cannula (0.5 mL rinse) (CO_2 evolved) and the reaction mixture was stirred at rt for 20 minutes before being cooled to –78°C. To this colourless solution was added LiHMDS (39 μL, 0.0389 mmol) dropwise and the resulting yellow solution was stirred at –78°C for 1 hour before being slowly warmed to rt (whereby the colour slowly discharged) and stirred for 21 hours. The reaction was diluted with Et_2O (5 mL) and quenched with NH_4Cl (sat, 5 mL). The phases were separated, the aqueous phase was extracted with Et_2O (3 x 10 mL) and the combined organic phases were washed with brine (10 mL) and dried ($MgSO_4$). The dried organic extracts were filtered and concentrated *in vacuo* to yield a colourless oil which was purified by flash chromatography on silica (5% Et_2O/CH_2Cl_2, R_f = 0.49) to yield the title compound **165** (0.0045 g, 0.0155 mmol, 80%) as a colourless oil. **IR** (film) 1722, 1704, 1664, 1458, 1375 cm^{-1}; **^{1}H NMR** δ 6.43-6.39 (m, 1H, C*H*=C(CH$_3$)CO), 5.17 (t, 1H, *J* = 7.2 Hz, C(CH$_3$)=C*H*CH$_2$), 3.06-2.95 (m, 1H, C*H*(CH$_3$)CH=C), 2.75 (dq, 1H, *J* = 18.1, 7.1 Hz, CH$_3$C*H*$_A$H$_B$CO), 2.63 (dd, 1H, *J* = 5.7, 1.2 Hz, C*H*C(CH$_3$)=CH), 2.17 (dq, 1H, *J* = 18.1, 7.1 Hz, CH$_3$CH$_A$*H*$_B$CO), 1.89-1.72 (m, 2H, C(CH$_3$)=CHC*H*$_2$), 1.82 (dd, 3H, *J* = 2.7, 1.2 Hz, CH=C(C*H*$_3$)CO), 1.60-1.47 (m,

1H, C*H*(CH_3)$_2$), 1.42 (app. s, 6H, C(C*H*$_3$), CHC(C*H*$_3$)=CH), 1.03 (d, 3H, *J* = 7.5 Hz, CH(C*H*$_3$)CH=C), 0.85 (d, 3H, *J* = 6.6 Hz, CH_2CH(C*H*$_3$)), 0.82 (d, 3H, *J* = 6.6 Hz, CH_2CH(C*H*$_3$)); **^{13}C NMR** δ 211.6, 199.6, 147.9, 134.4, 132.8, 132.2, 61.6, 60.4, 36.9, 34.5, 29.9, 28.6, 22.8, 22.6, 22.2, 17.5, 16.0, 7.8, (1 carbon unsighted); **EIMS** *m/z* (%): 290 (M^+, 8), 262 (18), 233 (1), 219 (1), 205 (69), 191 (5), 177 (9), 163 (6), 149 (39), 137 (39), 121 (25), 109 (23), 96 (23), 79 (22), 67 (41), 57 (47), 41 (100).

(3*S*,4a*R*,5*R*)-5-[(*E*)-1,4-Dimethylpent-1-enyl]-3,4a,6,8-tetramethyl-3,4,4a,5-tetrahydro-2H-1-benzopyran-2,4-dione (168)



40 **168**

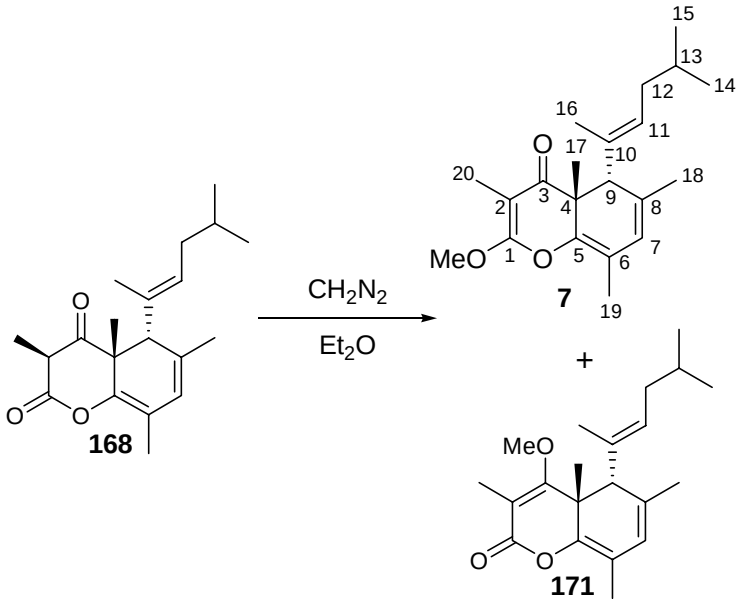
A mixture of oven-dried celite (0.150 g) and P_2O_5 (0.072 g, 0.508 mmol) was stirred rapidly under N_2 for 5 minutes. To this mixture was added acid **40** (0.034 g, 0.102 mmol) in dry CH_2Cl_2 (2 mL) *via* cannula (2 mL rinse) and the slurry was stirred at rt for 1 hour before being diluted with CH_2Cl_2 (10 mL) and filtered. The remaining solids were washed with CH_2Cl_2 and the filtrate was concentrated *in vacuo* to yield a pale yellow oil, which was purified by flash chromatography on silica (CH_2Cl_2, R_f = 0.50) to yield the title compound **168** (0.018 g, 0.0569 mmol, 56%) as a colourless oil, predominantly as the *keto* tautomer, as determined by ^{1}H NMR. **IR** (film) 3284 (br), 1783, 1732, 1672, 1640, 1451, 1384, 1364, 1322, 1260, 1201, 1165, 1150, 1106, 1031, 800 cm^{-1}; **HRESIMS** calculated for $C_{20}H_{29}O_3^+$ ($M+H^+$): 317.2117; found: 317.2113; **EIMS** *m/z* (%): 316 (M^+, 29), 301 (7), 273 (6), 260 (6), 245 (7), 232 (6), 217 (23), 203 (10), 189 (22), 175 (33), 168 (25), 161 (22), 147 (15), 133 (23), 119 (24), 105 (24), 91 (39), 83 (20), 65 (11), 55 (32), 41 (100).

Keto: **^{1}H NMR** δ 5.68-5.65 (m, 1H, C(CH_3)=C*H*C(CH_3)), 5.34 (t, 1H, *J* = 7.5 Hz, C(CH_3)=C*H*CH_2), 3.38 (q, 1H, *J* = 6.6 Hz, COC*H*(CH_3)CO), 2.75 (s, 1H, C*H*C(CH_3)=CH), 1.84-1.77 (m, 2H, C(CH_3)=CHC*H*$_2$), 1.82 (app. s, 3H, C(CH_3)=CHC(C*H*$_3$)), 1.71 (d, 3H, *J* = 1.5 Hz, C(C*H*$_3$)=CHC(CH_3)), 1.61-1.50 (m, 1H, C*H*(CH_3)$_2$), 1.53-1.51 (m, 3H, CHC(C*H*$_3$)=CH), 1.28 (s, 3H, C(C*H*$_3$)), 1.25 (d, 3H, *J* =

6.6 Hz, COCH(CH_3)CO), 0.84 (d, 3H, *J* = 6.6 Hz, $CH_2CH(CH_3)$), 0.83 (d, 3H, *J* = 6.6 Hz, $CH_2CH(CH_3)$); **^{13}C NMR** δ 204.0, 167.4, 142.4, 133.8, 131.9, 130.0, 122.8, 116.0, 59.9, 53.3, 51.4, 37.2, 28.7, 22.4 (2C), 22.2, 21.6, 15.8, 14.0, 7.4.

Enol: **^{1}H NMR** δ 5.60-5.57 (m, 1H, $C(CH_3)=CHC(CH_3)$), 5.43 (t, 1H, *J* = 7.0 Hz, $C(CH_3)=CHCH_2$), 3.65 (bs, 1H, O*H*), 2.73 (s, 1H, $CHC(CH_3)=CH$), 1.90-1.83 (m, 2H, $C(CH_3)=CHCH_2$), 1.80 (app. s, 3H, $C(CH_3)=CHC(CH_3)$), 1.75 (s, 3H, $C(CH_3)=C(OH)$), 1.72 (d, 3H, *J* = 1.5 Hz, $C(CH_3)=CHC(CH_3)$), 1.65-1.56 (m, 1H, $CH(CH_3)_2$), 1.52-1.50 (m, 3H, $CHC(CH_3)=CH$), 1.41 (s, 3H, $C(CH_3)$), 0.87 (d, 3H, *J* = 6.6 Hz, $CH_2CH(CH_3)$), 0.86 (d, 3H, *J* = 6.6 Hz, $CH_2CH(CH_3)$).

(4a*R*,5*R*)-5-[(*E*)-1,4-Dimethylpent-1-enyl]-2-methoxy-3,4a,6,8-tetramethyl-4a,5-dihydro-4H-1-benzopyran-4-one (7) and (4a*R*,5*R*)-5-[(*E*)-1,4-dimethylpent-1-enyl]-4-methoxy-3,4a,6,8-tetramethyl-4a,5-dihydro-2H-1-benzopyran-2-one (171)

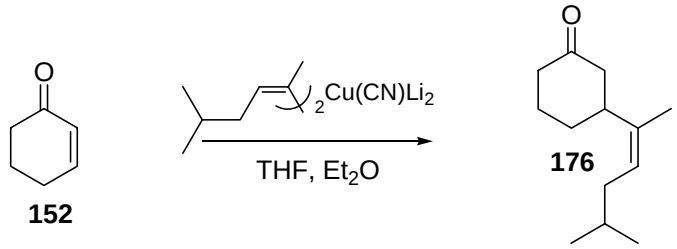


To a stirred solution of pyrone **168** (0.021 g, 0.0664 mmol) in Et_2O (2 mL) at rt was added CH_2N_2/Et_2O (excess) until the yellow colour persisted. The mixture was stirred at rt for a further 1 hour and N_2 was bubbled through the solution to remove excess diazomethane. The solvent was removed *in vacuo* to yield a pale yellow oil which was purified by flash chromatography on silica (10% hexanes/CH_2Cl_2, R_f = 0.40, 0.23) to afford firstly α-pyrone **171** (0.010 g, 0.0303 mmol, 45%) as a colourless oil, followed by γ-pyrone **7** (0.008 g, 0.0242 mmol, 36%) as a colourless oil.

α-pyrone **171**: **$[\alpha]_D$** = –716 (*c* 0.65, $CHCl_3$); **IR** (film) 1725, 1682, 1641, 1448, 1340, 1296, 1236, 1217, 1178, 1098 cm^{-1}; **UV/Vis** (MeOH) λ_{max} 242 (ε 10,390) nm; **^{1}H NMR** δ 5.54-5.52 (m, 1H, $C(CH_3)$=C*H*$C(CH_3)$), 5.33 (t, 1H, *J* = 7.2 Hz, $C(CH_3)$=C*H*CH_2), 3.87 (s, 3H, OCH_3), 2.72 (s, 1H, C*H*$C(CH_3)$=CH), 1.92 (s, 3H, $C(CH_3)$=$C(OCH_3)$), 1.83 (t, 2H, *J* = 7.2 Hz, $C(CH_3)$=CHCH_2), 1.73 (s, 3H, $C(CH_3)$=CHC(CH_3)), 1.71 (d, 3H, *J* = 1.5 Hz, $C(CH_3)$=CHC(CH_3)), 1.58 (sept, 1H, *J* = 6.6 Hz, C*H*$(CH_3)_2$), 1.45 (s, 3H, $C(CH_3)$=$CHCH_2$), 1.34 (s, 3H, $C(CH_3)$), 0.86 (d, 3H, *J* = 6.6 Hz, $CH_2CH(CH_3)$), 0.85 (d, 3H, *J* = 6.6 Hz, $CH_2CH(CH_3)$); **^{13}C NMR** δ 172.8 (C-3), 165.5 (C-1), 143.4 (C-5), 132.5 (C-10), 131.2 (C-8), 129.0 (C-11), 122.8 (C-7), 110.4 (C-6), 103.6 (C-2), 61.6 (OMe), 59.2 (C-9), 43.2 (C-4), 36.8 (C-12), 28.9 (C-13), 24.0 (C-17), 22.3 (C-14), 22.2 (C-15), 21.4 (C-18), 13.5 (C-19), 12.7 (C-16), 11.7 (C-20); **HRESIMS** calculated for $C_{21}H_{31}O_3^+$ ($M+H^+$): 331.2273; found: 331.2266; **EIMS** *m/z* (%): 330 (M^+, 3), 315 (5), 287 (2), 255 (2), 219 (8), 209 (2), 195 (3), 182 (100), 167 (6), 145 (15), 133 (16), 115 (10), 107 (25), 91 (28), 79 (22), 65 (15), 55 (18), 41 (94).

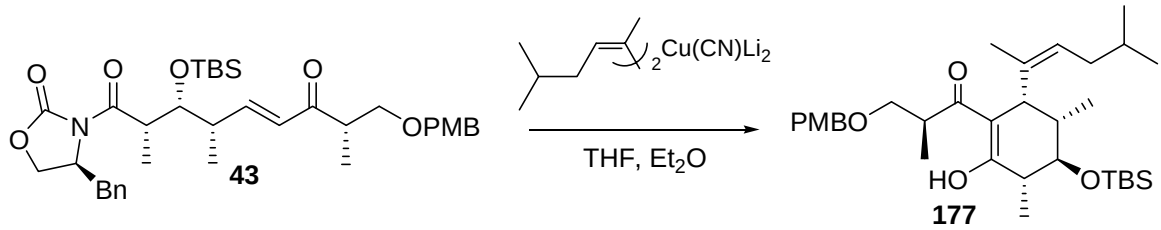
γ-pyrone **7**: **$[\alpha]_D$** = –542 (*c* 0.26, $CHCl_3$); **IR** (film) 1610 (with shoulder), 1462, 1386, 1367, 1352, 1289, 1202, 1160 cm^{-1}; **UV/Vis** (MeOH) λ_{max} 262 (ε 9,020) nm; **^{1}H NMR** δ 5.49-5.46 (m, 1H, $C(CH_3)$=C*H*C(CH*3*)), 5.39 (t, 1H, *J* = 7.2 Hz, $C(CH_3)$=C*H*CH_2), 3.94 (s, 3H, OCH_3), 2.91 (s, 1H, C*H*$C(CH_3)$=CH), 1.80 (t, 2H, *J* = 7.2 Hz, $C(CH_3)$=CHCH_2), 1.76-1.73 (m, 6H, $C(CH_3)$=CHC(CH_3), $C(CH_3)$=CHC(CH_3)), 1.61-1.52 (m, 1H, C*H*$(CH_3)_2$), 1.60 (s, 3H, $C(CH_3)$=$C(OCH_3)$), 1.47 (s, 3H, $C(CH_3)$=$CHCH_2$), 1.35 (s, 3H, $C(CH_3)$), 0.82 (d, 3H, *J* = 6.6 Hz, $CH_2CH(CH_3)$), 0.81 (d, 3H, *J* = 6.6 Hz, $CH_2CH(CH_3)$); **^{13}C NMR** δ 192.8 (C-3), 164.2 (C-1), 145.8 (C-5), 133.6 (C-8), 132.5 (C-10), 128.0 (C-11), 121.5 (C-7), 112.1 (C-6), 89.0 (C-2), 58.8 (C-9), 54.7 (OMe), 46.2 (C-4), 36.9 (C-12), 28.9 (C-13), 25.4 (C-17), 22.3 (C-14), 22.2 (C-15), 21.7 (C-18), 14.3 (C-19), 13.4 (C-16), 6.4 (C-20); **HRESIMS** calculated for $C_{21}H_{31}O_3^+$ ($M+H^+$): 331.2273; found: 331.2266; **EIMS** *m/z* (%): 330 (M^+, 2), 315 (15), 273 (20), 255 (5), 243 (10), 233 (7), 219 (18), 199 (6), 185 (4), 173 (38), 159 (15), 145 (20), 128 (16), 115 (19), 105 (14), 91 (32), 83 (28), 77 (24), 69 (15), 59 (24), 41 (100).

3-[(*Z*)-1,4-Dimethylpent-1-enyl]cyclohexanone (178)



To a stirred solution of vinyl bromide **143** (0.368 g, 2.08 mmol) in dry THF (5 mL) under Ar at –100°C was added *t*-BuLi (1.61 M in pentane, 2.58 mL, 4.16 mmol) dropwise and the yellow solution was stirred at -100°C for 15 minutes. The resultant organolithium solution was transferred *via* a pre-cooled cannula (pre-cooled by adding –78°C Et_2O to the CuCN) to a stirred suspension of CuCN (0.093 g, 1.04 mmol) in dry Et_2O (5 mL) under N_2 at -78°C and the resulting pale yellow, homogeneous solution was stirred at –50°C for 15 minutes. To this solution was added 2-cyclohexenone (**152**) (50 μL, 0.52 mmol) neat dropwise. The yellow solution was stirred at –50°C for 15 minutes before being allowed to warm slowly to rt (yellow discharged to pink then deep red) before being quenched with 90% NH_4Cl/10% NH_4OH (10 mL) and stirred at rt for 10 minutes. The mixture was filtered through celite and the layers were separated. The aqueous residue was extracted with Et_2O (3 x 20 mL) and the combined organic extracts were washed with brine (10 mL) and dried ($MgSO_4$). The dried organic extracts were filtered and concentrated *in vacuo* to yield a pale yellow oil which was purified by flash chromatography on silica (CH_2Cl_2, R_f = 0.46) to afford the title compound **176** as a colourless oil (0.097 g, 0.499 mmol, 96%). **^{1}H NMR** δ 5.10 (t, 1H, *J* = 7.2 Hz, C=C*H*CH_2), 2.88-2.77 (m, 1H, $COCH_2CH$), 2.38-2.21 (m, 3H, CH_2CH_2CO, $COCH_AH_BCH$), 2.19-2.00 (m, 2H, $COCH_AH_BCH$, $CH_2CH_AH_BCH$), 1.80 (t, 2H, *J* = 7.2 Hz, $CH_2CH(CH_3)_2$), 1.71-1.59 (m, 6H, $CH_2CH_AH_BCH$, $C(CH_3)$=CH, CH_2CH_2CO), 1.50 (sept, 1H, J = 6.6 Hz, $CH(CH_3)_2$), 0.82 (d, 6H, *J* = 6.6 Hz, $CH(CH_3)_2$); **^{13}C NMR** δ 211.6, 136.3, 125.3, 45.9, 41.1, 40.0, 36.2, 29.4, 28.7, 25.7, 22.26, 22.22, 18.7; **EIMS** *m/z* (%): 194 (M^+, 12), 177 (11), 151 (19), 137 (21), 133 (11), 123 (10), 109 (18), 105 (12), 93 (40), 81 (45), 67 (33), 55 (45), 41 (100).

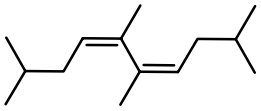
(2*S*,3*R*,4*S*,5*R*)-3-(*tert*-Butyldimethylsilyloxy)-5-[(*Z*)-1,4-dimethylpent-1-enyl]-6-[(2*S*)-3-(4-methoxybenzyloxy)-2-methylpropionyl]-2,4-dimethylcyclohexanone (177)



To a stirred solution of vinyl bromide **143** (0.694 g, 3.92 mmol) in dry THF (10 mL) under Ar at –100°C was added *t*-BuLi (1.61 M in pentane, 4.87 mL, 7.84 mmol) dropwise and the yellow solution was stirred at -100°C for 15 minutes. The resultant organolithium solution was transferred *via* a pre-cooled cannula (pre-cooled by adding –78 °C Et_2O to the CuCN) to a stirred suspension of CuCN (0.176 g, 1.96 mmol) in dry Et_2O (10 mL) under Ar at -78°C and the resulting pale yellow, homogeneous solution was stirred at –50°C for 15 minutes. To this solution was added enone **43** (0.250 g, 0.392 mmol) in dry Et_2O (3 mL) *via* cannula (3 mL rinse) and the resulting bright yellow solution was stirred at –50°C for 3 hours. The reaction was warmed to 0°C and the resulting pale yellow mixture was stirred at 0°C for 90 minutes before being quenched with 90% NH_4Cl/10% NH_4OH (15 mL) and stirred at rt for 10 minutes. The mixture was filtered through celite and the layers were separated. The aqueous residue was extracted with Et_2O (3 x 40 mL) and the combined organic extracts were washed with brine (20 mL) and dried ($MgSO_4$). The dried organic extracts were filtered and concentrated *in vacuo* to yield a pale yellow oil which was purified by flash chromatography on silica (CH_2Cl_2, R_f = 0.46) to afford the title compound **177** as a colourless oil (0.080 g, 0.143 mmol, 36%) which existed exclusively as the *enol* tautomer as determined by ^{1}H NMR. **$[\alpha]_D$** = +84.1 (*c* 0.61, $CHCl_3$); **IR** (film) 1700, 1612, 1588, 1514, 1464, 1249, 1081, 1039, 836, 774 cm^{-1}; **^{1}H NMR** δ 17.09 (s, 1H, O*H*), 7.20 (d, 2H, *J* = 9.0 Hz, Ar*H*), 6.86 (d, 2H, *J* = 9.0 Hz, Ar*H*), 5.43 (t, 1H, *J* = 6.9 Hz, C=C*H*CH_2), 4.44 (d, 1H, *J* = 11.7 Hz, ArC*H*$_A$H$_B$O), 4.36 (d, 1H, *J* = 11.7 Hz, ArCH$_A$*H*$_B$O), 3.84 (d, 1H, *J* = 6.0 Hz, C*H*C(CH_3)=CH), 3.76 (s, 3H, ArOC*H*$_3$), 3.57 (app. t, 1H, *J* = 9.0 Hz, PMBOC*H*$_A$H$_B$), 3.45 (dd, 1H, *J* = 11.2, 7.6 Hz, C*H*OTBS), 3.33 (dd, 1H, *J* = 9.0, 5.4 Hz, PMBOCH$_A$*H*$_B$), 3.06-2.95 (m, 1H, CH_2C*H*(CH_3)CO), 2.39 (app. qn, 1H, *J* = 7.6 Hz, =C(OH)C*H*(CH_3)), 2.09-1.97 (m, 2H, C=CHC*H*$_2$), 1.93-1.77

(m, 1H, C*H*(CH_3)CHOTBS), 1.69-1.56 (m, 1H, C*H*(CH_3)$_2$), 1.53 (s, 3H, C(CH_3)=CHCH$_2$), 1.32 (d, 3H, *J* = 7.2 Hz, =C(OH)CH(CH_3)), 0.96-0.88 (m, 21H, CH(CH_3)CHOTBS, CH$_2$CH(CH_3)CO, CH(CH_3)$_2$, SiC(CH_3)$_3$), 0.10 (s, 3H, SiCH_3), 0.072 (s, 3H, SiCH_3); **^{13}C NMR** δ 202.8, 187.1, 159.0, 133.5, 130.5, 129.7, 128.8, 113.6, 109.3, 75.8, 73.2, 72.8, 55.2, 46.1, 41.4, 39.7, 38.7, 37.9, 28.9, 26.1, 23.8, 22.8, 22.3, 18.3, 16.0, 15.6, 14.0, -3.2, -3.5; **HRESIMS** calculated for $C_{33}H_{55}O_5Si^+$ (M+H$^+$): 559.3812; found: 559.3812; **ESIMS/MS** *m/z* (%): 581 (M+Na$^+$, 100), 449 (38), 180 (19), 151 (8), 121 (39), 94 (5), 23 (16).

(*Z*,*Z*)-2,5,6,9-Tetramethyldeca-4,6-diene (178)

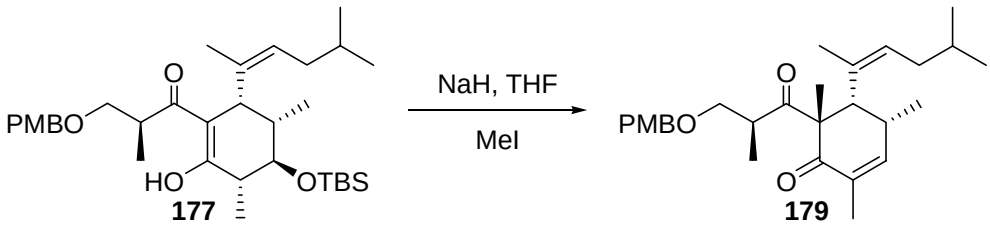


178

A small amount of dimer **178** was also obtained from the above reaction.

^{1}H NMR δ 5.16 (t, 2H, *J* = 6.3 Hz, C=C*H*CH$_2$), 1.76-1.70 (m, 10H, C=CHCH_2, C(CH_3)=CHCH$_2$), 1.61-1.48 (m, 2H, C*H*(CH_3)$_2$), 0.86 (d, 12H, *J* = 6.6 Hz, CH(CH_3)$_2$); **^{13}C NMR** δ 136.6, 124.5, 38.1, 29.7, 28.5, 22.65, 22.58; **EIMS** *m/z* (%): 194 (M$^+$, 10), 137 (8), 123 (24), 109 (10), 95 (100), 81 (14), 67 (29), 57 (8), 41 (48).

(4*S*,5*R*,6*S*)-5-[(*Z*)-1,4-Dimethylpent-1-enyl]-6-[(2*S*)-3-(4-methoxybenzyloxy)-2-methylpropionyl]-2,4,6-triamethylcyclohex-2-enone (179)



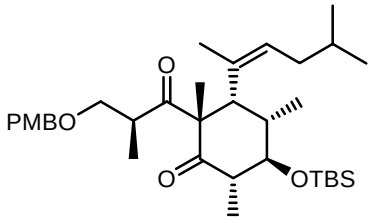
177 **179**

To a stirred suspension of NaH (60% dispersion in oil, 0.0080 g, 0.201 mmol) in dry THF (3 mL) was added diketone **177** (0.075 g, 0.134 mmol) in dry THF (2 mL) *via* cannula (2 mL rinse) and the mixture was stirred at rt for 10 minutes. To this yellow solution was added MeI (83 μL, 1.34 mmol) and the resulting pale yellow solution was stirred at rt for 17 hours. The yellow reaction mixture was quenched with $NaHCO_3$ (sat., 5 mL) and the volatiles were removed *in vacuo*. The aqueous residue was extracted with

CH_2Cl_2 (3 x 20 mL), the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a yellow oil. The product was purified by flash chromatography on silica (CH_2Cl_2, R_f = 0.18) to give the title compound **179** (0.041 g, 0.0930 mmol, 69%) as a colourless oil. **$[\alpha]_D$** = –33.3 (*c* 1.0, $CHCl_3$); **IR** (film) 1716, 1694, 1664, 1614, 1513, 1458, 1363, 1248, 1094, 1038, 1026 cm^{-1}; **^{1}H NMR** δ 7.21 (d, 2H, *J* = 8.4 Hz, Ar*H*), 6.85 (d, 2H, *J* = 8.4 Hz, Ar*H*), 6.36 (s, 1H, C*H*=C(CH_3)CO), 5.00 (t, 1H, *J* = 6.0 Hz, C=C*H*CH_2), 4.40 (d, 1H, *J* = 11.7 Hz, ArC*H*$_A$H$_B$O), 4.32 (d, 1H, *J* = 11.7 Hz, ArCH$_A$*H*$_B$O) 3.79 (s, 3H, ArOC*H*$_3$), 3.43 (dd, 1H, *J* = 9.0, 3.9 Hz, PMBOC*H*$_A$H$_B$), 3.25 (app. t, 1H, *J* = 9.3 Hz, PMBOCH$_A$*H*$_B$), 3.16 (dd, 1H, *J* = 5.7, 1.2 Hz, C*H*C(CH_3)=CH), 3.15-3.06 (m, 1H, CH_2C*H*(CH_3)CO), 3.01-2.90 (m, 1H, C*H*(CH_3)CH=C), 1.82-1.79 (m, 3H, CH=C(C*H*$_3$)CO), 1.77-1.69 (m, 1H, C=CHC*H*$_A$H$_B$), 1.68-1.60 (m, 1H, C=CHCH$_A$*H*$_B$), 1.54-1.41 (m, 1H, C*H*(CH_3)$_2$), 1.43 (s, 3H, C(C*H*$_3$)), 1.40 (d, 3H, *J* = 1.2 Hz, C(C*H*$_3$)=C*H*CH_2), 1.33 (d, 3H, *J* = 6.6 Hz, CH_2CH(C*H*$_3$)CO), 0.95 (d, 3H, *J* = 7.5 Hz, CH(C*H*$_3$)CH=C), 0.85 (d, 3H, *J* = 6.6 Hz, CH_2CH(C*H*$_3$)), 0.82 (d, 3H, *J* = 6.6 Hz, CH_2CH(C*H*$_3$)); ^{13}C NMR δ 214.1, 199.7, 159.1, 147.9, 134.3, 133.1, 131.9, 130.6, 129.2, 113.6, 72.5, 71.2, 61.4, 55.2, 49.9, 44.6, 36.7, 29.5, 28.5, 25.5, 24.0, 22.6, 22.5, 17.3, 16.9, 16.0; **HRESIMS** calculated for $C_{28}H_{40}O_4Na^+$ (M+Na^+): 463.2824; found: 463.2817; **ESIMS/MS** *m/z* (%): 463 (M+Na^+, 100), 435 (1), 367 (2), 341 (2), 325 (1), 256 (3), 213 (4), 200 (2), 177 (2), 159 (14), 145 (2), 131 (9), 121 (11), 108 (1), 23 (11).

If insufficient NaH (<1.5 eq) was used then the non-eliminated product below could also be isolated.

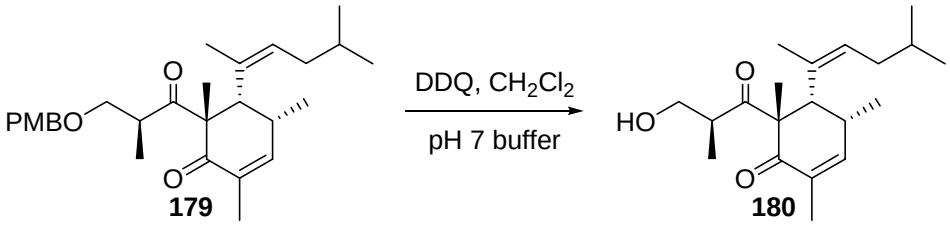
(2*S*,3*R*,4*S*,5*R*,6*S*)-5-(*tert*-Butyldimethylsilyloxy)-3-[(*Z*)-1,4-dimethylpent-1-enyl]-2-[(2*S*)-3-(4-methoxybenzyloxy)-2-methylpropionyl]-2,4,6-trimethylcyclohexanone



IR (film) 1708, 1690, 1614, 1514, 1463, 1384, 1363, 1303, 1249, 1173, 1081, 1037, 992, 836, 775 cm^{-1}; **^{1}H NMR** δ 7.23 (d, 2H, *J* = 8.7 Hz, Ar*H*), 6.86 (d, 2H, *J* = 8.7 Hz,

Ar*H*), 5.07 (t, 1H, *J* = 6.7 Hz, C=C*H*CH_2), 4.42 (d, 1H, *J* = 11.7 Hz, ArC*H*$_A$H$_B$O), 4.36 (d, 1H, *J* = 11.7 Hz, ArCH$_A$*H*$_B$O) 3.79 (s, 3H, ArOC*H*$_3$), 3.58 (app. t, 1H, *J* = 10.0 Hz, C*H*OTBS), 3.52 (dd, 1H, *J* = 7.5, 2.7 Hz, PMBOC*H*$_A$H$_B$), 3.36-3.26 (m, 2H, PMBOCH$_A$*H*$_B$, CH_2C*H*(CH_3)CO), 3.04 (d, 1H, *J* = 5.7, C*H*C(CH_3)=CH), 2.62 (dq, 1H, *J* = 9.3, 6.6 Hz, COC*H*(CH_3)CHOTBS), 2.40-2.28 (m, 1H, C*H*(CH_3)CHOTBS, 1.76 (t, 2H, *J* = 6.7 Hz, C=CHC*H*$_2$), 1.56 (s, 3H, C(C*H*$_3$)), 1.56-1.46 (m, 1H, C*H*(CH_3)$_2$), 1.37 (d, 3H, *J* = 1.5 Hz, C(C*H*$_3$)=CHCH$_2$), 1.23 (d, 3H, *J* = 6.0 Hz, CH_2CH(C*H*$_3$)CO), 1.17 (d, 3H, *J* = 6.6 Hz, COCH(C*H*$_3$)CHOTBS), 0.94 (d, 3H, *J* = 6.6 Hz, CH(C*H*$_3$)CHOTBS), 0.92 (s, 9H, SiC(C*H*$_3$)$_3$), 0.86 (d, 3H, *J* = 6.6 Hz, CH_2CH(C*H*$_3$)), 0.85 (d, 3H, *J* = 6.6 Hz, CH_2CH(C*H*$_3$)), 0.083 (s, 3H, SiC*H*$_3$), 0.073 (s, 3H, SiC*H*$_3$); **^{13}C NMR** δ 213.0, 212.1, 159.1, 132.8, 130.8, 130.7, 129.2, 113.6, 78.8, 72.5, 71.5, 63.4, 55.2, 50.0, 49.5, 44.5, 37.8, 37.3, 28.5, 26.1, 25.6, 23.8, 22.7, 22.6, 18.3, 17.1, 16.1, 12.6, -3.1, -3.2.

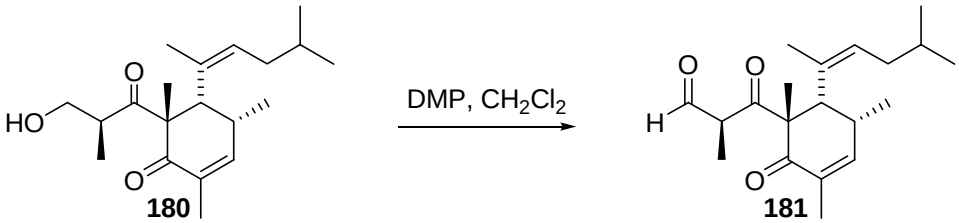
(4*S*,5*R*,6*S*)-5-[(*Z*)-1,4-Dimethylpent-1-enyl]-6-[(2*S*)-3-hydroxy-2-methylpropionyl]-2,4,6-trimethylcyclohex-2-enone (180)



To a stirred solution of PMB ether **179** (0.074 g, 0.170 mmol) in CH_2Cl_2 (8 mL) and pH 7 buffer (1 mL) at 0°C was added DDQ (0.050 g, 0.218 mmol) and the solution was stirred at 0°C for 3 hours. The reaction was diluted with CH_2Cl_2 (15 mL) and quenched with $NaHCO_3$ (sat., 15 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were washed with $NaHCO_3$ (sat., 10 mL) and brine (10 mL). The dried ($MgSO_4$) organic extracts were filtered and concentrated *in vacuo* to yield a colourless oil which was purified by flash chromatography on silica (10% Et_2O/CH_2Cl_2, R_f = 0.26) to yield the title compound **180** (0.044 g, 0.137 mmol, 81%) as a colourless oil. **$[\alpha]_D$** = –70.9 (*c* 0.85, CH_2Cl_2); **IR** (film) 3448 (br), 1713, 1691, 1665, 1458, 1385, 1374, 1162, 1148, 1021, 992 cm^{-1}; **^{1}H NMR** (C_6D_6) δ 5.78-5.73 (m, 1H, C*H*=C(CH_3)CO), 5.18 (t, 1H, *J* = 6.6 Hz, C(CH_3)=C*H*CH_2), 3.67 (m, 2H, C*H*$_2$OH), 3.23-3.13 (m, 2H, CH_2C*H*(CH_3)CO, C*H*C(CH_3)=CH), 2.49-2.36 (m, 1H, C*H*(CH_3)CH=C), 2.33 (bs, 1H, O*H*), 1.98-1.87 (m, 1H, C(CH_3)=CHC*H*$_A$H$_B$),

1.86-1.75 (m, 1H, C(CH_3)=CHC$H_A$$H_B$), 1.77-1.74 (m, 3H, CH=C(CH_3)CO), 1.61-1.46 (m, 1H, CH(CH_3)$_2$), 1.49 (d, 3H, J = 6.9 Hz, CH_2CH(CH_3)CO), 1.39-1.37 (m, 3H, C(CH_3)=CHCH_2), 1.31 (s, 3H, C(CH_3)), 0.92 (d, 3H, J = 6.6 Hz, CH_2CH(CH_3)), 0.86 (d, 3H, J = 6.6 Hz, CH_2CH(CH_3)), 0.66 (d, 3H, J = 7.8 Hz, CH(CH_3)CH=C); **^{13}C NMR** (C_6D_6) δ 217.0, 199.2, 147.4, 134.4, 133.1, 132.9, 64.9, 61.1, 50.2, 46.5, 37.3, 29.6, 28.8, 25.5, 24.3, 22.8, 22.7, 16.9, 16.4, 16.2; **HRESIMS** calculated for $C_{20}H_{32}O_3Na^+$ (M+Na^+): 343.2249; found: 343.2242; **ESIMS/MS** *m/z* (%): 321 (M+H^+, 6), 303 (80), 292 (31), 207 (100), 165 (90), 154 (35), 137 (35), 109 (5), 69 (9), 57 (4).

(2*R*)-3-[(1*S*,5*S*,6*R*)-6-[(*Z*)-1,4-Dimethylpent-1-enyl]-1,3,5-trimethyl-2-oxocyclohex-3-enyl]-2-methyl-3-oxo-propionaldehyde (181)

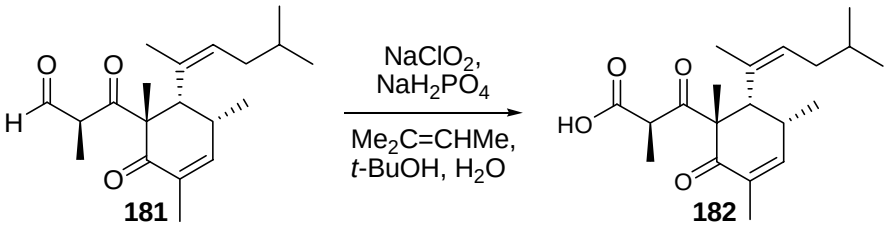


180 **181**

To a stirred suspension of Dess-Martin periodinane[65] (0.083 g, 0.196 mmol) in dry CH_2Cl_2 (1mL) under N_2 was added a solution of alcohol **180** (0.042 g, 0.131 mmol) in dry CH_2Cl_2 (2 mL) *via* cannula (2 mL rinse) and the reaction was stirred at rt for 1 hour. The reaction mixture was diluted with Et_2O (15 mL) and quenched with a solution of $NaHCO_3$ (sat., 5 mL) containing $Na_2S_2O_3.5H_2O$ (0.330 g, 1.33 mmol) and stirring was continued for 10 minutes. The phases were separated, and the organic phase was washed with $NaHCO_3$ (sat., 5 mL) and brine (5 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield the title compound **181** (0.041 g, 0.129 mmol, 98%) as a colourless oil. **IR** (film) 1731, 1695, 1662, 1458, 1377, 1366, 1161, 1149, 1036, 992 cm^{-1}; **^{1}H NMR** δ 9.34 (d, 1H, J = 4.5 Hz, CHO), 6.45 (app. s, 1H, CH=C(CH_3)CO)), 5.16-5.12 (m, 1H, C(CH_3)=CHCH_2), 3.58 (qd, 1H, J = 6.9, 4.5 Hz, COCH(CH_3)CO), 3.20 (dd, 1H, J = 6.0, 1.2 Hz, CHC(CH_3)=CH), 3.08-2.96 (m, 1H, CH(CH_3)CH=C), 1.86-1.75 (m, 4H, CH=C(CH_3)CO), C(CH_3)=CHCH_AH$_B$), 1.66-1.54 (m, 1H, C(CH_3)=CHCH$_A$$H_B$), 1.56-1.45 (m, 7H, C(C$H_3$), C(C$H_3$)=CHC$H_2$, C$H$($CH_3$)$_2$), 1.41 (d, 3H, J = 6.9 Hz, COCH(CH_3)CO), 0.99 (d, 3H, J = 7.5 Hz, CH(CH_3)CH=C), 0.87 (d, 3H, J = 6.6 Hz, CH_2CH(CH_3)), 0.83 (d, 3H, J = 6.6 Hz, CH_2CH(CH_3)); **^{13}C NMR** δ 210.4, 200.4, 200.0, 148.9, 134.7, 134.1, 131.2, 61.2, 58.0, 50.4, 36.8, 29.7, 28.6, 25.6, 22.9, 22.6, 22.5, 16.7, 16.5, 15.9; **HRESIMS** calculated for $C_{20}H_{30}O_3Na^+$

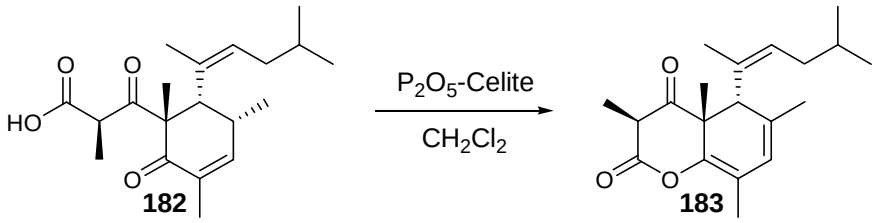
(M+Na$^+$): 341.2093; found: 341.2082; **ESIMS/MS** *m/z* (%): 319 (M+H$^+$, 100), 291)22), 223 (7), 195 (18), 181 (27), 153 (74), 69 (5), 57 (12).

(2*R*)-3-[(1*S*,5*S*,6*R*)-6-[(*Z*)-1,4-Dimethylpent-1-enyl]-1,3,5-trimethyl-2-oxocyclohex-3-enyl]-2-methyl-3-oxo-propionic acid (182)



To a stirred solution of crude ketoaldehyde **181** (0.040 g, 0.126 mmol) in *t*-BuOH (2.8 mL) and Me_2C=CHMe (2.8 mL) at rt was added a solution of $NaClO_2$ (0.057 g, 0.628 mmol) and $NaH_2PO_4.2H_2O$ (0.074 g, 0.477 mmol) in water (1 mL) dropwise. The resulting colourless solution was stirred at rt for 1 hour before being diluted with CH_2Cl_2/H_2O (2:1, 45 mL) and slightly acidified with TFA (4 drops, pH 3). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a colourless oil. Purification by flash chromatography on silica (40% Et_2O/CH_2Cl_2 + 0.5% AcOH, R_f = 0.31) yielded the title compound **182** (0.036 g, 0.108 mmol, 86%) as a colourless oil. **$[\alpha]_D$** = –17.9 (*c* 0.45, $CHCl_3$); **IR** (film) 3230 (br), 1734, 1717, 1701, 1664, 1457, 1385, 1378, 1367, 1327, 1288, 1220, 1194, 1150, 1026, 991 cm^{-1}; **^{1}H NMR** δ 8.91 (bs, 1H, CO_2H), 6.50-6.46 (m, 1H, C*H*=C(CH_3)CO), 5.31-5.25 (m, 1H, C(CH_3)=C*H*CH_2), 3.79 (q, 1H, *J* = 7.2 Hz, COC*H*(CH_3)CO), 3.22 (dd, 1H, *J* = 6.0, 1.5 Hz, C*H*C(CH_3)=CH), 3.09-2.98 (m, 1H, C*H*(CH_3)CH=C), 1.84 (dd, 3H, *J* = 2.7, 1.5 Hz, CH=C(C*H*$_3$)CO), 1.81-1.67 (m, 1H, C(CH_3)=CHC*H*$_A$H$_B$), 1.63 (d, 3H, *J* = 7.2 Hz, COCH(C*H*$_3$)CO), 1.62-1.50 (m, 5H, C(CH_3)=CHCH$_A$*H*$_B$, CHC(C*H*$_3$)=CH, C*H*(CH_3)$_2$), 1.49 (s, 3H, C(C*H*$_3$)), 1.01 (d, 3H, *J* = 7.5 Hz, CH(C*H*$_3$)CH=C), 0.88 (d, 3H, *J* = 6.6 Hz, CH_2CH(C*H*$_3$)), 0.82 (d, 3H, *J* = 6.6 Hz, CH_2CH(C*H*$_3$)); **^{13}C NMR** δ 212.6, 199.2, 172.6, 148.9, 134.7, 134.0, 130.8, 62.5, 50.6, 50.4, 37.0, 29.8, 28.5, 25.6, 22.9, 22.6, 22.5, 18.6, 16.8, 15.9; **HRESIMS** calculated for $C_{19}H_{31}O_2^+$ (M-CO_2+H$^+$): 291.2324; found: 291.2318; **EIMS/MS** *m/z* (%): 313 ([M-CO_2+Na]$^+$, 100).

(3*S*,4a*R*,5*R*)-5-[(*Z*)-1,4-Dimethylpent-1-enyl]-3,4a,6,8-tetramethyl-3,4,4a,5-tetrahydro-2H-1-benzopyran-2,4-dione (184)



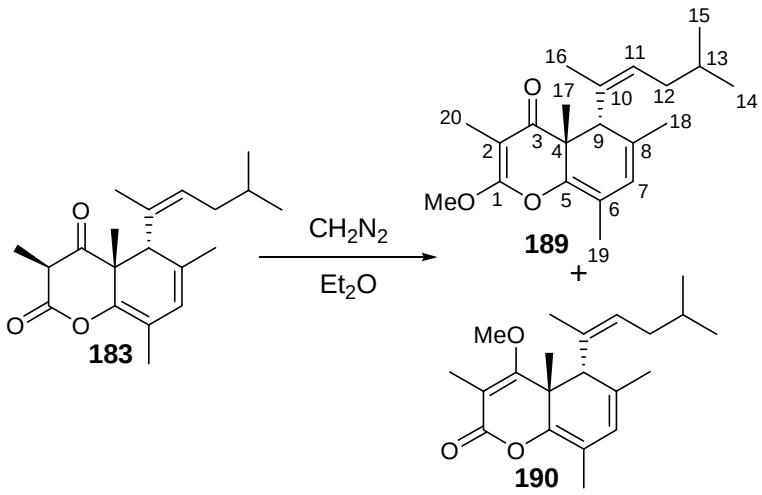
A mixture of oven-dried celite (0.180 g) and P_2O_5 (0.089 g, 0.628 mmol) was stirred rapidly under N_2 for 5 minutes. To this mixture was added ketoacid **182** (0.042 g, 0.126 mmol) in dry CH_2Cl_2 (2 mL) *via* cannula (2 mL rinse) and the slurry was stirred at rt for 2 hours before being diluted with CH_2Cl_2 (10 mL) and filtered. The remaining solids were washed with CH_2Cl_2 and the filtrate was concentrated *in vacuo* to yield a pale yellow oil, which was purified by flash chromatography on silica (CH_2Cl_2, R_f = 0.50) to yield the title compound **183** (0.023 g, 0.0727 mmol, 58%) as a colourless oil, predominantly as the *keto* tautomer as determined by ^{1}H NMR. **IR** (film) 3306 (br), 1783, 1732, 1676, 1636, 1619, 1450, 1382, 1366, 1324, 1220, 1203, 1190, 1150, 1103 cm^{-1}; **HRESIMS** calculated for $C_{20}H_{29}O_3^+$ ($M+H^+$): 317.2117; found: 317.2118; **EIMS** *m/z* (%): 316 (M^+, 60), 301 (14), 273 (9), 259 (6), 245 (8), 231 (11), 217 (37), 203 (17), 189 (36), 175 (78), 161 (46), 147 (22), 133 (36), 119 (38), 105 (46), 91 (49), 83 (36), 67 (10), 55 (33), 41 (100).

Keto: **^{1}H NMR** δ 5.72-5.68 (m, 1H, $C(CH_3)$=C*H*$C(CH_3)$), 5.31-5.24 (m, 1H, $C(CH_3)$=C*H*CH_2), 3.46 (q, 1H, *J* = 6.6 Hz, $C(CH_3)$=CHC(C*H*$_3$)), 3.29 (s, 1H, C*H*$C(CH_3)$=CH), 1.97-1.83 (m, 1H, $C(CH_3)$=CHC*H*$_A$H$_B$), 1.81 (app. s, 3H, CH=C(C*H*$_3$)CO), 1.73-1.66 (m, 7H, $C(CH_3)$=CHCH$_A$*H*$_B$, C(C*H*$_3$)=CHC(CH_3), CHC(C*H*$_3$)=CH), 1.64-1.48 (m, 1H, C*H*$(CH_3)_2$), 1.28 (s, 3H, C(C*H*$_3$)), 1.24 (d, 3H, *J* = 6.6 Hz, COCH(C*H*$_3$)CO), 0.91 (d, 3H, *J* = 6.6 Hz, CH_2CH(C*H*$_3$)), 0.87 (d, 3H, *J* = 6.6 Hz, CH_2CH(C*H*$_3$)); **^{13}C NMR** δ 202.8, 167.4, 142.6, 132.7, 132.3, 130.5, 123.7, 115.8, 52.3, 51.1, 50.5, 37.2, 28.6, 22.6, 22.3, 21.8, 21.5, 20.3, 14.0, 7.5.

Enol: **^{1}H NMR** δ 5.65 (bs, 1H, O*H*), 5.59-5.56 (m, 1H, $C(CH_3)$=C*H*$C(CH_3)$), 5.19-5.13 (m, 1H, $C(CH_3)$=C*H*CH_2), 3.28 (s, 1H, C*H*$C(CH_3)$=CH), 2.06-1.99 (m, 1H, $C(CH_3)$=CHC*H*$_A$H$_B$), 1.81 (app. s, 3H, $C(CH_3)$=CHC(C*H*$_3$)), 1.81-1.74 (m, 1H, $C(CH_3)$=CHCH$_A$*H*$_B$), 1.73 (s, 3H, C(C*H*$_3$)=C(OH)), 1.71 (d, 3H, *J* = 1.5 Hz,

C(C*H*$_3$)=CHC(CH$_3$)), 1.64-1.48 (m, 4H, C*H*(CH$_3$)$_2$, C(C*H*$_3$)=CHCH$_2$), 1.43 (s, 3H, C(C*H*$_3$)), 0.92 (d, 3H, *J* = 6.6 Hz, CH$_2$CH(C*H*$_3$)), 0.91 (d, 3H, *J* = 6.6 Hz, CH$_2$CH(C*H*$_3$)).

(4a*R*,5*R*)-5-[(*Z*)-1,4-Dimethylpent-1-enyl]-2-methoxy-3,4a,6,8-tetramethyl-4a,5-dihydro-4H-1-benzopyran-4-one (189) and (4a*R*,5*R*)-5-[(*Z*)-1,4-dimethylpent-1-enyl]-4-methoxy-3,4a,6,8-tetramethyl-4a,5-dihydro-2H-1-benzopyran-2-one (190)



To a stirred solution of pyrone **183** (0.0140 g, 0.0442 mmol) in Et$_2$O (2 mL) at rt was added CH$_2$N$_2$/Et$_2$O (excess) until the yellow colour persisted. The mixture was stirred at rt for a further 1 hour and N$_2$ was bubbled through the solution to remove excess diazomethane. The solvent was removed *in vacuo* to yield a pale yellow oil which was purified by flash chromatography on silica (30% Et$_2$O/hexanes, R$_f$ = 0.46, 0.35) to afford firstly γ-pyrone **189** (0.0053 g, 0.0160 mmol, 36%) as a colourless oil, followed by α-pyrone **190** (0.0055 g, 0.0166 mmol, 38%) as a colourless oil.

γ-pyrone **189**: **[α]$_D$** = –517 (*c* 0.30, CHCl$_3$); **IR** (film) 1611 (with shoulder), 1462, 1387, 1370, 1352, 1249, 1275, 1203, 1160 cm^{-1}; **UV/Vis** (MeOH) λ$_{max}$ 255 (ε 5,450) nm; **^{1}H NMR** δ 5.51-5.48 (m, 1H, C(CH$_3$)=C*H*C(CH$_3$)), 5.08 (tq, 1H, *J* = 6.6, 1.5 Hz, C(CH$_3$)=C*H*CH$_2$), 3.94 (s, 3H, OC*H*$_3$), 3.43 (s, 1H, C*H*C(CH$_3$)=CH), 2.21-2.10 (m, 1H, C(CH$_3$)=CHC*H*$_A$H$_B$), 2.09-1.98 (m, 1H, C(CH$_3$)=CHCH$_A$*H*$_B$), 1.74 (app. s, 6H, C(CH$_3$)=CHC(C*H*$_3$), C(C*H*$_3$)=CHC(CH$_3$)), 1.71-1.60 (m, 1H, C*H*(CH$_3$)$_2$), 1.62 (s, 3H, C(C*H*$_3$)=C(OCH$_3$)), 1.52 (q, 3H, *J* = 1.5 Hz, C(C*H*$_3$)=CHCH$_2$), 1.35 (s, 3H, C(C*H*$_3$)), 0.95 (d, 3H, *J* = 6.6 Hz, CH$_2$CH(C*H*$_3$)), 0.90 (d, 3H, *J* = 6.6 Hz, CH$_2$CH(C*H*$_3$)); **^{13}C NMR** δ 192.5 (C-3), 163.9 (C-1), 145.5 (C-5), 132.5 (C-10), 132.2 (C-8), 128.8 (C-11),

122.2 (C-7), 111.9 (C-6), 88.4 (C-2), 54.7 (OMe), 49.9 (C-9), 45.5 (C-4), 37.6 (C-12), 28.8 (C-13), 25.5 (C-17), 22.8 (C-14), 22.7 (C-15), 21.6 (C-18), 20.4 (C-16), 13.4 (C-19), 6.6 (C-20); **HRESIMS** calculated for $C_{21}H_{31}O_3^+$ ($M+H^+$): 331.2273; found: 331.2271; **EIMS** *m/z* (%): 330 (M^+, 21), 315 (30), 273 (29), 255 (8), 243 (17), 233 (21), 219 (20), 201 (8), 185 (8), 173 (53), 159 (26), 145 (31), 129 (20), 115 (23), 105 (21), 91 (33), 83 (28), 77 (14), 65 (13), 55 (25), 41 (100).

α-pyrone **190**: **$[\alpha]_D$** = –609 (*c* 0.32, $CHCl_3$), **IR** (film) 1725, 1683, 1638, 1449, 1380, 1350, 1304, 1284, 1224, 1177, 1098 cm^{-1}; **UV/Vis** (MeOH) λ_{max} 245 (ε 10,750) nm; **^{1}H NMR** δ 5.56-5.53 (m, 1H, $C(CH_3)=CHC(CH_3)$), 5.12 (tq, 1H, *J* = 6.4, 1.5 Hz, $C(CH_3)=CHCH_2$), 3.88 (s, 3H, OCH_3), 3.24 (s, 1H, $CHC(CH_3)=CH$), 2.20-1.95 (m, 2H, *J* = 7.1 Hz, $C(CH_3)=CHCH_2$), 1.95 (s, 3H, $C(CH_3)=C(OCH_3)$), 1.73 (s, 3H, $C(CH_3)=CHC(CH_3)$), 1.70 (d, 3H, *J* = 1.5 Hz, $C(CH_3)=CHC(CH_3)$), 1.70-1.57 (m, 1H, $CH(CH_3)_2$), 1.54 (q, 3H, *J* = 1.5 Hz, $C(CH_3)=CHCH_2$), 1.36 (s, 3H, $C(CH_3)$), 0.94 (d, 3H, *J* = 6.6 Hz, $CH_2CH(CH_3)$), 0.93 (d, 3H, *J* = 6.6 Hz, $CH_2CH(CH_3)$); **^{13}C NMR** δ 172.4 (C-3), 165.4 (C-1), 143.2 (C-5), 132.7 (C-10), 130.4 (C-8), 128.8 (C-11), 123.4 (C-7), 110.3 (C-6), 103.1 (C-2), 61.4 (OMe), 49.0 (C-9), 42.7 (C-4), 37.5 (C-12), 28.8 (C-13), 24.1 (C-17), 22.8 (C-14), 22.7 (C-15), 21.5 (C-18), 20.0 (C-16), 13.6 (C-19), 11.8 (C-20); **HRESIMS** calculated for $C_{21}H_{31}O_3^+$ ($M+H^+$): 331.2273; found: 331.2270; **EIMS** *m/z* (%): 330 (M^+, 20), 315 (7), 287 (2), 255 (4), 231 (2), 219 (12), 197 (6), 182 (85), 167 (8), 149 (24), 133 (22), 121 (15), 107 (37), 91 (33), 77 (19), 65 (15), 55 (24), 41 (100).

References

1. Faulkner, D. J. *Nat. Prod. Rep.* **2002,** *19*, 1-48.
2. Faulkner, D. J. *Nat. Prod. Rep.* **1986,** *3*, 1-33.
3. Lee, J. S.; Murata, M.; Yasumoto, T. Analytical methods for determination of diarrhetic shellfish toxins. In *Mycotoxins and Phycotoxins '88;* Natori, S.; Hashimoto, K.; Ueno, Y. Eds.; Elsevier Science: Amsterdam, **1989**; pp. 327-334.
4. Norte, M.; Cataldo, F.; Gonzalez, A. G.; Rodriguez, M. L.; Ruiz-Perez, C. *Tetrahedron* **1990,** *46*, 1669-1678.
5. Paul, M. C.; Zubia, E.; Ortega, M. J.; Salva, J. *Tetrahedron* **1997,** *53*, 2303-2308.
6. Hochlowski, J. E.; Faulkner, D. J. *Tetrahedron Lett.* **1983,** *24*, 1917-1920.
7. Biskupiak, J. E.; Ireland, C. M. *Tetrahedron Lett.* **1983,** *24*, 3055-3058.
8. Manker, D. C.; Faulkner, D. J.; Xe, C. F.; Clardy, J. J. *J. Org. Chem.* **1986,** *51*, 814-816.
9. Dawe, R. D.; Wright, J. L. C. *Tetrahedron Lett.* **1986,** *27*, 2559-2562.
10. O'Hagan, D. *The Polyketide Metabolites*; Horwood: New York, 1991.
11. Rodriguez, J.; Riguera, R.; Debitus, C. *Tetrahedron Lett.* **1992,** *33*, 1089-1092.
12. Suenaga, K.; Kigoshi, H.; Yamada, K. *Tetrahedron Lett.* **1996,** *37*, 5151-5154.
13. Rodriguez, J.; Riguera, R.; Debitus, C. *J. Org. Chem.* **1992,** *57*, 4624-4632.
14. Ksebati, M. B.; Schmitz, F. J. *J. Org. Chem.* **1985,** *50*, 5637-5642.
15. Ireland, C. M.; Scheuer, P. J. *Science* **1979,** *205*, 922-923.
16. Gavagnin, M.; Marin, A.; Mollo, E.; Crispino, A.; Villani, G.; Cimino, G. *Comp. Biochem. Physiol.* **1994,** *108B*, 107-115.
17. Di Marzo, V.; Vardaro, R. R.; De Petrocellis, L.; Villani, G.; Minei, R.; Cimino, G. *Experientia* **1991,** *47*, 1221-1227.
18. Manker, D. C.; Garson, M. J.; Faulkner, D. J. *J. Chem. Soc., Chem. Commun.* **1988**, 1061-1062.
19. Ireland, C.; Faulkner, D. J.; Solheim, B. A.; Clardy, J. *J. Am. Chem. Soc.* **1978,** *100*, 1002-1003.
20. Ireland, C.; Faulkner, D. J.; Finer, J. S.; Clardy, J. *J. Am. Chem. Soc.* **1979,** *101*, 1275-1276.
21. Ireland, C. M.; Faulkner, D. J. *Tetrahedron* **1981,** *37, Suppl. No. 1*, 233-240.

22. Gavagnin, M.; Spinella, A.; Castelluccio, F.; Cimino, G. *J. Nat. Prod.* **1994,** *57*, 298-304.
23. Gavagnin, M.; Mollo, E.; Cimino, G.; Ortea, J. *Tetrahedron Lett.* **1996,** *37*, 4259-4262.
24. Gavagnin, M.; Mollo, E.; Castelluccio, F.; Montanaro, D.; Ortea, J.; Cimino, G. *Nat. Prod. Lett.* **1997,** *10*, 151-156.
25. Fu, X.; Hong, E. P.; Schmitz, F. J. *Tetrahedron* **2000,** *56*, 8989-8993.
26. Marin, A.; Ros, J. *Scientia Marina* **2004,** *68 (Suppl. 1)*, 227-241.
27. Burn, R. Order Sacoglossa. In *Mollusca: The Southern Synthesis. Fauna of Australia;* Beesley, P. L.; Ross, G. J. B.; Wells, A. Eds.; CSIRO Publishing, Melbourne, **1998**; Vol. 5, Part B; pp. 961-974.
28. Faulkner, D. J.; Ghiselin, M. T. *Mar. Ecol. Prog. Ser.* **1983,** *13*, 295-301.
29. Pawlik, J. R. *Chem. Rev.* **1993,** *93*, 1911-1922.
30. Miller, A. K.; Trauner, D. *Angew. Chem. Int. Ed.* **2003,** *42*, 549-552.
31. Perkins, M. V.; Sampson, R. A. *Org. Lett.* **2002,** *4*, 1655-1658.
32. Ciavatta, M. L.; Trivellone, E.; Villani, G.; Cimino, G. *Tetrahedron Lett.* **1993,** *34*, 6791-6794.
33. Arimoto, H.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1990,** *31*, 5619-5620.
34. Arimoto, H.; Cheng, J.-F.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1993,** *34*, 5781-5784.
35. Ishibashi, Y.; Ohba, S.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1996,** *37*, 2997-3000.
36. Birkbeck, A. A.; Enders, D. *Tetrahedron Lett.* **1998,** *39*, 7823-7826.
37. Stetter, H.; Marten, K. *Liebigs. Ann. Chem.* **1982**, 240-249.
38. Stetter, H.; Marten, K. *Liebigs. Ann. Chem.* **1982**, 250-253.
39. Bunce, R. A.; Harris, C. R. *J. Org. Chem.* **1992,** *57*, 6981-6985.
40. Bunce, R. A.; Harris, C. R. *Synthetic Commun.* **1996,** *26*, 1969-1975.
41. DeVille, J. P.; Behar, V. *Org. Lett.* **2002,** *4*, 1403-1405.
42. Martinez, A. D.; DeVille, J. P.; Stevens, J. L.; Behar, V. *J. Org. Chem.* **2004,** *69*, 991-992.
43. Kozhinov, D. V.; Behar, V. *J. Org. Chem.* **2004,** *69*, 1378-1379.
44. Zimmerman, H. E. *J. Org. Chem.* **1955,** *20*, 549-557.
45. Piers, E.; Tse, H. L. S. *Tetrahedron Lett.* **1984,** *25*, 3155-3158.

46. Paquette, L. A.; Wiedeman, P. E.; Bulman-Page, P. C. *J. Org. Chem.* **1988,** *53*, 1441-1450.
47. Piers, E.; Llinas-Brunet, M. *J. Org. Chem.* **1989,** *54*, 1483-1484.
48. Trova, M. P.; Wang, Y. *Tetrahedron* **1993,** *49*, 4147-4158.
49. Sieburth, S. M.; Chen, C.-A. *Synlett* **1995**, 928-930.
50. Vanderwal, C. D.; Vosburg, D. A.; Weiler, S.; Sorensen, E. J. *Org. Lett.* **1999,** *1*, 645-648.
51. Hinterding, K.; Singhanat, S.; Oberer, L. *Tetrahedron Lett.* **2001,** *42*, 8463-8465.
52. Vanderwal, C. D.; Vosburg, D. A.; Weiler, S.; Sorensen, E. J. *J. Am. Chem. Soc.* **2003,** *125*, 5393-5407.
53. Wild, H.; Born, L. *Angew. Chem. Int. Ed. Engl.* **1991,** *30*, 1685-1687.
54. Huang, H.; Forsyth, C. J. *J. Org. Chem.* **1995,** *60*, 5746-5747.
55. Hareau, G. P.-J.; Koiwa, M.; Hikichi, S.; Sato, F. *J. Am. Chem. Soc.* **1999,** *121*, 3640-3650.
56. Demeke, D.; Forsyth, C. J. *Org. Lett.* **2000,** *2*, 3177-3179.
57. Paczkowski, R.; Maichle-Mossmer, C.; Maier, M. E. *Org. Lett.* **2000,** *2*, 3967-3969.
58. Imuta, S.; Ochiai, S.; Kuribayashi, M.; Chida, N. *Tetrahedron Lett.* **2003,** *44*, 5047-5051.
59. Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981,** *103*, 2127-2129.
60. Evans, D. A. *Aldrichimica acta* **1982,** *15*, 23.
61. Evans, D. A.; Gage, J. R. *Org. Synth.* **1990,** *68*, 77-91.
62. Smith, N. D.; Kocienski, P. J.; Street, S. D. A. *Synthesis* **1996**, 652-666.
63. Corey, E. J.; Nicolaou, K. C.; Toru, T. *J. Am. Chem. Soc.* **1975,** *97*, 2287-2288.
64. Barrett, A. G. M.; Edmunds, J. J.; Hendrix, J. A.; Horita, K.; Parkinson, C. J. *J. Chem. Soc., Chem. Commun.* **1992**, 1238-1240.
65. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991,** *113*, 7277-7287.
66. Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165-185.
67. Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975,** *31*, 2647-2650.
68. Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972,** *94*, 6190-6191.
69. Stork, G.; Paterson, I.; Lee, F. K. C. *J. Am. Chem. Soc.* **1982,** *104*, 4686-4688.
70. Walkup, R. D.; Kane, R. R.; Boatman Jr., P. D.; Cunningham, R. T. *Tetrahedron Lett.* **1990,** *31*, 7587-7590.

71. Nakajima, N.; Horita, K.; Abe, R.; Yonemitsu, O. *Tetrahedron Lett.* **1988,** *29*, 4139-4142.
72. Walkup, R. D.; Kahl, J. D.; Kane, R. R. *J. Org. Chem.* **1998,** *63*, 9113-9116.
73. Smith, A. B., III; Beauchamp, T. J.; LaMarche, M. J.; Kaufman, M. D.; Qiu, Y.; Arimoto, H.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **2000,** *122*, 8654-8664.
74. Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P.; Sereinig, N. *J. Am. Chem. Soc.* **2001,** *123*, 9535-9544.
75. House, H. O.; Chu, C.-Y.; Wilkins, J. M.; Umen, M. J. *J. Org. Chem.* **1975,** *40*, 1460-1469.
76. Chounan, Y.; Ono, Y.; Nishii, S.; Kitahara, H.; Ito, S.; Yamamoto, Y. *Tetrahedron* **2000,** *56*, 2821-2831.
77. Boring, D. L.; Sindelar, R. D. *J. Org. Chem.* **1988,** *53*, 3617-3621.
78. Critcher, D. J.; Pattenden, G. *Tetrahedron Lett.* **1996,** *37*, 9107-9110.
79. Corey, E. J.; Kwiatkowski, G. T. *J. Am. Chem. Soc.* **1966,** *88*, 5654-5656.
80. Coe, J. W.; Roush, W. R. *J. Org. Chem.* **1989,** *54*, 915-930.
81. Edmonds, M. K.; Abell, A. D. *J. Org. Chem.* **2001,** *66*, 3747-3752.
82. Deziel, R.; Plante, R.; Caron, V.; Grenier, L.; Llinas-Brunet, M.; Duceppe, J.-S.; Malenfant, E.; Moss, N. *J. Org. Chem.* **1996,** *61*, 2901-2903.
83. Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984,** *25*, 2183-2186.
84. Bonadies, F.; Cardilli, A.; Lattanzi, A.; Orelli, L. R.; Scettri, A. *Tetrahedron Lett.* **1994,** *35*, 3383-3386.
85. Paterson, I.; Yeung, K.-P.; Smaill, J. B. *Synlett* **1993**, 774-776.
86. Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron Lett.* **1980,** *37*, 2091-2096.
87. Inanaga, J.; Hirata, K.; Saeki, T.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979,** *52*, 1989-1993.
88. Hikota, M.; Sakurai, Y.; Horita, K.; Yonemitsu, O. *Tetrahedron Lett.* **1990,** *31*, 6367-6370.
89. Hanford, W. E.; Sauer, J. C. *Org. React.* **1947,** *3*, 124-126.
90. Chaudhari, S. S.; Akamanchi, K. G. *Synlett* **1999**, 1763-1765.
91. Eaton, P. E.; Carlson, G. R.; Lee, J. T. *J. Org. Chem.* **1973,** *38*, 4071-4073.
92. Schultz, A. G.; Yee, Y. K. *J. Org. Chem.* **1976,** *41*, 561-563.

93. Murthy, Y. V. S.; Pillai, C. N. *Tetrahedron* **1992,** *48*, 5331-5346.
94. Smithers, R. H. *J. Org. Chem.* **1978,** *43*, 2833-2838.
95. Kim, H.; Lee, S.-K.; Lee, D.; Cha, J. K. *Synthetic Commun.* **1998,** *28*, 729-735.
96. Villa, M.-J.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1569-1572.
97. Brittelli, D. R. *J. Org. Chem.* **1981,** *46*, 2514-2520.
98. Norris, W. P. *J. Org. Chem.* **1959,** *24*, 1579-1580.
99. Suffert, J. *J. Org. Chem.* **1989,** *54*, 509-510.
100. House, H. O.; Latham, R. A.; Slater, C. D. *J. Org. Chem.* **1966,** *31*, 2667-2669.
101. For an excellent book on cuprates consult *Organocopper reagents: A practical approach*; Oxford University Press: New York, **1994**.
102. Lipshutz, B. H.; Koerner, M.; Parker, D. A. *Tetrahedron Lett.* **1987,** *28*, 945-948.
103. Mulzer, J.; Mantoulidis, A.; Ohler, E. *J. Org. Chem.* **2000,** *65*, 7456-7467.
104. Puglisi, C. J.; Elsey, G. M.; Prager, R. H.; Skouroumounis, G. K.; Sefton, M. A. *Tetrahedron Lett.* **2001,** *42*, 6937-6939.
105. Adler, R. W. *Chem. Ind. London* **1973**, 983-986.
106. Beak, P.; Lee, J. S.; McKinnie, B. G. *J. Org. Chem.* **1978,** *43*, 1367-1372.
107. Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983,** *24*, 4405-4408.
108. Ando, K. *Tetrahedron Lett.* **1995,** *36*, 4105-4108.
109. Ando, K. *J. Org. Chem.* **1999,** *64*, 6815-6821.
110. Motoyoshiya, J.; Kusaura, T.; Kokin, K.; Yokoya, S.-i.; Takaguchi, Y.; Narita, S.; Aoyama, H. *Tetrahedron* **2001,** *57*, 1715-1721.
111. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon Press: Oxford, 1988.
112. Hartmann, C.; Meyer, V. *Chem. Ber.* **1893,** *26*, 1727-1732.
113. Paterson, I.; Patel, S. K.; Porter, J. R. *Tetrahedron Lett.* **1983,** *24*, 3395-3396.

Glossary/Abbreviations

Δ	heat
AcOH	acetic acid (glacial)
Ac_2O	acetic anhydride
Anal.	analytical
app.	apparent
APT	attached proton test
$BF_3.OEt_2$	boron trifluoride-diethyl ether complex
$BH_3.SMe_2$	borane-dimethyl sulfide complex
bp	boiling point
Bu_2BOTf	dibutylboron triflate
n-BuLi	butyllithium
t-BuLi	*tert*-butyllithium
c	concentration (g/100 mL)
ca.	*circa* (approximately)
Calcd.	calculated
cat.	catalytic
CDI	1,1'-carbonyldiimidazole
COSY	correlation spectroscopy
δ	chemical shift (parts per million)
de novo	from the beginning
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL	diisobutylaluminium hydride
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess Martin periodinane
DMSO	dimethyl sulfoxide
ds	diastereoselectivity
E	*entgegen* (opposite)
EI	electron impact

EIMS	electron impact mass spectroscopy (spectrum)
eq	equivalent(s)
ESI	electrospray ionisation
et al.	*et alia* (and others)
EtCOCl	propionyl chloride
Et_2O	diethyl ether
$(EtO)_2CO$	diethyl carbonate
EtOH	ethanol
GC/MS	gas chromatography/mass spectrometry
HMBC	heteronuclear multiple bond connectivity
HMQC	heteronuclear multiple quantum coherence
HRMS	high resolution mass spectroscopy (spectrum)
Hz	hertz
IR	infrared
J	coupling constant (Hz)
$KBrO_3$	potassium bromate
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
lit.	literature
LSI	liquid secondary ionisation
Me	methyl
MeCN	acetonitrile
MeOH	methanol
MHz	megahertz
mmol	millimole
mol	mole
mp	melting point
m/z	mass-to-charge ratio
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser and exchange spectroscopy
OTf	trifluoromethanesulfonate (triflate)
PCC	pyridinium chlorochromate
PPTS	pyridinium *para*-toluenesulfonic acid

PMB	*para*-methoxybenzyl
PPA	polyphosphoric acid
ppm	parts per million
Pyr.	pyridine
R_f	retention factor
rt	room temperature
sat.	saturated
TBDPS	*tert*-butyldiphenylsilyl
TBDPSCl	*tert*-butyldiphenylsilyl chloride
TBS	*tert*-butyldimethylsilyl
TBSOTf	*tert*-butyldimethylsilyl trifluoromethanesulfonate
TES	triethylsilyl
TESOTf	triethylsilyl trifluoromethanesulfonate
TFA	trifluoroacetic acid
TfOH	triflic acid
THF	tetrahydrofuran
tlc	thin layer chromatography
TMSCl	trimethylsilyl chloride
p-TsOH	*para*-toluenesulfonic acid
Z	*zusammen* (together)

Appendix A

This appendix contains reprints and/or preprints of publications that have resulted from research outlined in this thesis.

1. Formation of Highly Substituted Chiral Cyclohexanone Derivatives Using a Tandem Conjugate Addition/Cyclisation
   Jeffery, D.W.; Perkins, M.V. *Tetrahedron Lett.* **2004**, *45*, 8667-8671.

2. Synthesis of an Analogue of the Marine Polypropionate Tridachiahydropyrone
   Jeffery, D.W.; Perkins, M.V.; White, J.M. *Org. Lett.* **2005**, *7*, 407-409.

3. Synthesis of the Putative Structure of Tridachiahydropyrone
   Jeffery, D.W.; Perkins, M.V.; White, J.M. *Org. Lett.* **2005**, accepted.