INVESTIGATIONS OF THE
TYPE II INTRAMOLECULAR DIELS-ALDER
REACTION DIRECTED TOWARD NATURAL
PRODUCT SYNTHESIS

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A thesis

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"Chemical synthesis always has some element of planning in it. But, the planning should never be too rigid. Because, in fact, the specific objective which the synthetic chemist uses as an excuse for his activity is often not of special importance in the general sense; rather, the important things are those that he finds out in the course of attempting to reach his objective."

R. B. Woodward*. Proc. Robert A. Welch Foundation Conf. Chem. Res.* **1969***, 12, 3.*

Abstract

This thesis describes synthetic studies directed towards the total synthesis of the nakafuran and florlide marine natural products. **Chapter One** provides an overview of the importance of natural products to current medicinal chemistry and describes how the "supply issue" associated with these biologically derived compounds can be resolved through the process of total synthesis. Two families of marine natural products, the nakafurans and the florlides, are introduced as synthetic targets and strategies utilising a type II intramolecular Diels-Alder (IMDA) reaction to achieve their total synthesis are delineated.

The efficient preparation of regio- and stereodefined vinyl coupling fragments *via* hydrostannylation and hydrohalogenation methodology is described in **Chapter Two**. The palladium-catalysed cross-coupling of these fragments, *via* Stille or Negishi coupling methodology, yielded dienes which were successfully advanced to IMDA triene precursors.

Chapter Three describes investigation of the type II IMDA reaction to give bicyclo[4.3.1]decene carbocyclic skeletons. A facile acid-catalysed $\Delta^{6,7} \rightarrow \Delta^{7,8}$ olefinic isomerisation, *via* a proposed oxonium intermediate, and the inability to appropriately functionalise the desired adducts impeded progress along the synthetic route. Molecular modelling was conducted to investigate the causes of this unexpected reactivity.

Investigations in **Chapter Four** describe the successful synthesis and cyclisation of homomethyl triene analogues prepared *via* application of enyne metathesis chemistry. The use of an *exo*-cyclopropylcarbinyl fragmentation was found to be unsuccessful as a means of installing the desired 6-methyl-bicyclo[4.3.1]decan-2-one core with a competing *endo*-ring expansion giving rise to a bicyclo[4.4.1]undecane ring system.

Chapter 5 summarises the above results and gives a brief discussion of the future potential of this research to provide for a total synthesis of the nakafuran and florlide natural products.

Table of Contents

Chapter Three   The Diels-Alder Reaction Directed Towards the Synthesis of Bicyclic Natural Products

Chapter Six   Experimental Details

Abbreviations

This dissertation uses standard abbreviations and acronyms as recommended by the American Chemical Society.[*] Additional terms are listed below.

BHT	2,6-di-*tert*-butyl-4-methylphenol
cat.	catalytic
CIGAR	constant time inverse-detected gradient accordion rescaled
COSY	correlation spectroscopy
2D NMR	two dimensional nuclear magnetic resonance spectroscopy
dba	dibenzylideneacetone
DHP	dihydropyran
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H)*-pyridimidinone
DNB	1,3-dinitrobenzoyl
EDCI	1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride
HMBC	heteronuclear multiple bond coherence
HSQC	heteronuclear single quantum coherence
HMDS	hexamethyldisilazane
Hünig's base	*N,N*-diisopropylethylamine
Imid	imidazole
MPLC	medium-pressure liquid chromatography
MS	mass spectrometry
NMO	*N*-methylmorpholine-*N*-oxide
NMP	1-methyl-2-pyrrolidinone
NOESY	nuclear Overhauser effect spectroscopy
PMB	*para*-methoxybenzyl
PDC	pyridinium dichromate
sat.	saturated
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
TFP	tri(2-furyl)phosphine
TMP	2,2,6,6-tetramethylpiperidine
TMSI	iodotrimethylsilane
TOCSY	total correlation spectroscopy
TPAP	tetra-*n*-propylammonium perruthenate

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[*] ACS Guidelines for Authors, *J. Org. Chem*, **2006**, *71*, 1, 1A-11A.

Chapter One

Introduction to Natural Product Synthesis

1.1 The Origins of Natural Products

The processes of nature result in the synthesis of a remarkable array of primary and secondary metabolites. The primary metabolic system, which refers to the normal anabolic and catabolic biochemical processes common to all cellular organisms, generates and utilises ubiquitous compounds such as proteins, nucleic acids, carbohydrates and lipids. By contrast, secondary metabolism consists of a large number of diverse biochemical processes that are characteristic or unique to certain cell types or species. Plants, fungi and bacteria produce a profusion of structurally diverse secondary metabolites, also known as natural products, which encompass such elements as the alkaloids, glycosides, terpenes, phenols and rare amino acid products.

Secondary metabolites are often described as having no explicit role within the internal economy of the producing organism.[1] It is postulated that the expression of natural products has evolved to provide a selective survival advantage to the producing organism, by either attracting or repelling other organisms.[2] Whilst many natural products deter predation or infection through the cellular expression of noxious, bactericidal or antimitotic compounds, secondary metabolites have also been observed to serve integral functions in such diverse roles as differentiation effectors, metal transporting agents, sex hormones and in symbiotic communication.

1.2   Therapeutic Applications of Natural Products

Historically, it has been the pharmacological properties and physiological effects of natural products that have elicited the most interest. From aspirin and caffeine, to morphine and quinine; human society has pursued the ingestion of biologically derived compounds to elicit a desired physiological effect.[3] In the present day, natural products continue to provide most of the world's population with their pharmacopoeia, and represent the source, or inspiration, for a significant proportion of the Western world's pharmaceuticals.

Secondary metabolites contained within terrestrial plant extracts have, for thousands of years, played an essential role in traditional medicine systems. Historical pharmacopoeias such as the Eber's Papyrus, compiled by Egyptian priest-physicians in 1550 BC and the writings of Galen (129-199 AD) illustrate the extensive use of plant-derived materials in a medicinal context. Knowledge of the bioactive constituents was limited and the discovery process was largely empirical or observationally derived. Principal examples included the use of the bark of the willow tree (order *Salicaceae*) as an analgesic, extracts of *Papaver somniferum* poppy to treat pain, and extracts from the bark of the Peruvian *Cinchona* tree for the treatment of malaria.

These bioactive compounds, identified by present day nomenclature as salicin (**1.1**), morphine (**1.2**) and quinine (**1.3**) respectively, occupy not only a role as traditional medicinal agents but also as prominent chemical milestones that illustrate the isolation, elucidation and synthesis of natural products (**Figure 1.1**).[4,5]
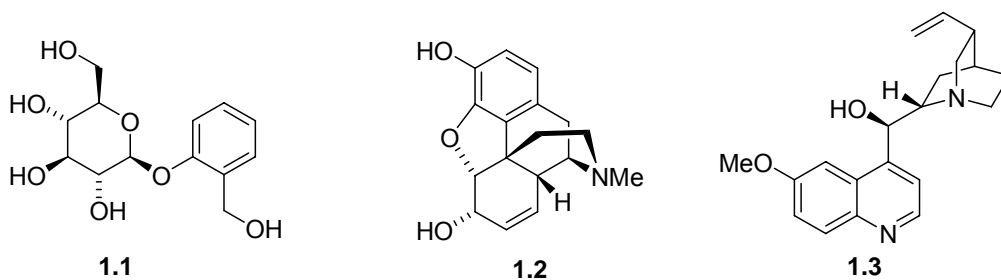
Figure 1.1   Historically significant natural products.

Natural products have played, and continue to play, an important role in drug discovery and the advancement of organic chemistry.[5-7] The clinical success of the sulfonamides and penicillins in the period 1938-1945 transformed the treatment of bacterial infection. It led to the acceptance of the idea that many human diseases would be amenable to treatment with selectively toxic chemicals of a synthetic or biological origin.[8,9]

In this context, the enormous biodiversity inherent in nature represents a tremendous resource for scientific researchers. Over the past two centuries, a strikingly diverse array of secondary metabolites have been isolated from plant, fungal, animal, and recently, microbial sources.[10] These isolated natural products display a diverse range of physiological and pharmacological properties which are intimately related to the often novel and structurally complex molecular architecture. Some of these molecules have served as biochemical tools to assist in the elucidation of metabolic pathways and intracellular interactions and many have been developed into medicinal agents for the treatment of disease.[9] It has been estimated that 39% of the new drugs approved in the period 1983-1994 and 60-80% of the antibacterial, anticancer and anti-HIV drugs were derived from natural products.[5]

1.3 Marine Natural Products

1.3.1 Biochemical and Structural Diversity Arising from Biological Diversity

Whilst initial endeavours to discover substances of therapeutic potential focused primarily on terrestrial plants, fungi and micro-organisms, pioneering work by academic chemists in the 1970s stimulated interest in the field of marine natural products.[11,12] The extension of bioprospecting to the oceans is a natural progression, when the biodiversity inherent in the marine environment is considered.[13] It is estimated that the majority of all species live in the oceans, which cover 70% of the planet's surface. Of the 38 phyla in the animal kingdom, 26 are exclusively aquatic and only one is exclusively terrestrial.[2] Furthermore, the marine environment encompasses a tremendous variety of habitats, differing markedly in temperature, pressure, light,

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[2] Velvet worms from the phyla *Onchyophora,* are the only known exclusively terrestrial phyla. Fossils discovered in the Burgess Shale, from the Cambrian period, indicate that this phylum evolved in the oceans.

pH, salinity and anaerobic conditions. The marine environment is yet to be extensively investigated; discoveries are being continually made of new sea life and unique ecosystems in the pelagic region.

Advancement of modern scientific methods, especially bioassay-guided screening in conjunction with advanced spectroscopic techniques (2D-NMR, HPLC, LC/MS), have made it possible to detect, fractionate and elucidate the structure of natural products of low abundance and high structural complexity. These advances have resulted in the rapid and steady growth of marine natural product literature over the last thirty years. For example, in the period 2000 to 2003, 2450 new natural products of marine origin were reported. This compares to around 100 in the period 1965 to 1970.[14]

Compounds isolated from the marine environment are extraordinary for their complexity and connectivity, with substantial incorporation of heteroatom and halogen functionality. Faulkner suggested that marine organisms possess a greater prevalence of bioactive metabolites than do terrestrial organisms.[15] Indeed, secondary metabolites isolated from marine environments have been a rich source of antibiotic and antimitotic agents.[14] Published reviews clearly indicate the tremendous potential of taxonomically diverse marine micro- and macro-organisms as a source of pharmaceuticals, possessing a wide range of pharmacological activities including antitumour, antibacterial, anti-inflammatory, antifungal and antiviral activities (**Figure 1.2**).[7,13,16]

Spongistatin 1
antimicrotubule

(-)-Diazonamide A
antitumour

Cephalostatin 1
antitumour

Manzamine A
antimalarial and antituberculosis

Variolin B
antitumour

Sceptrin
antimicrobial

Tetrodotoxin
Na⁺ channel voltage-gate blocker

Macrolactin A
antiviral

Phomactin A
platelet activating
factor antagonist

Eleutherobin
microtubule-stabilizing
anticancer agent

Callipeltoside A
antitumor

(-)-Mirabazole C
antitumour
HIV-1 protease inhibitor

Figure 1.2 A selection of marine secondary metabolites, illustrative of the structural and pharmacological diversity, which have been successfully synthesised.

Marine compounds commonly display remarkably high levels of bioactivity. The high potency is believed to be an evolutionary adaptation to counteract the effect of high dilution in an aqueous environment. An example of this phenomenon is ciguatera, which is an important form of human poisoning. Ciguatera is caused by the consumption of affected shellfish and seafood following algal blooms or "red tides". More than 20 000 people are affected annually, making it the most common form of non-bacterial food poisoning. Epiphytic dinoflagellates, such as *Gambierdiscus toxicus*, are the causative organism. They produce a number of highly-toxic polycyclic ether macrolides such as ciguatoxin (**1.4**) (**Figure 1.3**),[17] maitotoxin,[18] brevetoxin,[19,20] gambierol,[21-23] gymnocin A[24] and palytoxin.[25] These molecules are remarkable not only for their extraordinary toxicity (inducing neurological, gastrointestinal, and cardiovascular disorders at concentrations as low as 0.25 μg to 100 μg/kg) but also due to their stereochemically complex linear macrocyclic arrays.[26]

1.4
Ciguatoxin (CTX)
Na$^+$ channel voltage gate-blocker
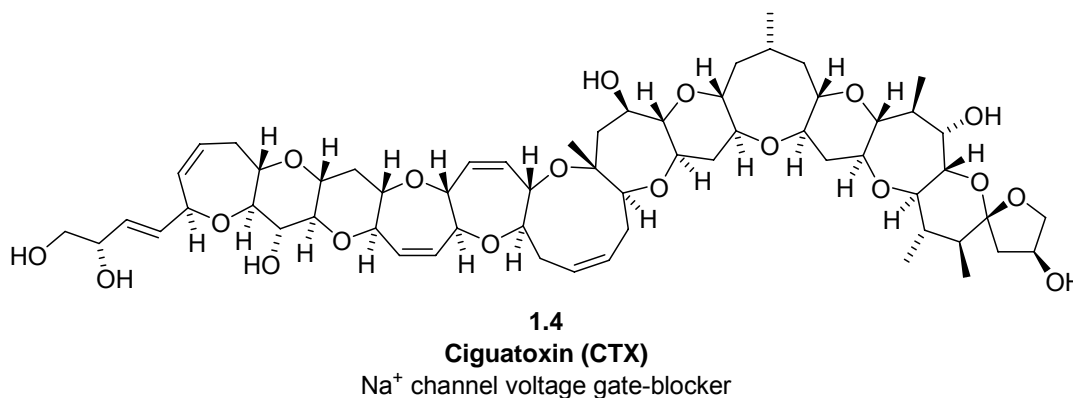
Figure 1.3   Ciguatoxin, elucidated in 1989 by Yasumoto *et al.*[27] was recently synthesised by Hirama *et al.*[28]

1.3.2   Marine Natural Product Pharmaceuticals

There is little doubt that marine biodiversity is a source of chemical and structural diversity. However, of the over 14 000 compounds described,[29] many of which display potent biological activity and have been utilised as bio-medical leads, few have proceeded to become approved pharmaceutical drugs.[7,3]

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[3] Drugs currently on the market of a marine "origin", whether an isolate or derived from a lead compound, are the antiviral drug Acyclovir, anticancer agent Cytarabine, the antibiotic Cephalosporin, (which is also expressed by many terrestrial microorganisms) and Ziconotide (*Conus* toxin) for the treatment of severe chronic pain. Yondelis (ecteinascidin 743) is currently in Phase III trials in Europe.

The reasons for this are manifold. Most significant is simply the later emergence of marine natural product chemistry compared with the established chemistry of terrestrial natural products. However, specific difficulties associated with the isolation and study of marine natural products have also delayed the progress of them or their analogues through clinical trials. Promising bioactive compounds are often expressed in low natural abundance (~10^{-6} % net weight) within the source organism. Consequently, it has proven notoriously difficult to obtain adequate, reliable and, most importantly, renewable supplies of these compounds from the marine environment. Compounding this problem is the inherent structural complexity of many marine natural products, which eliminates the possibility of commercial synthesis.

An example of this is the isolation of Spongistatin 1 from the marine sponge *Spongia*. An initial extraction from 400 kg of *Spongia* yielded 13.8 mg of Spongistatin 1, a potent antitumour agent (**Figure 1.2**).[30] Attempted recollection of 20 tonnes failed to yield significantly larger amounts.[31] Many researchers believe that the Spongistatin compounds are actually produced by symbiotic micro-organisms, yet bacteria or fungi that provide these metabolites have not been isolated from the parent organism. The successful total syntheses of the Spongistatins are yet to yield pharmaceutically viable quantities.[32] Without an adequate and reproducible resource of supply, it is impossible to advance a compound forward into therapeutic use.

Considerable effort has been expended attempting to find a solution to the issues of supply. Aquaculture of marine organisms, genomic expression in bacterial hosts, tissue culture and total synthesis have all been advanced as potential solutions.[33]

1.3.3   Total Synthesis as a Solution to the Supply Problem

The total synthesis of an isolated natural product was originally pursued to unequivocally confirm the postulated structural assignment through a sequence of well-defined chemical transformations. With the advent of sophisticated spectroscopic, mass spectral and X-ray analysis techniques, structural elucidation has increasingly been completed before the commencement of a synthetic endeavour. However, while modern techniques such as NMR spectroscopy have been very successful in allowing the structures of even very complex natural products to be determined, the unambiguous structure determination of stereochemical issues are often difficult or impossible to elucidate by spectroscopic methodology alone. The synthesis of one or more of the possible stereoisomers is required to establish the correct structure. A recent

review illustrated that it is not uncommon for a total synthesis to be achieved, only to find that the natural product structural assignment was incorrect.[34] These incorrect natural product assignments can have implications in the development of biosynthetic proposals for entire classes of compounds.

As well as maintaining its importance in structural elucidation, total synthesis is often pursued for the purpose of providing sufficient material and structural analogues to assist in biological testing, structure-activity relationships (SAR) or for pharmaceutical purposes.

A topical example that illustrates the use of chemical synthesis to establish supply is the industrial synthesis of discodermolide (**1.5**). In 1990, Gunasekera and co-workers reported the isolation and structural elucidation of (+)-discodermolide, derived from the deep sea marine sponge *Discodermia dissolute* (**Figure 1.4**).[35]

1.5
(+)-Discodermolide
antitumour, microtubule stabilizer
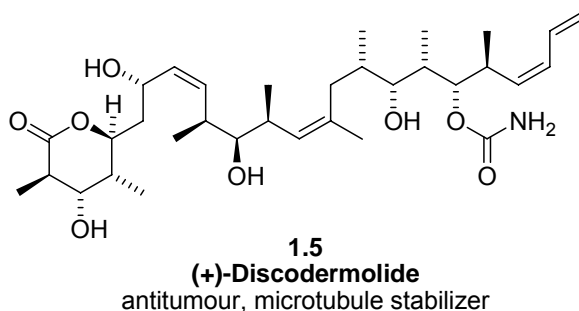
Figure 1.4   (+)-Discodermolide, isolated from *Discodermia dissolute* (0.002% w/w from the frozen sponge).

Subsequently, the groups of ter Haar[36] and Schreiber[37] independently revealed that (+)-discodermolide possesses potent antimitotic activity, akin to the clinically proven anticancer agent Taxol[TM] (paclitaxel), with a similar mechanism of action that entails binding to and stabilising of microtubule structures. Importantly, (+)-discodermolide displayed significant tumour cell growth inhibitory activity against a wide range of known cancer cell lines, including Taxol-resistant cells.[38,39]

The limited availability of discodermolide from natural sources compromised access to practical quantities required to investigate the promising biological activity. Considerable interest in this natural product led to a total synthesis by Schreiber and co-workers,[40] followed by the groups of Smith,[41] Myles,[42] Marshall[43] and Paterson[39,44] and a number of advanced fragment syntheses.[41] Novartis Pharmaceuticals, utilising a hybrid synthetic scheme incorporating elements of the

Paterson, Smith and Marshall routes, were able to prepare 60 grams of (+)-discodermolide in 26 linear steps and 1% overall yield (**Scheme 1.1**).[45]
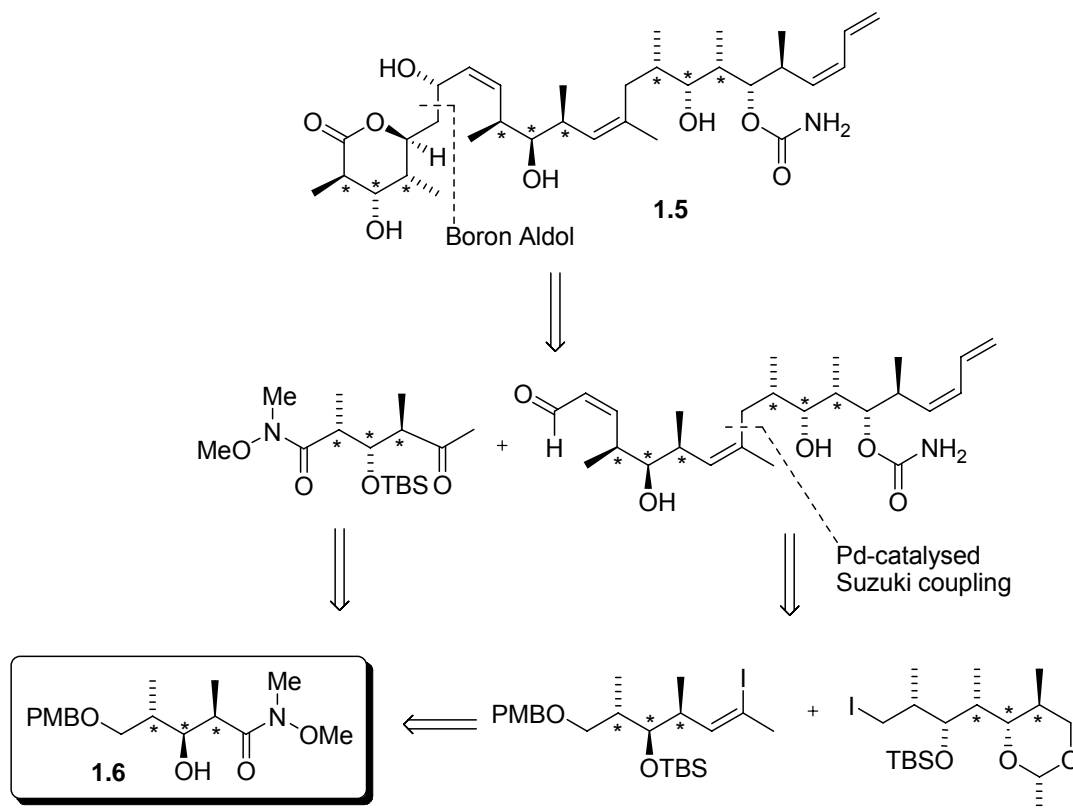
Scheme 1.1   Novartis's retrosynthetic scheme to (+)-discodermolide.

The successful synthesis benefited from the identification of a common stereotriad which is repeated three times in the linear polypropionate chain, allowing the synthesis to proceed from a common precursor (**1.6**), readily available from (+)-*S*-Roche's ester. Successive improvements by the groups of Smith[41] and Paterson,[46] aimed at facilitating large scale production, have reduced the number of steps to 17 and 23 respectively whilst increasing the total overall yield to 9%. These studies have also resulted in the preparation of numerous simplified structural analogues that have assisted in determining the biological profile.[47] The synthetic preparation of significant quantities has allowed (+)-discodermolide to progress to Phase I clinical trials.[7]

As described, chemical synthesis presents an attractive solution to the supply problem. This can either be by *de-novo* synthesis, as in the case of (+)-discodermolide, or *via* semi-synthesis from a naturally available starting material, such as that utilised in the preparation of Taxol™ (paclitaxel) (**1.7**)[48,49] and ecteinascidin 743 (**1.8**)[50-52] (**Figure 1.5**).

1.7
Paclitaxel
from the bark of *Taxus brevifolia*

10-Deacetylbaccatin III
from *Taxus baccata* needles

1.8
Ecteinascidin 743
from marine tunicate
Ecteinascidia turbinata

Cyanosafracin B
via fermentation of bacteria
Pseudomonas fluorescen
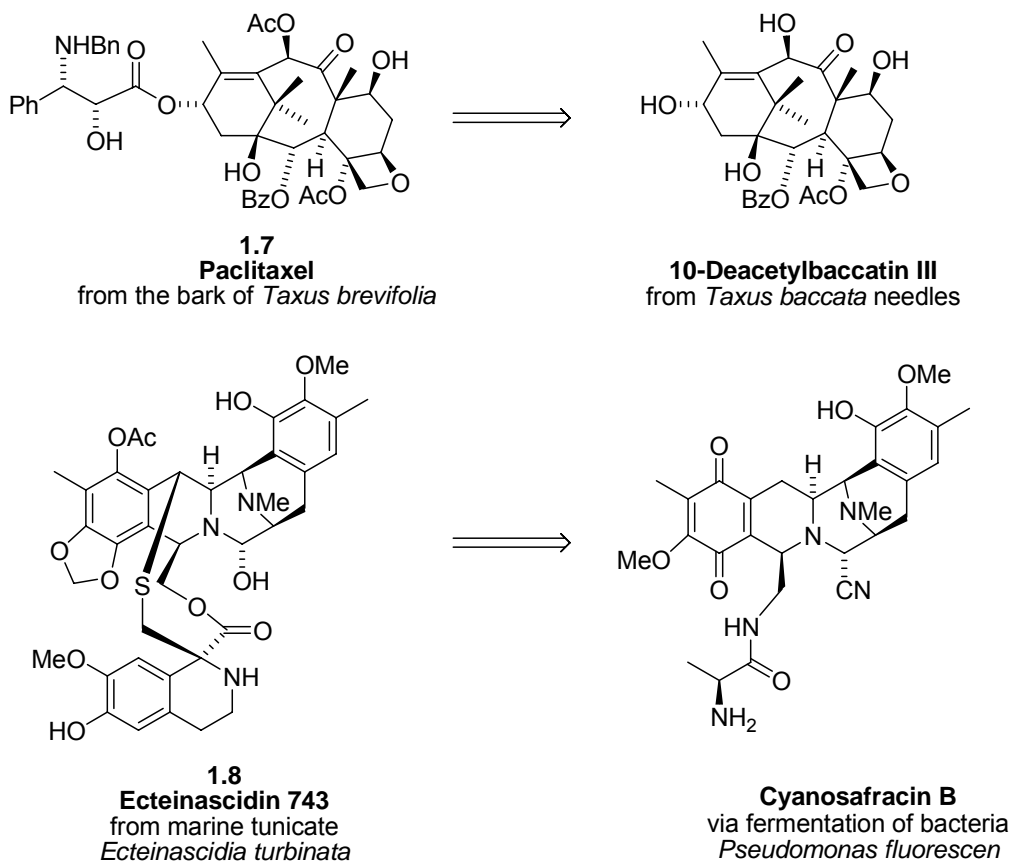
Figure 1.5   Semi-synthetic preparation of pharmaceutical drugs from abundant natural compounds.

Natural products can also be seen as playing a major role in driving forward the science and theory of organic synthesis. The structural diversity presented by natural products encourages the investigation of novel transformations and the discovery and implementation of new synthetic methodology to achieve the total synthesis of these increasingly complex, densely functionalised chemical targets. The structurally complex marine natural products illustrated in **Figure 1.2**, by necessity, have required the development of unique and inventive synthetic transformations in their successful total syntheses.[53]

The continued discovery of new and unique natural products from the marine environment, and the synthetic endeavours conducted towards their total synthesis, represents a strong motivation for the continued development and application of organic synthetic methodology. The advancement of the field of contemporary organic synthesis can be gauged by the ease and the specificity with which selected synthetic transformations can be achieved within such complex systems.

1.4   Marine Natural Product Target Structures

Marine sponges (Phylum *Porifera*) are considered to be primitive organisms with relatively simple internal organisation. Sponges, particularly those without spicules, frequently produce large quantities of secondary metabolites that are thought to deter potential predators and to inhibit the growth of fouling organisms. As many sponges contain symbiotic micro-organisms, there is always some uncertainty concerning the true origin of isolated sponge metabolites. An unusually diverse array of bioactive metabolites have been isolated from various specimens of *Dysidea herbacea*[54] including polybrominated biphenyl ethers (**1.9**), chlorinated nitrogenous metabolites (**1.10**), sesquiterpenoids (**1.11**) and sterols (**1.12**) (**Figure 1.6**).[55-58] It is believed that the majority of terpenoid metabolites are produced by the sponges, possibly in specialised spherulous cells,[59,60] whereas the halogenated metabolites show strong resemblances to metabolites of epiphytic blue-green algae known to co-exist with *D. herbacea.*

| **1.9** | **1.10** | **1.11** | **1.12** |
| | dysideathiazole | arenarol | herbasterol |
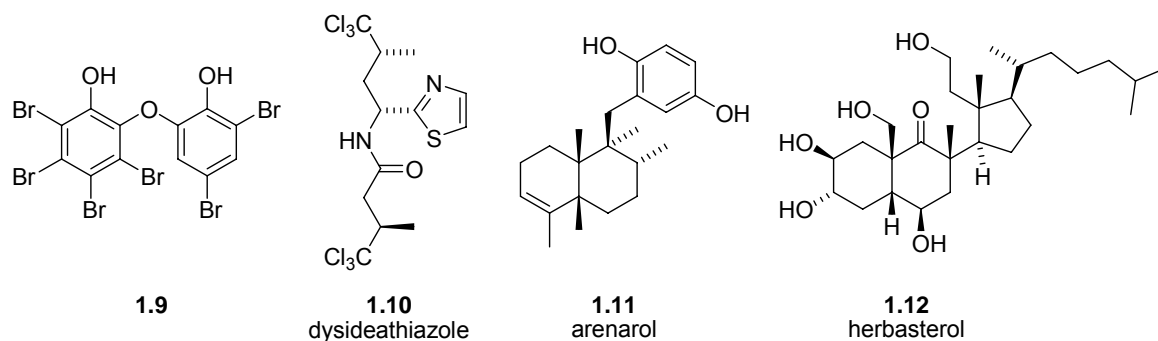
Figure 1.6   Structurally diverse bioactive metabolites isolated from various specimens of *Dysidea herbacea.*

Nudibranchs are marine molluscs of the order *Gastropod*, subclass *Opisthobranchia* which are soft-bodied, unprotected, and highly colourful members of the coral reef ecosystem. Despite

having a sedentary lifestyle and no physical defence mechanisms, they have few predators. In order to deter predation, many nudibranch concentrate selected metabolites from their sponge diet in non-mucous skin-glands located in the dorsum and employ these ichthyodeterrent allomones in defensive secretions. In most cases, the nudibranch can be found in the immediate vicinity of the dietary source of its metabolites, although a few nudibranchs are capable of *de-novo* synthesis of defensive chemicals.[61,62] Most nudibranchs appear capable of modifying dietary chemicals to provide more effective allomones.[63-66]

The discussion of marine metabolites in this thesis will be restricted to those containing the bicyclo[4.3.1]decane core (**1.13**) as a common structural motif (**Figure 1.7**).

1.13
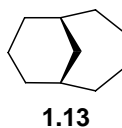
Figure 1.7   Bicyclo[4.3.1]decane core structure common to targeted marine natural products.

1.4.1   Nakafuran Metabolites

Investigation of the marine sponge *Dysidea fragilis,* and the secretions of three distinct nudibranchs (*Phyllidia varicose, Hypselodoris godeffroyana* and *Chromodoris maridadilus*) observed to be grazing on the sponge, resulted in the isolation of the furanosesquiterpenes, nakafuran-8 (**1.14**) and nakafuran-9 (**1.15**) (**Figure 1.8**).[67] These metabolites have antimicrobial activity against a range of bacteria, inhibitory activity against P388 (murine leukaemia) cells in cytotoxicity assays and the capacity to repel reef fish in laboratory assays. It is postulated that the nakafuran metabolites are selectively retained from dietary sources by the molluscs for their defence against predators.[54] A single large nudibranch, (*H. godeffroyana,* 1.5 grams) was extracted with methanol and the purification of the extract led to the isolation of 32 mg of nakafuran-8 and 5 mg of nakafuran-9. This is a remarkable ratio of 2.5% mass to body weight.[67]

In feeding experiments, two species of reef fish, *Chaetodons sp.*, were repelled by the nakafurans **1.14** and **1.15**, whilst another *Dysidea* sesquiterpene, upial (**1.16**), which was not present in the nudibranch, had no repellent properties, indicating a selective retention of ingested metabolites.[67]
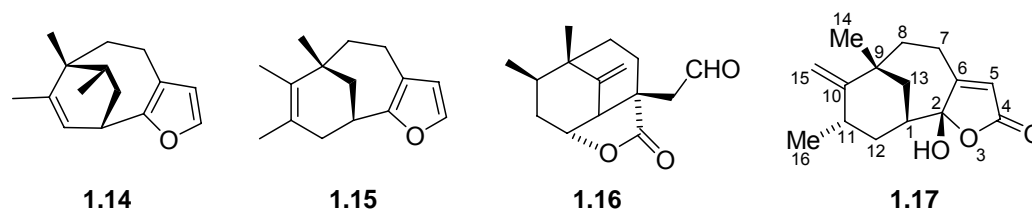
Figure 1.8   Members of the nakafuran family of marine isolates.

In 1999, Sera and colleagues reported the bio-assay guided fractionation of 39 mg of a new furanosesquiterpene (**1.17**), isolated as a pure white solid, from 1.6 kg of *D. herbacea* collected from the Milky Way marine lake in Palau.[68] The structural assignment, based on NMR spectroscopy, was determined to be 2-hydroxy-9,11-dimethyl-10-methylene-3-oxatricyclo-[7.3.1.0^{2,6}]tridec-5-en-4-one.[4]

This bioactive metabolite was observed to exhibit antifouling activity against blue foot mussels (*Mytilus edulis galloprovincialis)* at 100 ppm. The unnamed sesquiterpene possesses structural homology with the nakafuran-9 carbocycle, with the γ-hydroxy-α,β-unsaturated-γ-lactone presumably derived from oxidation of the furan moiety.

Both furan and butenolide sesquiterpene metabolites are common in marine invertebrates.[69] Furan to lactone oxidation *via* a hydroperoxide intermediate is observed with the related metabolite furodysinin (**1.18**), isolated from *Chromodoris funerea,* a nudibranch found on sponges of the *Dysidea* genus.[70] This transformation could be duplicated experimentally by reacting a methanolic solution of **1.18** at -78°C with singlet oxygen, generated photolytically using Rose Bengal as a catalyst, to yield the hydroperoxide **1.19**. Oxidation with manganese dioxide yielded the *O*-methoxyfurodysinin lactone **1.20** (**Scheme 1.2**).
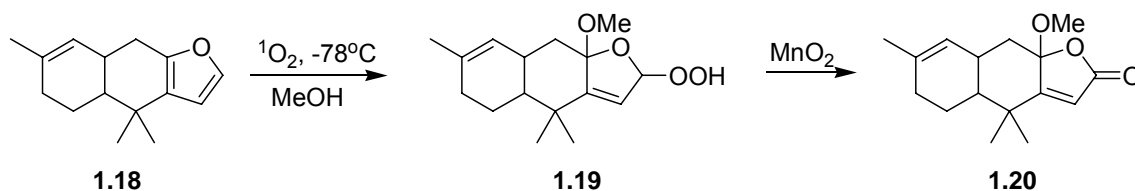
Scheme 1.2   Synthetic oxidation of furodysinin.

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[4] Flowers *et al.* used a numbering system for the nakafuran-9 series (**1.15**) which commences from the furan CH, while Sera *et al.* and Fusetani *et al.* number from the bridgehead atom adjacent to the furan.

1.4.1.1   Biological Origins

The biogenetic origin of the nakafuran skeleton is postulated to be an extension of established biogenetic transformations.[67] Farnesylpyrophosphate (**1.21**) serves as a starting material for a large number of naturally occurring sesquiterpenes.[62] As indicated in **Figure 1.9**, sequences involving transannular carbocation cyclisations, cationic rearrangement and oxidations give rise to the drimane, pallascensin, microcionin and nakafuran families of natural products observed in *Dysidea sp.*[62,71]
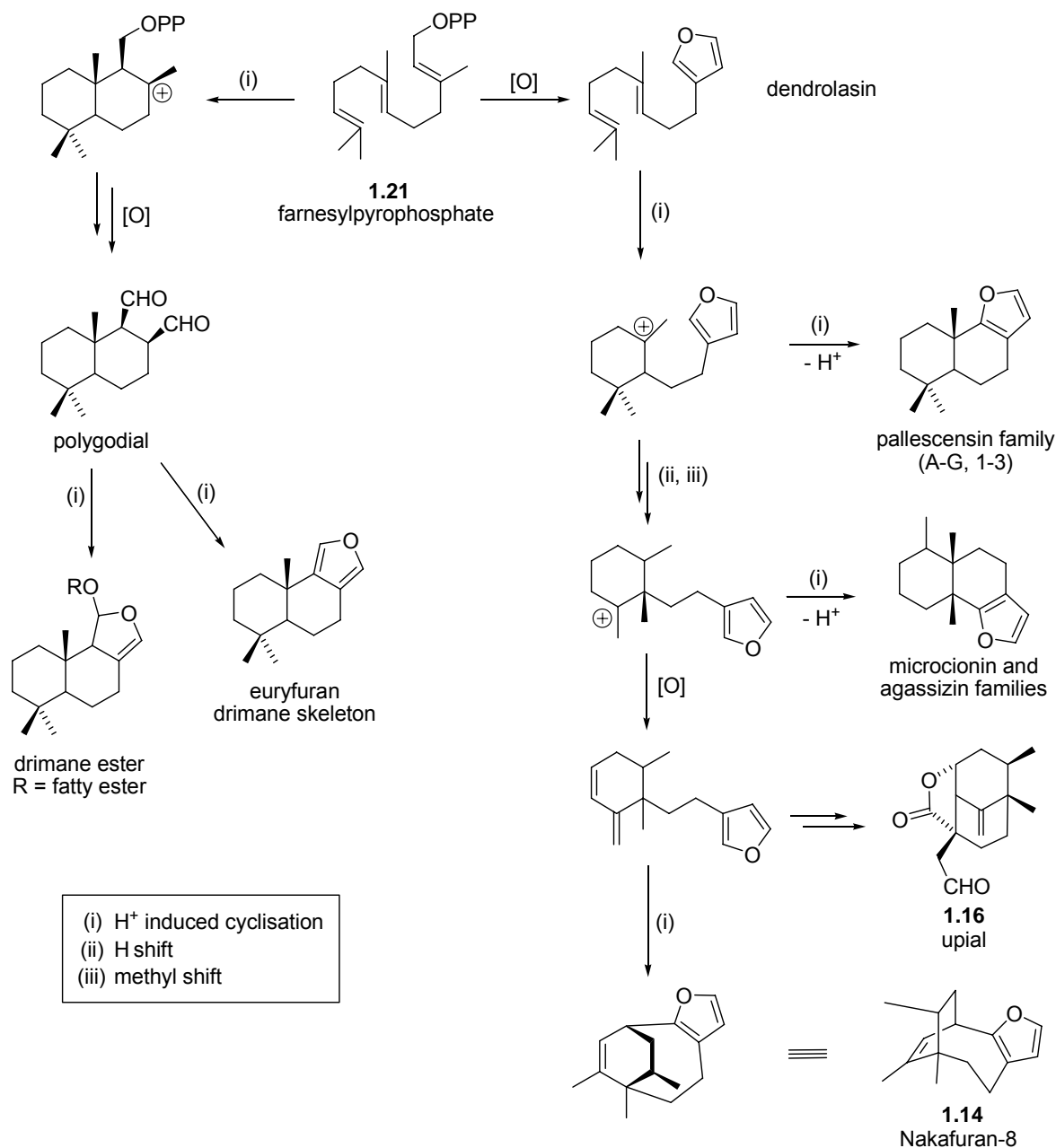
Figure 1.9   Postulated biological origin of a number of marine secondary metabolite families.

Nakafuran-8 (**1.14**) can participate in further rearrangement *via* a Wagner-Meerwein-like carbocation intermediate. Elimination of a β-hydrogen gives rise to three isomeric nakafuran-9 species **1.22**, **1.23** and **1.15**, differing only in the position of the double bond. As discussed for furodysinin, sequential oxidation of the furan moiety to a hydroperoxide and then butenolide gives rise to the known isolated nakafuran natural products **1.17** and **1.24-1.26** (**Figure 1.10**).[71-74]
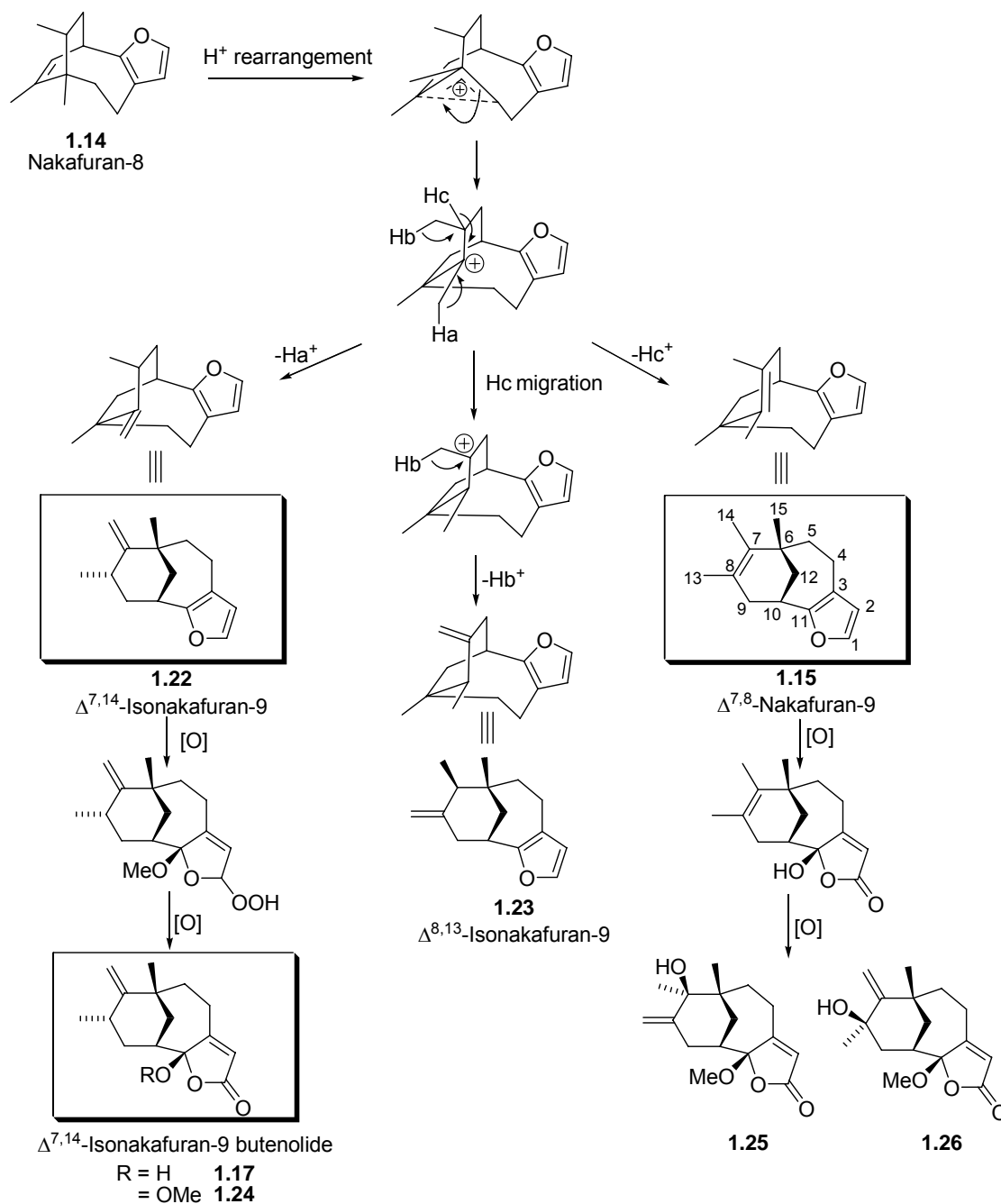
Figure 1.10   Extension of the postulated biogenetic pathway to provide for the synthesis of the known members of the nakafuran family of marine natural products.

1.4.1.2   Prior Syntheses

Tanis and Herrinton disclosed a route to the nakafuran family of metabolites exploiting a cationic π-cyclisation in the construction of the bridged ring system.[75] The cyclisation precursor was prepared *via* a sequence commencing with the conjugate addition of a methylfuryl cuprate to vinyl epoxide **1.27**. Subsequent manipulations yielded the enone **1.28** required for the electrophilic addition. Cyclisation was effected with a biphasic mixture of anhydrous formic acid and cyclohexane, affording the bicyclo[4.3.l]decanone **1.29** as a 60:40 mixture at C7. The methyl group and double bond were introduced *via* a Wittig reaction with subsequent double bond migration under acidic conditions yielding a 95:5 mixture of nakafuran-9 (**1.15**) and $\Delta^{8,9}$-isonakafuran-9 (**1.30**) (**Scheme 1.3**).
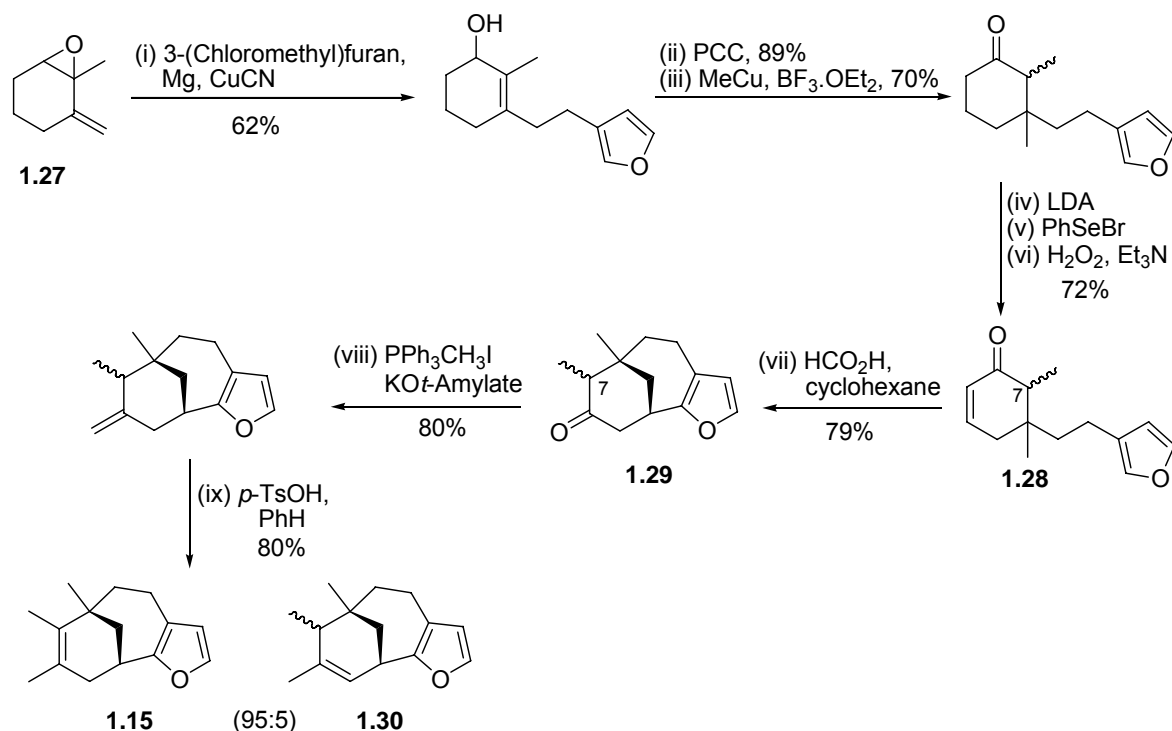
Scheme 1.3   Cationic π-cyclisation formation of the bicyclo[4.3.1]decane system.

Uyehara *et al.* reported the synthesis of nakafuran-8, in which they constructed the bicyclo[4.2.2]decadiene skeleton *via* sequential Shioiri ring enlargement[76,77] of a bicyclo[2.2.2]oct-5-en-2-one ring system (**1.31**).[78] The ring expansions also generated significant amounts of the isomeric bridged bicyclic ketones (~30% of isolated crude product), resulting from insertion of the carbene at the bridgehead carbon. Alkylation with excess ethyl iodoacetate

to generate the keto ester **1.32**, was followed by hydrolysis, lactonisation and reduction to furnish nakafuran-8 (**1.14**) (**Scheme 1.4**).
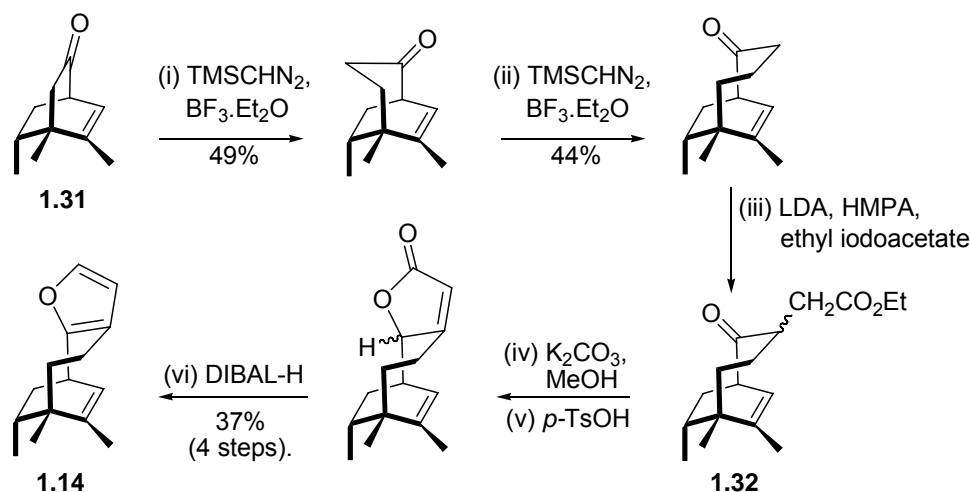
Scheme 1.4   Ring expansion route of a bicyclo[2.2.2]octane skeleton to nakafuran-8.

White *et al.* reported the free radical annulation of an olefinic β-keto ester **1.33**, mediated by Mn(OAc)$_3$, to form the bicyclo[4.3.l]decane core **1.34** in a synthesis of 2,3-dihydropallescensin D (**1.35**) (**Scheme 1.5**).[79]
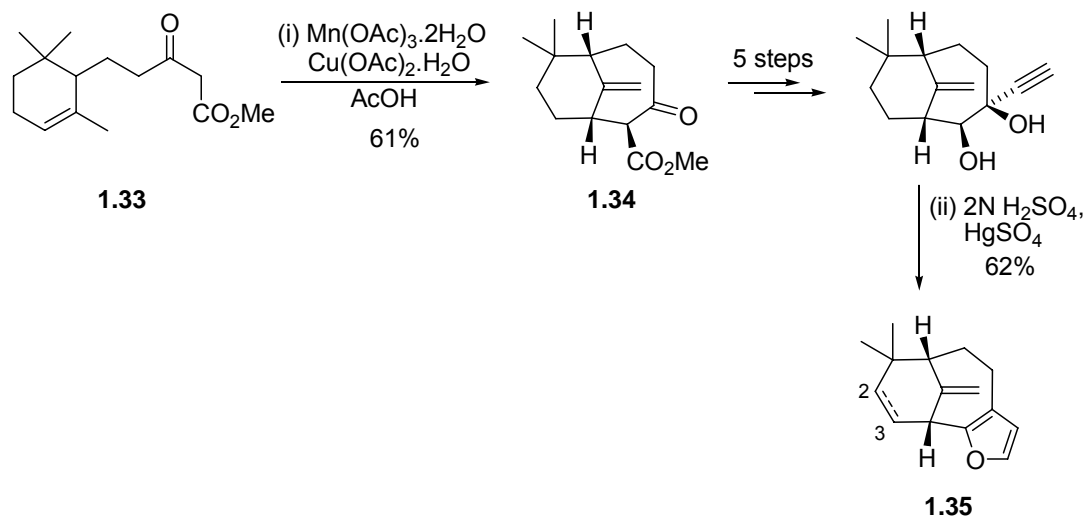
Scheme 1.5   Manganese(III) mediated cyclisation to derive the bicyclo[4.3.1] core.

Also pertinent to the synthetic preparation of the nakafuran compounds was the initial report detailing the isolation of Δ^{7,14}-nakafuran by Flowers *et al.* which indicated that it was possible to isomerise the Δ^{7,14}- (**1.22**) and Δ^{8,13}-nakafuran (**1.23**) to the Δ^{7,8}-nakafuran-9 (**1.15**) using mild acid catalysis, (*p*-TsOH, benzene, reflux, 20 min).[73]

1.4.2   Xenicane Metabolites

Xenicanes are a class of diterpenes and norditerpenes isolated from soft corals of the genus *Xenia*, (order *Alcyonacea*, family *Xeniidae*), but are also frequently found in the brown algae genus *Dictyolaceae*. Isolated metabolites have been found to possess substituted bicyclo[7.4.0]tridecane, bicyclo[7.2.0]undecane or bicyclo[4.3.1]decane ring structures, presumably derived from a common xeniaphyllenol precursor. Xenicanes (**1.36**) are diterpenoid analogues of the caryophyllene (**1.37**) class of natural products, which are common herbaceous secondary metabolites (**Figure 1.11**).[80-83]

The structure of xenicin (**1.38**), a metabolite of *Xenia elongate*, was established by single crystal X-ray diffraction in 1977 by Schmitz *et al.*[84] Numerous examples have subsequently been isolated from the xenicane family and can be classified into five main groups; xenicins (possessing a 11-oxabicyclo[7.4.0]tridecane ring system), xeniolides (the lactone derivatives of the xenicins), xeniaphyllanes (having a bicyclo[7.2.0]undecane ring system), xeniaethers (bearing a oxabicyclo[7.3.0]undecane ring system), and more recently, the azamilides and dictyotadial groups (with an opened A-ring and the nine-membered monocarbocyclic skeleton acylated with a series of C16-C20 saturated fatty acids) (**Figure 1.11**).[69,85] The xenicanes display biological activity, including ichthyotoxicity, cytotoxicity, anti-inflammatory and antifungal activities.
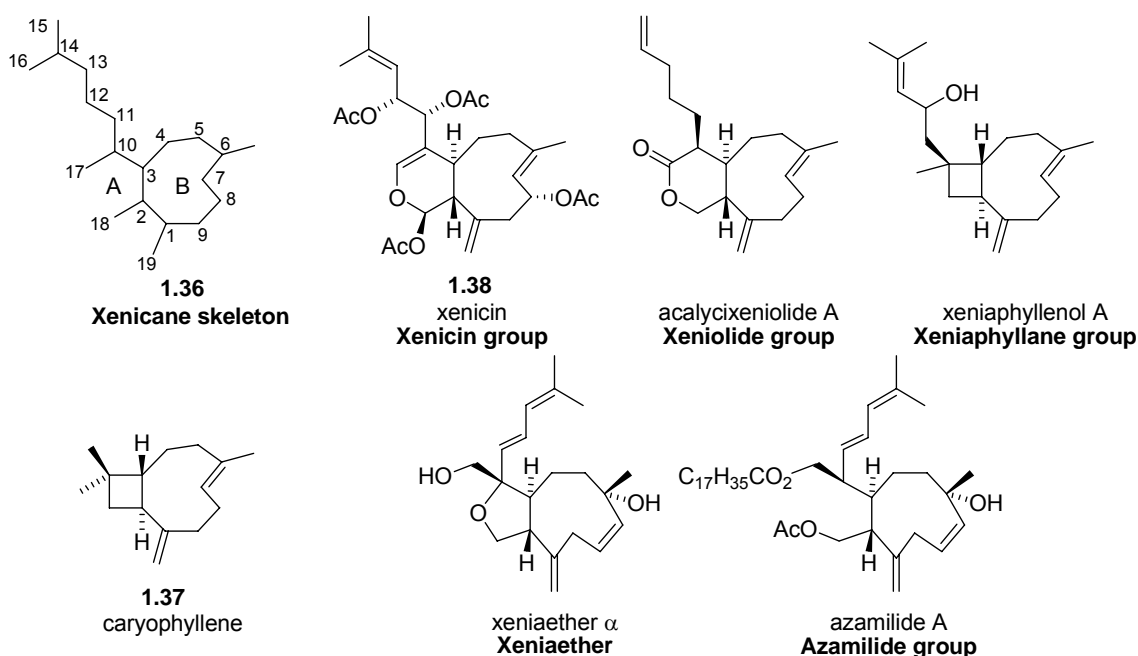
Figure 1.11   Structures of the five main groups of the xenicane family, bearing the xenicane skeleton **1.36**.

The proposed biosynthesis of the xenicane skeleton **1.36** is based on the initial transannular carbocation cyclisation of geranylgeraniol pyrophosphate (**1.39)** to the xeniaphyllane core **1.40**. Subsequent modification through a series of oxidation, reduction and cyclisation pathways forms a profusion of natural products, members of which are illustrated in **Figure 1.12**.[86] Members of the xenicane sub-families contain variable carbon oxidation states, including hydroxylation or epoxidation of the double bonds, variable oxidation levels of alcohol and carbonyl functionality, extensive double bond migration, and halogenation.
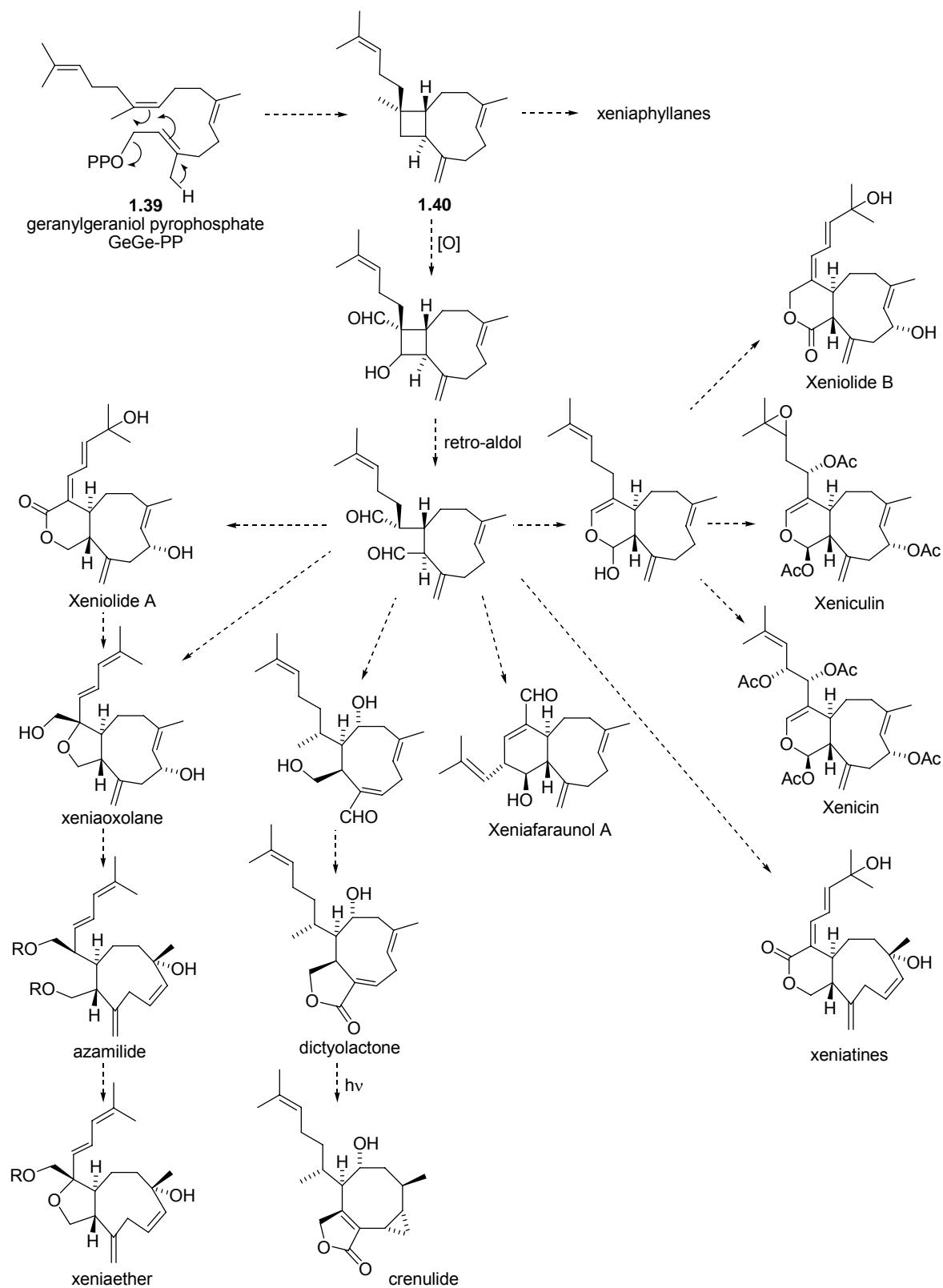
Figure 1.12   Postulated biosynthetic pathways to members of the xenicane family from geranylgeraniol pyrophosphate.

1.4.3   Florlide Metabolites

The second class of natural products that are of synthetic interest to this dissertation are the related florlide and florether families which contain the bicyclo[4.3.1]decane core **1.13** (**Figure 1.13**).

R = OH Florlide A **1.41**	R = β-CH$_2$OH Florether A **1.43**	R^1 = OAc R^2 = OH R^3 = OH **1.45**
R = H Florlide B **1.42**	R = α-CH$_2$OH Florether B **1.44**	R^1 = OH R^2 = OH R^3 = OH **1.46**
		R^1 = OAc R^2 = OAc R^3 = OAc **1.47**

R = H Florlide C **1.48**	R^1 = CHO R^2 = OH Floridicin **1.51**	Floridicin B (*Z*) **1.54**
R = OH Florlide D **1.49**	R^1 = CHO R^2 = OMe *O*-Methyl floridicin **1.52**	Floridicin C (*E*) **1.55**
R = OOH Florlide E **1.50**	R^1 = CH$_2$OH R^2 = OH Floridicin A **1.53**	
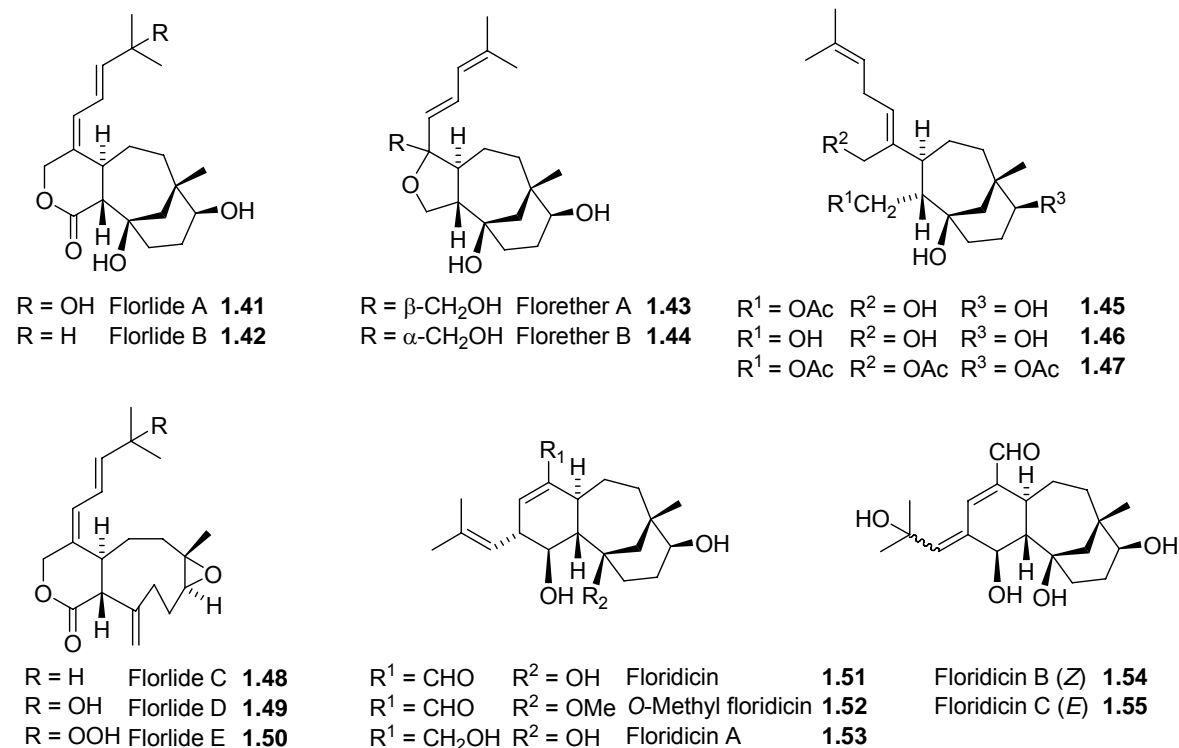
Figure 1.13   Florlide, florether and floridicin natural products.

Iwagawa proposed that the Florlide C (**1.48**) and D (**1.49**) epoxy-nonane skeletons are the biosynthetic precursors of the Florlide A (**1.41**) and B (**1.42**) bicyclo[4.3.1]decane core *via* a hydrolytic *6-endo-Tet* transannular epoxide cleavage (**Figure 1.14**).[87,88] A similar rearrangement can be assumed for the formation of the floridicin core from the xeniafaraunol skeleton. The recently reported Xenibellol A (**1.56**),[89] which contains a tetrahydrofuran ring, presumably arises *via* an alternative *4-exo-Tet* transannular cyclisation.[90,91]
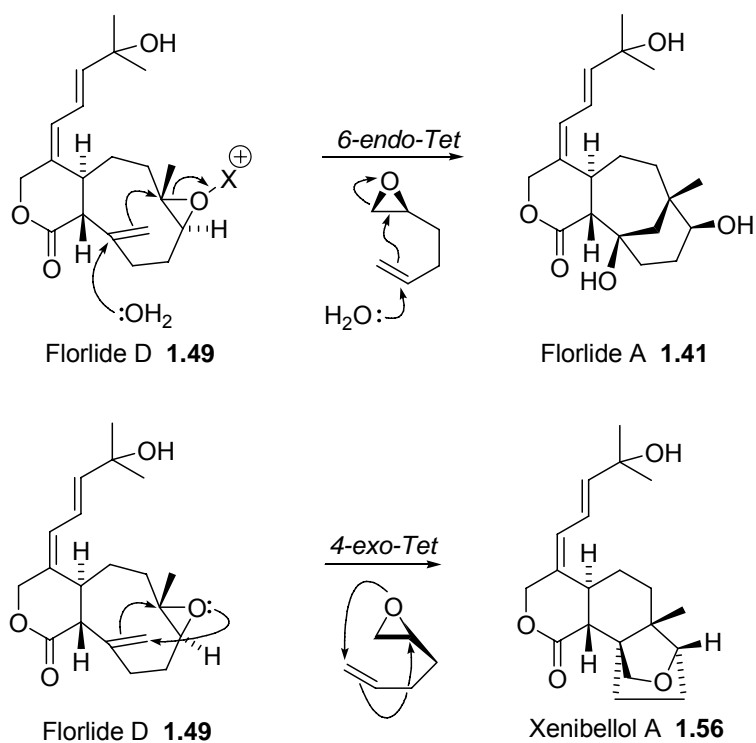
Figure 1.14   Proposed biogenesis of Florlide A and Xenibellol A.

The predisposition for this rearrangement was observed in the pursuit of the total synthesis of coraxeniolide A (**1.57**) by Leumann *et al.*[92] An attempt to oxidise the acetal **1.58** to lactone **1.59**, using a two step protocol involving acidic hydrolysis of the methyl acetal followed by treatment with Fetizon's reagent (Ag_2CO_3 on Celite), resulted in the isolation of a 1:1 mixture of bicyclo[4.3.1]decane core isomers **1.60** in 61% yield. Despite variation in the nature and concentration of the acid (H_2SO_4, HCl, AcOH) **1.60a** and **1.60b** were always isolated as the main products (**Scheme 1.6**). Similar carbocation-induced transannular cyclisations are well-known in the caryophyllene series.[93]
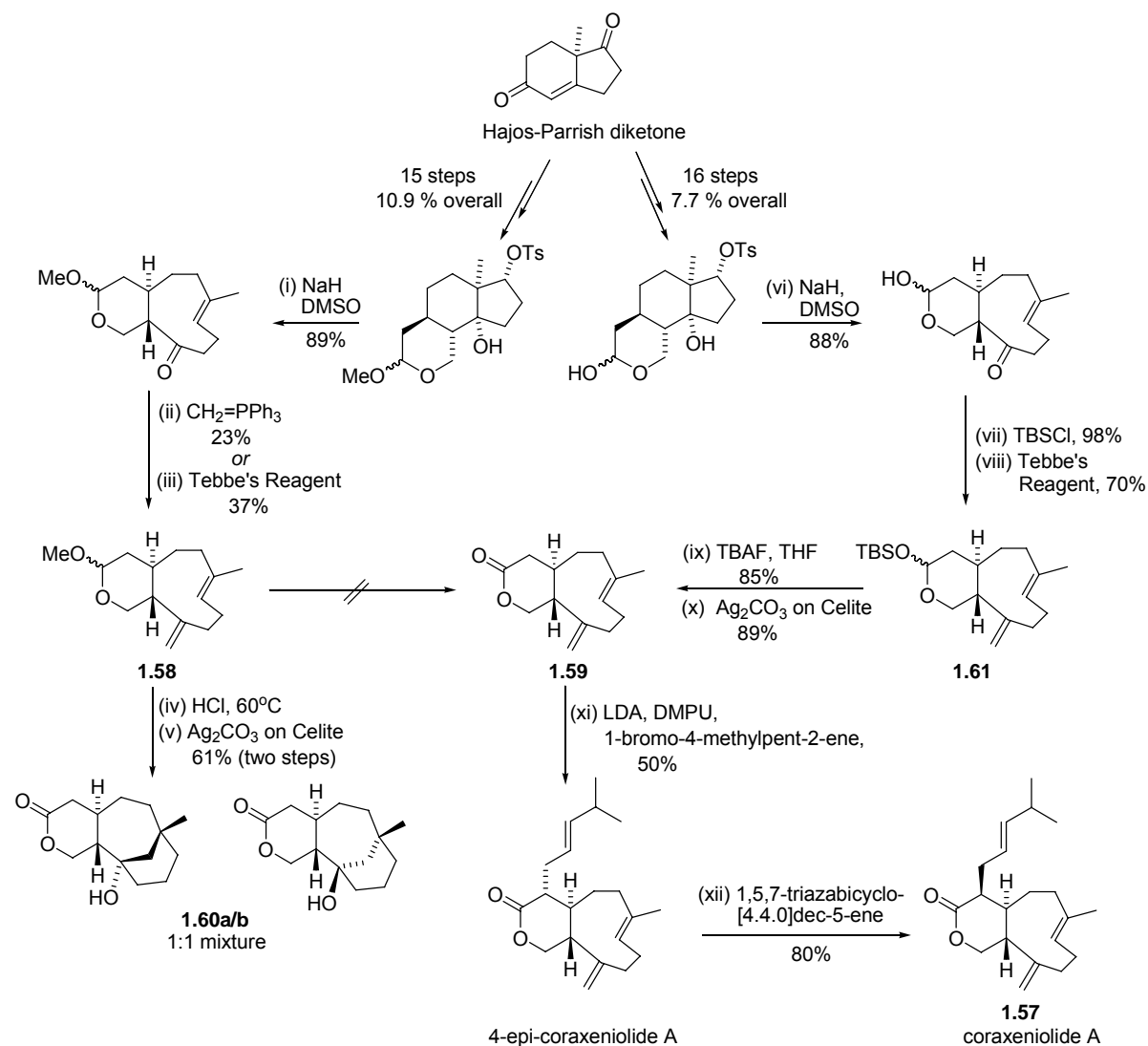
Scheme 1.6   Leumann *et al.*'s synthesis of coraxeniolide A.

A solution to this problem was found by employing the TBS-silyl acetal **1.61** which simultaneously increased the yield of the *exo*-methylene formation and allowed deprotection under basic conditions. Oxidation to the desired lactone **1.59** occurred without any observed transannular cyclisation products.

In this context it can be seen that the florlide skeleton is closely related to the xeniolide core structure.

1.5   Retrosynthetic Approach

The nakafuran and florlide natural products targeted in this thesis all contain the common motif of a 6-methyl-bicyclo[4.3.1]decane core **1.62** (**Figure 1.15**).
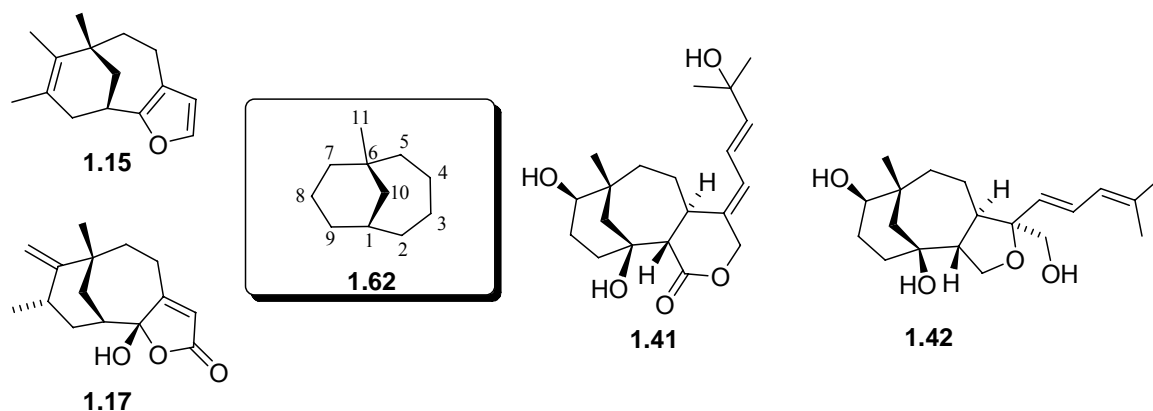
Figure 1.15   Targeted natural products that contain the core structure **1.62**.

In addition to the common carbon skeleton (**1.62**), the nakafurans and florlides possess a similar disposition of functional groups upon the ring system. The synthesis of a common intermediate 7-alkoxy-bicyclo[4.3.1]dec-6-en-2-one (**1.63**) could be envisaged to allow selective elaboration to both target systems. As such, the preparation and functionalisation of this molecule is central to both retrosynthetic schemes as depicted in **Scheme 1.7**.
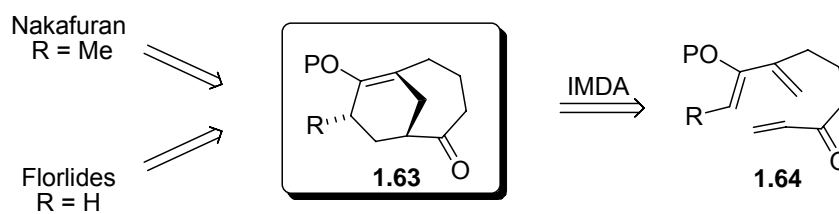
Scheme 1.7   The central retrosynthetic concept showing the pivotal transformation of an acyclic triene **1.64** to the bridged bicyclic system **1.63**.

The proposed retrosynthetic routes to **1.63** feature a type II intramolecular Diels-Alder reaction (IMDA) as the key transformation to secure the desired bicyclo[4.3.1]decane core (**Schemes 1.8** and **1.9**). The IMDA reaction has been demonstrated to achieve facile access to bicyclo[4.3.1] and bicyclo[5.3.1] ring systems in a single step from acyclic precursors. The utility of this reaction can be seen in the recent application of type II IMDA reactions in the total synthesis of a number of complex natural products (**Chapter Three**).

It is necessary to ensure that sufficient functionality is present in the acyclic precursor **1.64** to allow subsequent modification of the Diels-Alder adduct **1.63** to readily conclude the synthesis. In this respect the C2 ketone is integral to installation of the furan moiety, in the case of the nakafurans, and the conjugated olefinic system at C3 of the florlide metabolites. The $\Delta^{6,7}$-olefinic bond and the C7 ether will assist in establishing the C6 quaternary bridgehead methyl group and the C7 oxidation state. Introduction of the appropriate functionality is advantageous prior to cyclisation in terms of end game analysis, but the functionality should not hinder the IMDA reaction from occurring.

1.5.1   Nakafuran Retrosynthetic Analysis

The proposed route for the synthesis of a number of nakafuran natural products is depicted in **Scheme 1.8**. The formation of $\Delta^{7,14}$-nakafuran-9 (**1.22**) constitutes one of the primary objectives of this synthetic scheme, as it will serve as an intermediate which can be used to access a number of closely related nakafuran products. Isomerisation of the $\Delta^{7,14}$-olefinic bond to the $\Delta^{7,8}$ position under acidic conditions will generate nakafuran-9 (**1.15**), whereas photochemical oxidation of the furan functionality with singlet oxygen, and subsequent reduction will generate the butenolide functionality of the recently isolated natural product target (**1.17**).
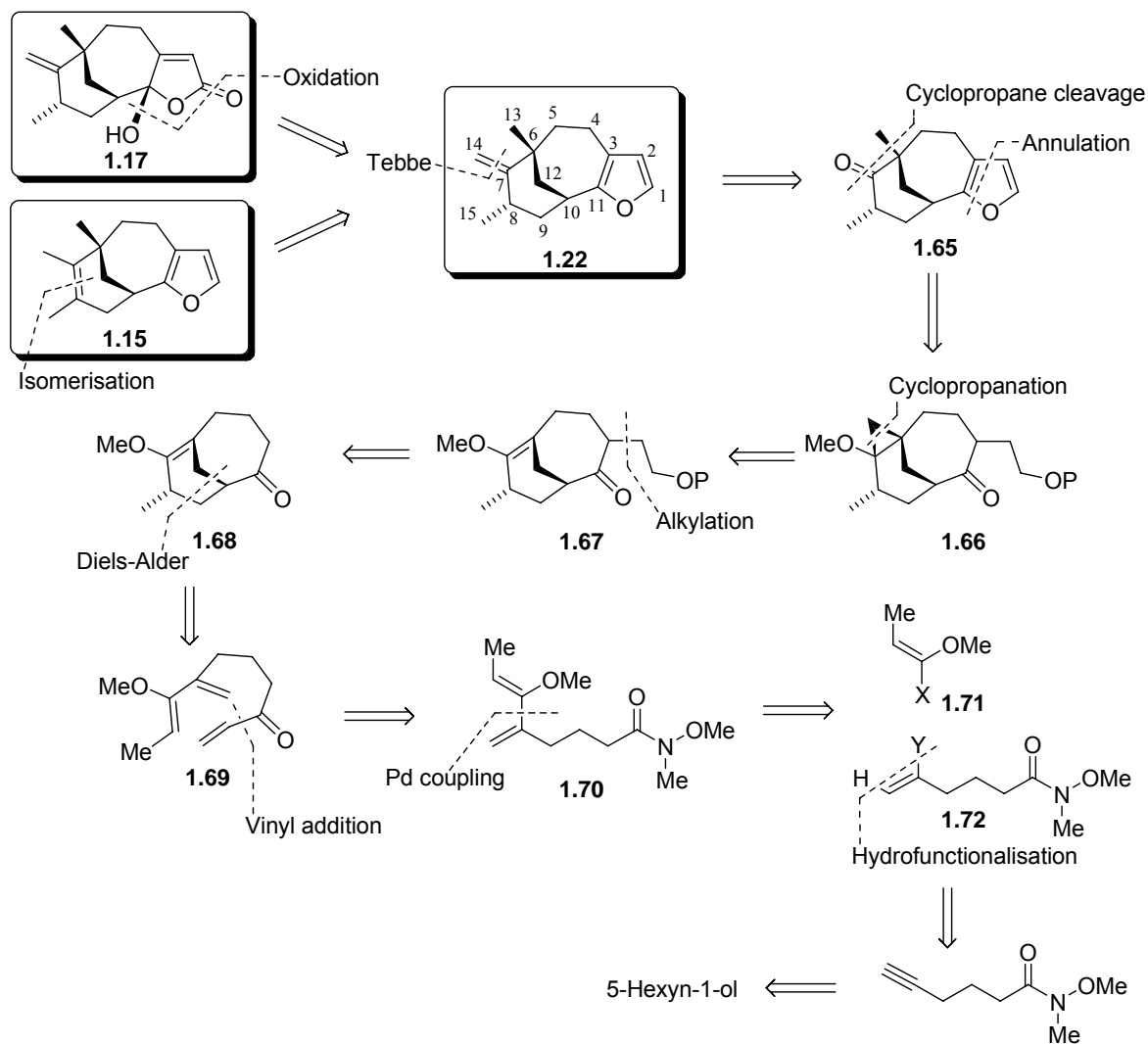
Scheme 1.8   Retrosynthetic scheme for the synthesis of the nakafuran compounds **1.15**, **1.17** and **1.22**.

It is anticipated that deprotection and oxidation of the C3 side-chain of **1.66** to an aldehyde should establish the requisite functionality to effect the one-step furan annulation with a concomitant C7 methyl-ether hydrolysis-cyclopropane cleavage reaction to generate **1.65**. To deliver the desired quaternary C6 methyl group, it is crucial that the external C7-C13 cyclopropane bond is regioselectively cleaved in preference to the internal C6-C7 bond. Application of the Tebbe reaction conditions to the newly revealed C7 ketone of **1.65** should allow installation of the exocyclic methylene group to form $\Delta^{7,14}$-nakafuran-9 (**1.22**).

The formation of **1.66** can be envisaged *via* the sequential regioselective alkylation at C3 on the cycloheptane ring of **1.68** adjacent to the C2 ketone functionality and cyclopropanation of the $\Delta^{6,7}$-bridgehead alkene.

The IMDA adduct **1.68**, derived from the cyclisation of the triene precursor **1.69**, represents the key intermediate in this retrosynthetic sequence. The Diels-Alder reaction will simultaneously form the carbocyclic core structure, establish the desired stereochemistry of the C15 methyl group relative to the bridgehead and position the olefinic bond at the C6-C7 bridgehead position to allow subsequent cyclopropanation.

The palladium-catalysed cross-coupling of two appropriately functionalised fragments **1.71** and **1.72** would result in the stereoselective formation of the Weinreb amide **1.70**. Exposure of this adduct to vinylmagnesium bromide should result in the generation of the triene system **1.69** required for the Diels-Alder cyclisation. The two coupling fragments **1.71** and **1.72** will be stereoselectively prepared from 5-hexyn-1-ol and 1-methoxypropyne respectively.

1.5.2   Florlide Retrosynthetic Analysis

Retrosynthetically, a similar sequence can be envisaged to achieve a synthesis of the florlide and florether natural products (**Scheme 1.9**). From the common intermediate **1.73**, esterification leads to the florlide products **1.41**. Reduction and subsequent nucleophilic addition to the extended Michael acceptor of **1.74** delivers the desired florether core structure **1.43**. It is anticipated that **1.73** would be accessible *via* the conjugate addition of the mixed cuprate species **1.75** to **1.76**. Consideration of the molecular conformation of **1.76** indicates that cuprate addition should occur predominantly from the less hindered convex face of the bicyclo[4.3.1]decene core. This would deliver the thermodynamically more stable *trans*-stereochemical relationship between the unsaturated chain and the ester group present in **1.73**. Installation of the C6 quaternary methyl and C7 hydroxyl groups can be achieved *via* cyclopropane cleavage and reduction of the resultant ketone as described in the nakafuran retrosynthetic scheme (**Scheme 1.8**). Formation of the C2,C3 α,β-unsaturated ester is envisaged to occur *via* the palladium-catalysed carbonylation of an enol triflate derived from the C2 ketone of **1.78**.

Insertion of the C1 bridgehead hydroxyl group observed in the florlide and florether targets will be achieved *via* the regioselective hydroxylation of the C1 bridgehead carbon, under conditions of kinetic deprotonation developed by Shea *et al.* for a closely related bicyclo[5.3.1]decane system.[94]

The synthetic methodology required to deliver the cyclopropanated intermediate **1.78** and precursors to this species (**1.79**, **1.80**, **1.81** and **1.82)** closely resemble those required in the synthesis of the nakafuran IMDA product **1.68**. The palladium-catalysed coupling, however, utilises the enol ether **1.82** to generate the conjugated diene **1.81**, instead of the three carbon propene equivalent used in the nakafuran synthesis.
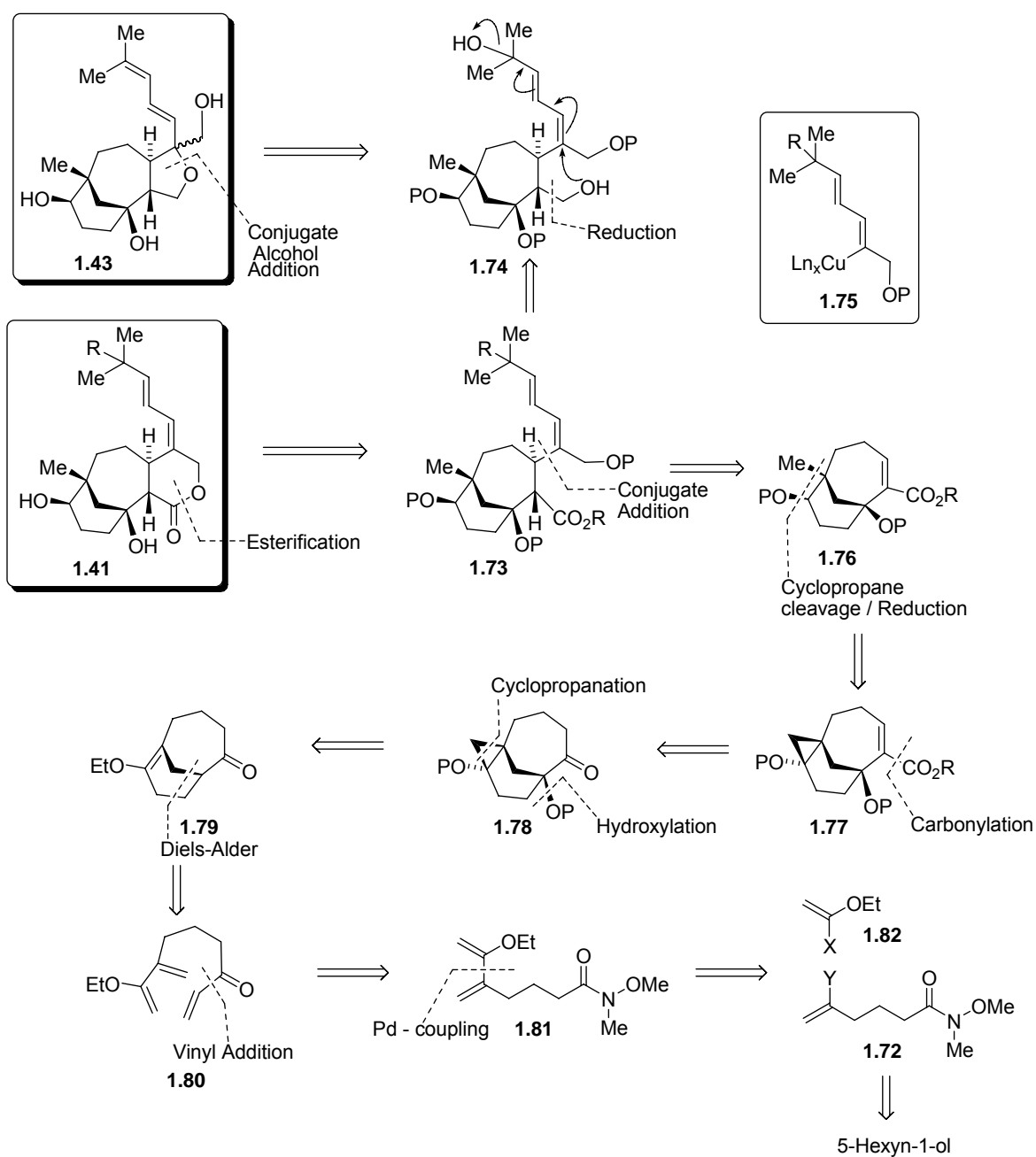
Scheme 1.9   Retrosynthetic scheme for the synthesis of the florlide compounds **1.41** and **1.43**.

1.6   Work Described in this Thesis

The research described in this thesis deals with the synthetic studies conducted to form the bicyclo[4.3.1]dec-6-en-2-one core common to the nakafuran and florlide marine natural products. Elaboration of these intermediates towards the total synthesis of these products is detailed.

The initial aims of this research were as follows:

- To design a method for the synthesis of type II IMDA precursors of variable functionality and investigate their reactivity with respect to forming the desired bicyclo[4.3.1]dec-6-en-2-one carbocycles.
- To elaborate the bicyclic intermediates so as to obtain routes to the nakafuran-9 natural product and related metabolites.
- To design and implement a synthesis of the florlide natural product sidechain and stereoselectively introduce it into the elaborated carbocycle to provide access to the florlide and florether natural products.

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Gamboni, R.; Chen, S.; Chen, W.; Jagoe, C. T.; Kinder, F. R., Jr.; Loo, M.; Prasad, K.; Repic, O.; Shieh, W.-C.; Wang, R.-M.; Waykole, L.; Xu, D. D.; Xue, S. *Org. Process Res. Dev.* **2004**, *8*, 92-100.

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Chapter Two

Preparation of IMDA Precursors

2.1 Analysis of the Retrosynthetic Scheme

The central transformation of the proposed syntheses is a type II intramolecular Diels-Alder (IMDA) reaction, which should allow a rapid and stereoselective formation of the bridged bicyclic core **1.68**, as depicted in **Scheme 2.1**. The stereochemical outcomes of IMDA processes are increasingly predictable on the basis of well-established concepts such as diene-dienophile conformational geometry, non-bonding interactions in the transition-state and extensive empirical observation.[1-4] Based upon such considerations, a *cis*-diene structure **1.69** is required to deliver the desired anti-relationship between the methyl group and the bridgehead carbon, observed in the natural product target **1.17**.
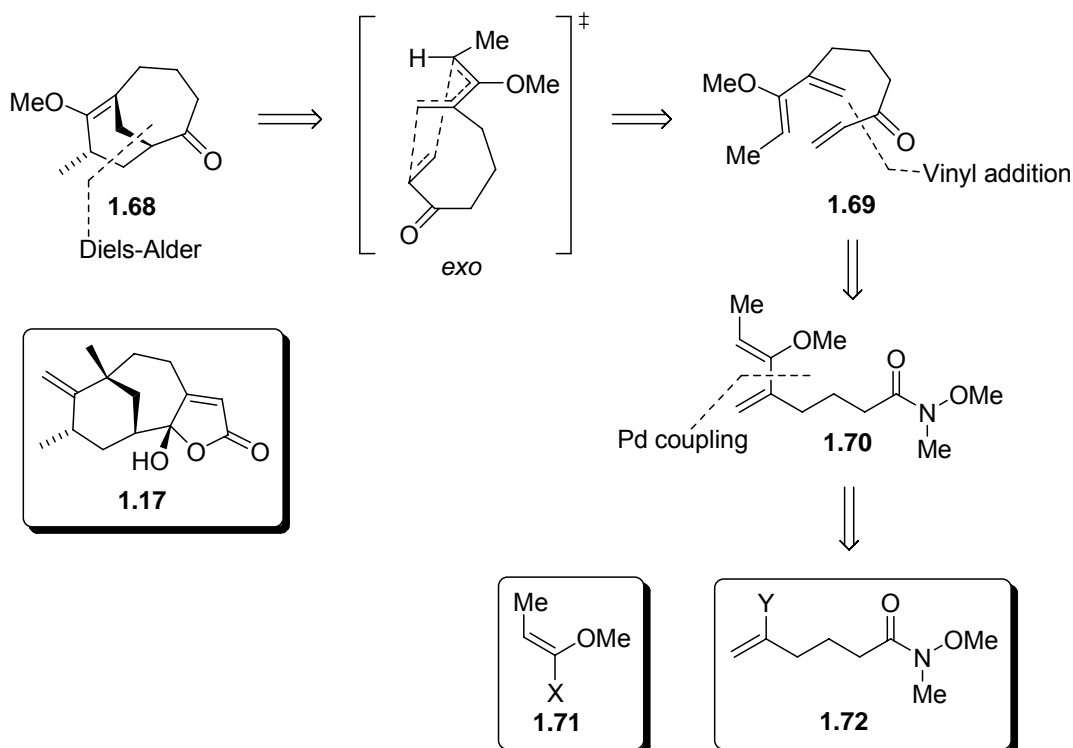
Scheme 2.1 Retrosynthesis of **1.68** derives coupling fragments **1.71** and **1.72**.

The stereoselective synthesis of triene **1.69** is envisaged to be secured through a palladium-catalysed cross-coupling reaction of two fragments, **1.71** and **1.72**, to yield the diene system **1.70**. The nature of the X and Y groups in the coupling fragments are variable and transposable, such that palladium-catalysed couplings can be conducted utilising a number of different methodologies such as Stille (Sn, Halogen), Negishi (Zn, Halogen) and Suzuki (B, Halogen). The flexibility incorporated into these two complementary coupling fragments should allow access to a number of synthetic analogues and coupling protocols.

2.2   Transition Metal-Catalysed Cross-Coupling Reactions

At the most basic level, organic synthesis focuses on the controlled chemo-, regio- and stereoselective formation of carbon-carbon bonds. The discovery of nickel- and palladium-mediated cross-coupling reactions between organometallic Grignard reagents and sp^2 alkenyl-halides can be viewed as the seminal discovery that has revolutionised the practice of organic synthesis in the past few decades.[5] The original protocols have been substantially improved and expanded to include the coupling reactions of a wide range of organometallic compounds.[6-12] Applications of these protocols allow the transformations of organic molecules in manners not achievable by traditional synthetic methods. As such, transition metal-catalysed cross-coupling reactions have become a simple yet indispensable method to achieve often complex transformations of organic molecules.

The general reaction for the cross-coupling of an organometallic reagent (R-M) with an organic electrophile (R_1-X) mediated by the presence of a Group 8-10 metal-catalyst [M] is depicted in **Figure 2.1**. These reactions are accessible for a range of organometallic reagents and electrophiles, and are characterised to a large extent by the simplicity of synthesis of the reagents, the ease of isolation of products and the compatibility of coupling conditions with a wide range of functional groups.

$$R\text{-}M \quad + \quad R_1\text{-}X \xrightarrow{\text{[M]}} R\text{-}R_1$$

M	= Li	(Murahashi)
	= Mg	(Kumada-Tamao, Corriu)
	= B	(Suzuki-Miyara)
	= Al	(Nozaki-Oshima, Negishi)
	= Si	(Tamao-Kumada, Hiyama-Hatanaka)
	= Zn	(Negishi)
	= Cu	(Normant)
	= Zr	(Negishi)
	= Sn	(Migita-Kosugi, Stille)

cat. [M] = Ni, Pd, Cu, Rh, Fe, ...

X = I, Br, Cl, OTf

R, R_1 = alkynyl, alkenyl, aryl, allyl, alkyl, ...
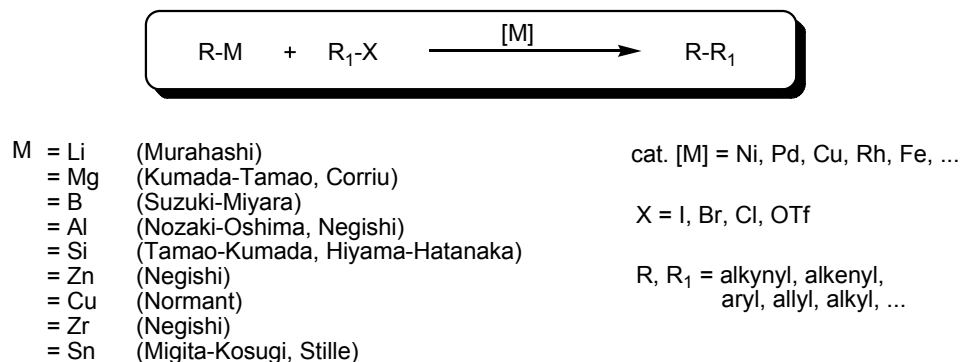
Figure 2.1   Transition metal-catalysed cross-couplings.

The reaction of lithium and magnesium Grignard reagents with electrophiles, in the presence of catalytic amounts of a transition metal, were first discovered by Kochi and Tamao[13] and by Kumada.[14] However these highly electropositive metal reagents displayed appreciable nucleophilicity and basicity, which restricted the functionality that could be incorporated in the coupling species. Successive extensions of this methodology saw the use of less reactive organometallic reagents (Li, Mg → Al, Zn, Zr, Cu → Sn, B, Si) which allowed greater functional group compatibility in the cross-coupling. Investigations revealed that the use of coordinating phosphine-ligand metal complexes diminished the extensive homocoupling, previously observed with unsupported transition metal salts, and that palladium-catalysed processes proceeded in greater yield and with superior retention of stereochemistry than the analogous nickel-catalysed reactions. The utilisation of highly covalently bonded carbon-metal organometallic reagents such as organostannanes, organoboranes and organosilanes, allowed the isolation and purification of these intermediates, ensuring highly homogenous stereochemical yields in subsequent cross-coupling reactions.

The advantages conferred by transition metal-mediated cross-couplings have seen their extensive application in the synthesis of natural products and fine chemicals. Coupling reactions have been used as key steps in numerous natural product syntheses, allowing synthetic disconnections to be contemplated that are inaccessible *via* traditional carbon-carbon bond forming reactions.[11,12,15] The facile synthesis of many natural products can be seen as showcases of the synthetic coupling methodology, as demonstrated by the rapid iterative synthesis of β-carotene (**2.1**) reported by the laboratory of Negishi (**Figure 2.2**).[16]
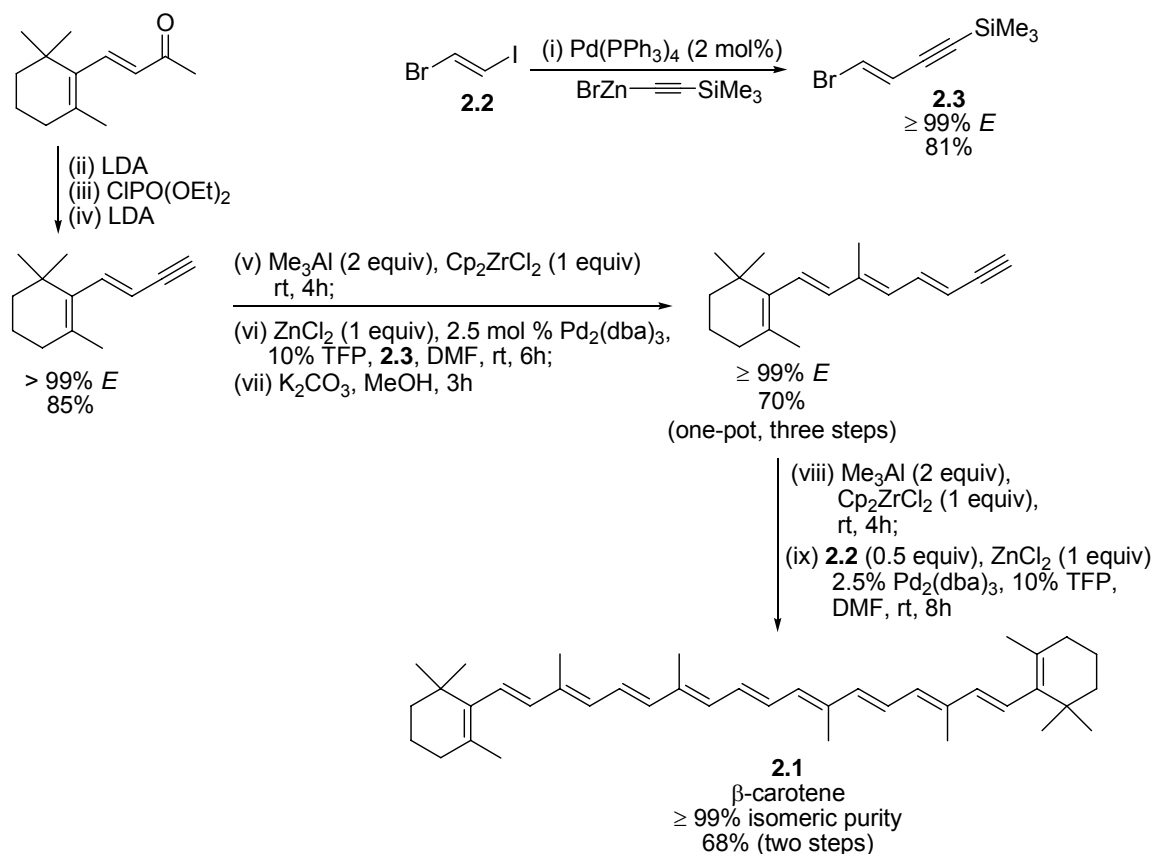
Figure 2.2   Iterative coupling methodology for polyene synthesis.

2.2.1   Palladium-Catalysed Cross-Coupling Cycle

The palladium-catalysed cross-coupling reaction has been extensively investigated synthetically and mechanistically, but remains to be conclusively defined due to intrinsic variations that occur as a function of substrate, palladium catalyst, ligand, temperature, solvent and additive effects. It is generally agreed that the first step in the catalytic cycle is the oxidative addition of R_1-X to the coordinatively unsaturated, active catalyst, $[L_nPd^{(0)}]$, to give a *cis*-$[R_1$-Pd(X)$L_n]$ species *(i)*, which rapidly isomerises to the *trans*-$[R_1$-Pd(X)$L_n]$ species *(ii)* (**Figure 2.3**). Transmetallation by the organometallic species R-M to generate the bis-substituted complex $[R_1,R$-PdL$_n]$ has been identified as the rate limiting step in the catalytic cycle *(iii)*. Ligand displacement, to allow co-ordination of the organometallic species to the active catalyst, has been postulated to occur *via* either a dissociative, associative or cyclic associative mechanism and is still an active area of research.[8] Reductive elimination releases the cross-coupled product R_1-R and regenerates the active catalyst $[L_nPd^{(0)}]$ *(iv)*.
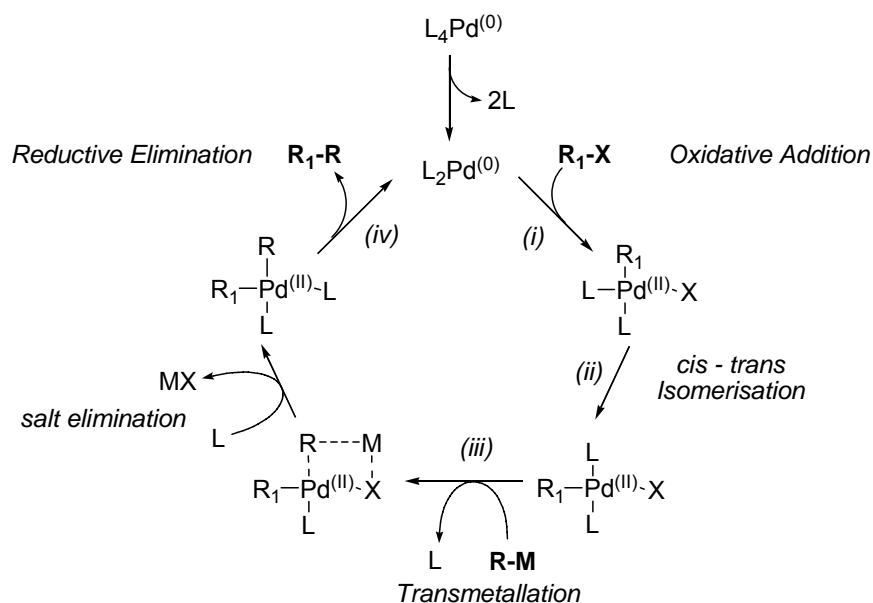
Figure 2.3   Proposed catalytic cycle of palladium-catalysed cross-coupling reactions.

Based on the proposed catalytic cycle displayed in **Figure 2.3**, a number of important palladium-catalysed couplings have been developed, including alkene, terminal alkyne, carbon-heteroatom (N, O, P), carbonylation and cycloisomerisations.[8-10] With the exception of reactions that proceed *via* free radical intermediates, all the above mentioned carbon-carbon and carbon-heteroatom bond-forming reactions generally proceed with retention of the double bond geometry of the starting organometallic species providing highly chemioselective, regioselective and stereoselective reactions.

2.3   *Transition-Metal Catalysed Couplings of Organometallics with Electrophiles*

2.3.1   Synthetic Preparation of Dienes *via* Organostannane Coupling

The transition metal-catalysed coupling of organostannane species with organo-halides or triflates is known as the Migita-Kosugi-Stille coupling, or more commonly the Stille coupling, after the influential mechanistic and synthetic studies of J. K. Stille (**Figure 2.4**).[17]

$$R\text{-}Sn(R_2)_3 \quad + \quad R_1\text{-}X \quad \xrightarrow{\quad [M] \quad} \quad R_1\text{-}R \quad + \quad (R_2)_3Sn\text{-}X$$

cat. [M] = Ni, Pd,   X = I, Br, Cl, OTf, R_1, R_2 = alkynyl, alkenyl, aryl,
        Cu, Rh,   OCO$_2$R   heteroaryl, allyl, alkyl...
        Fe, ...
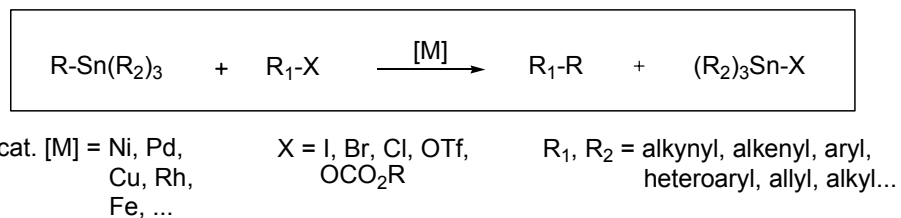
Figure 2.4   The Migita-Kosugi-Stille coupling.

The ability to achieve stereoselective carbon-carbon bond formation, under mild and neutral conditions, with a tolerance of virtually all functional groups has contributed to the extensive use of the Stille reaction in the synthesis of natural products and complex molecules *via* intra- or inter-molecular couplings.[8,18]

Particularly instructive examples have emerged from the laboratories of Pattenden[19] (amphidinolide A,[20] pateamine,[21] rhizoxin D[22]); Nicolaou (apoptolidin,[23] epothilone E,[24] rapamycin,[25] sanglifehrin A[26]); Smith (macrolactin A,[27] rapamycin[28]) and numerous others,[29] which illustrate the power of the Stille reaction to form macrocycles, sensitive polyene systems and unprotected natural products as a final synthetic step.

Pattenden *et al.* accessed the presumed amphidinolide A structure **2.4** through the novel use of sequential selective Stille reactions.[20] An intermolecular sp^2-sp^2 Stille reaction of the alkenyl stannane and vinyl iodide functionality was followed by an intramolecular sp^2-sp^3 Stille reaction achieving a macrocyclisation with the union of the alkenyl stannane and the allylic acetate moieties (**Figure 2.5**).

(i) Pd$_2$(dba)$_3$, Ph$_3$As, THF, 60°C, 4h, 51%;
(ii) PPTS, MeOH, CH$_2$Cl$_2$, rt, 6h, 60%;
(iii) Pd$_2$(dba)$_3$, Ph$_3$As, LiCl, cyclohexane, 3h, 42%.

2.4

Figure 2.5   Final steps in the Pattenden synthesis of amphidinolide A.

The synthesis of potent antiviral agent (-)-macrolactin A (**2.5**) by Smith *et al.* utilised multiple Stille reactions to achieve a convergent union of the macrolide core.[27] Key to achieving these couplings in high yield was the ability to transpose terminal coupling functionality (**Figure 2.6**).
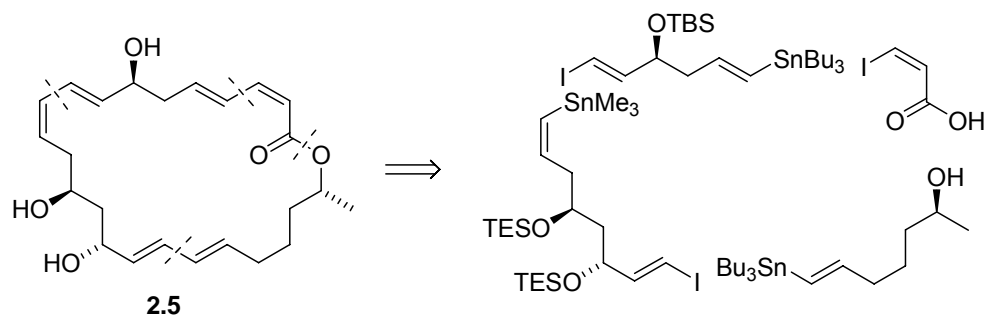
Figure 2.6   Key bond formations in the Smith synthesis of (-)-macrolactin A.

The extensive application that the Stille reaction has received in the field of total synthesis and in the preparation of complex molecules has led to a sustained effort to define the catalytic cycle through which the palladium-catalysed union of the organostannane and the organoelectrophile occurs.[17,30] The generally accepted mecha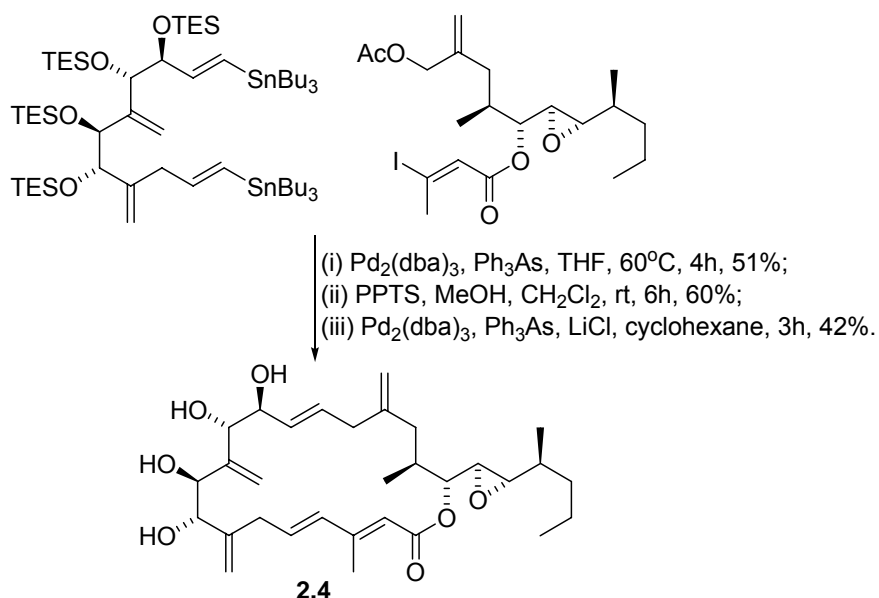nistic cycle is depicted in **Figure 2.3**, in which the catalytic cycle proceeds *via* a rapid oxidative addition step, followed by a relatively slow rate determining transmetallation reaction. Reductive elimination of this intermediate generates the cross-coupled product and a halostannane by-product. However, mechanistic and synthetic studies[18,31] have demonstrated that the nuances of this reaction are heavily dependent on such factors as the nature and concentration of the metal-coordinating ligands,[32,33] the solvent polarity and coordinating ability, the nature of the R and R_1 coupling partners, internal heteroatom coordination,[34] the inclusion of copper salts,[33,35,36] halide salts[37] or additives,[38] and the temperature regime under which the reaction is conducted. The number of influencing factors implicated in the Stille reaction allows considerable scope for the optimisation of reaction conditions.

2.3.2   Synthetic Preparation of Dienes *via* Organozinc Coupling

The palladium-catalysed coupling of an organozinc reagent with an organic electrophile is commonly referred to as the Negishi reaction.[39] Organozinc species exhibit reduced basicity and nucleophilicity relative to more cationic organometallics (Li, Na, K, Mg) and can be generated in the presence of sensitive functional groups.[40-42] The organozinc species also demonstrate higher

reactivity than the analogous organostannanes, with the Negishi couplings being successfully applied to the synthesis of a number of complex natural products,[43] especially in instances in which the Stille reaction was observed to proceed in moderate to low yield.[44,45] **Figure 2.2** depicts the application of the Negishi coupling to the concise synthesis of the polyene β-carotene **2.1** in high yield with excellent retention of stereochemistry.

The application of the Stille and Negishi coupling methodologies to the preparation of dienes **1.70** and **1.81** is described in **Section 2.8**.

2.4   *Organometallic Coupling Fragments*

The selective synthesis of vinyl organometallic compounds is of importance in contemporary organic synthesis due to their extensive use as intermediates in natural product synthesis and in materials sciences.[10-12] The need to access vinyl organometallic species with different substitution patterns, geometry and functionalities requires a diverse and complementary set of methodologies.

Vinyl-metal moieties may exist as non-isolable species formed *in-situ* (Li, Mg, Cu, Zn, Al, Zr) or as isolable species (Sn, B, Si) amenable to purification procedures. However, the primary requirement remains that the formation of these species proceeds regioselectively with the retention of stereochemistry and that the process of generation of the organometallic species displays tolerance to other functionality present in the coupling partners.

It was decided to investigate the use of organotin species as stable vinyl-metalloid equivalents. This decision was based on the demonstrated synthetic utility of organostannane intermediates.[46,47] The routes of preparation and versatility of organostannanes are depicted in **Figure 2.7**. Preparation of organostannanes can be achieved *via* a number of complementary synthetic methods that achieve regioselective and stereoselective control through the influence of steric interactions, electronic differentiation and neighbouring heteroatom coordination. The derived organostannanes [R-Sn(R$_1$)$_3$] display significant stability to moisture and oxygen, thus being amenable to isolation and purification[48,49] to obtain stereochemically and regiochemically homogenous materials.
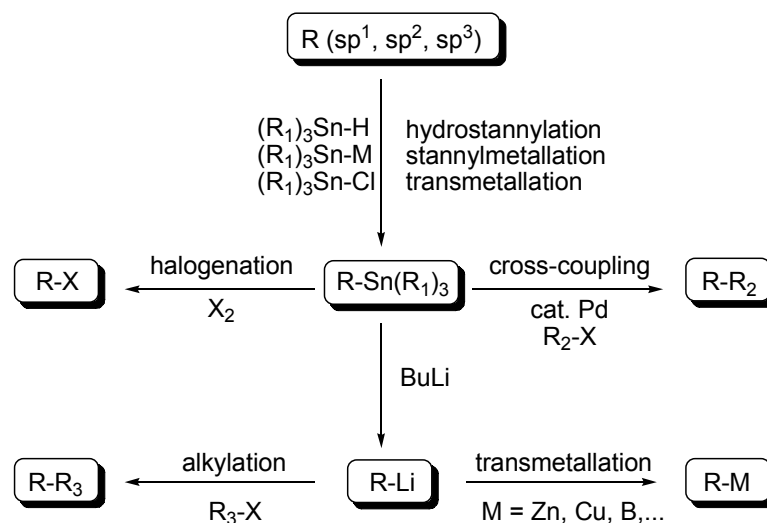
Figure 2.7   Synthetic transformation of organostannanes.

The organostannane material [R-Sn(R$_1$)$_3$] can be advanced through a number of protocols including halogenation, transition metal-catalysed cross-coupling and transmetallation with lithium to yield nucleophilic species that can undergo alkylative procedures, or be modified through additional transmetallation.[9,50]

An important aspect of the organostannane coupling methodology, which lends to its synthetic versatility, is the capacity to reverse the functionality of the organostannane and electrophile components to optimise the coupling conditions or to enable the facile synthesis of coupling components.[27] Application of this principle can be observed in the planned synthesis of diene **1.70** depicted in **Scheme 2.2**.
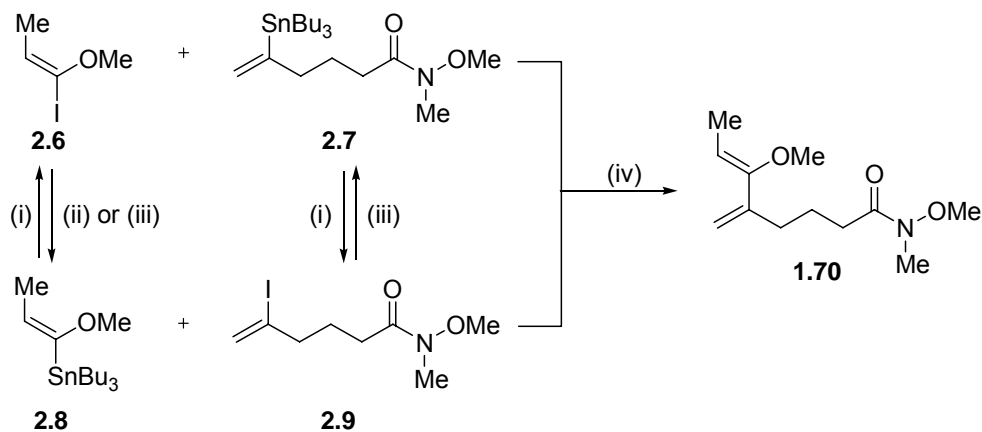
Scheme 2.2   Transposition of coupling functionality to generate homologous products.

Reagents: (i) I$_2$, cyclohexane; (ii) BuLi, -78°C; Bu$_3$SnCl; (iii) (Bu$_3$Sn)$_2$, (PPh$_3$)$_2$PdCl$_2$; (iv) cat. Pd$^{(0)}$.

Access to the stereo-defined diene system **1.70** can be achieved *via* the Stille coupling of *E*-1-methoxy-1-iodopropene **2.6** and α-vinyl stannane **2.7**, or alternatively *via* the coupling of the reciprocal *E*-1-methoxy-1-stannylpropene **2.8** and α-vinyl iodide **2.9**.

The vinyl coupling partners **2.6/2.8** and **2.7/2.9** can be readily interconverted *via* facile high yielding halogenation or metallation reactions, such that a stereoselective route to either coupling partner can be utilised to form both the halogen and stannane coupling variants.

2.5   Synthetic Preparation of Coupling Fragments 2.6 and 2.8

Three distinct routes can be envisaged to generate the desired α-functionalised α-alkoxypropenes **2.6** and **2.8** as depicted in **Figure 2.8**.
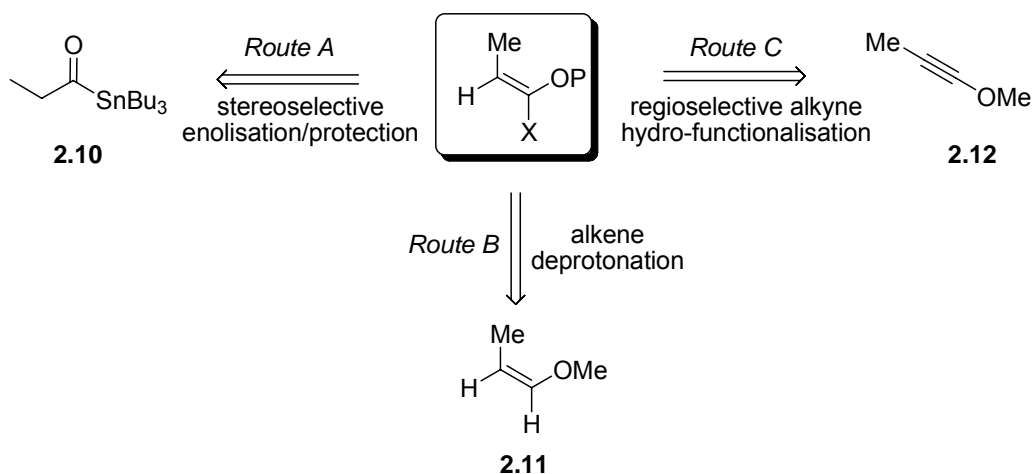
Figure 2.8   Retrosynthetic analysis of routes to 1-alkoxy-1-functionalised propenes.

These routes are specifically the:

(a)   stereoselective enolisation of a carbonyl functionality (**2.10**), with *in-situ* capture of the oxygen anion to generate a protected enol ether, (*Route A*);

(b)   the regiospecific α-metallation adjacent to an alkoxy-group (**2.11**), (*Route B*);

(c)   the regioselective hydro-functionalisation of an alkyne (**2.12**), where the addition would proceed stereospecifically to yield a *E*-alkene, (*Route C*).

2.5.1   Route A: Enolisation Strategy

Ireland *et al.* systematically investigated methods for the stereoselective deprotonation and silylation of esters as intermediates in the stereocontrolled ester-enolate Claisen rearrangement.[51]

The observed silyl ketene acetal geometry of **2.13E** and **2.13Z** is controlled by the stereoselective formation of the respective **2.14Z** and **2.14E** ester enolates. Changing the solvent, additives and base resulted in a change in selectivity between the kinetic (*E*) and the thermodynamic (*Z*) silyl ketene acetals (**Figure 2.9**).
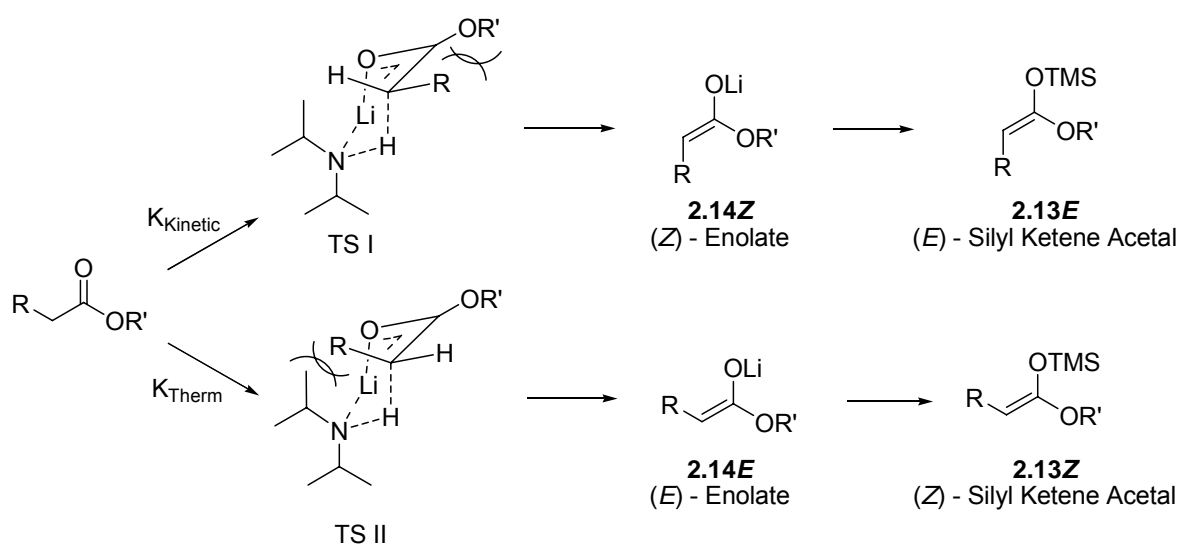
Figure 2.9   Silyl ketene acetals observed as a function of enolate geometry.

A cyclic transition state model is proposed for the enolisation of carbonyl esters with amide bases.[52] In THF solutions, the metal cation is closely coordinated to and interacts with the carbonyl oxygen and the base. The severe 1,3-diaxial interactions between the isopropyl group and the R substituent in TS II favour deprotonation *via* TS I to form the *Z*-enolate. In a dipolar solvent, caused by the inclusion of additives such as HMPA, DMPU or TMEDA, a greater degree of solvation of the metal cation weakens the metal-carbonyl interaction and expands the transition state. The 1,3-diaxial strain (TS II) is diminished in comparison to the $A_{1,3}$-strain (TS I) favouring the formation of the *E*-enolate *via* TS II. The inclusion of bulky substituents on the carbonyl carbon also favours the formation of the *E*-enolate due to increased $A_{1,3}$-strain.

The enolisation of acyl stannane **2.10**[53] with LDA in a dipolar solvent was anticipated to lead to an exclusive *E*-enolate **2.15E**, due to the bulky stannane substituent. *In-situ* anion capture would yield the desired *E*-silyl ketene stannane **2.16E** (**Scheme 2.3**).[54-56]
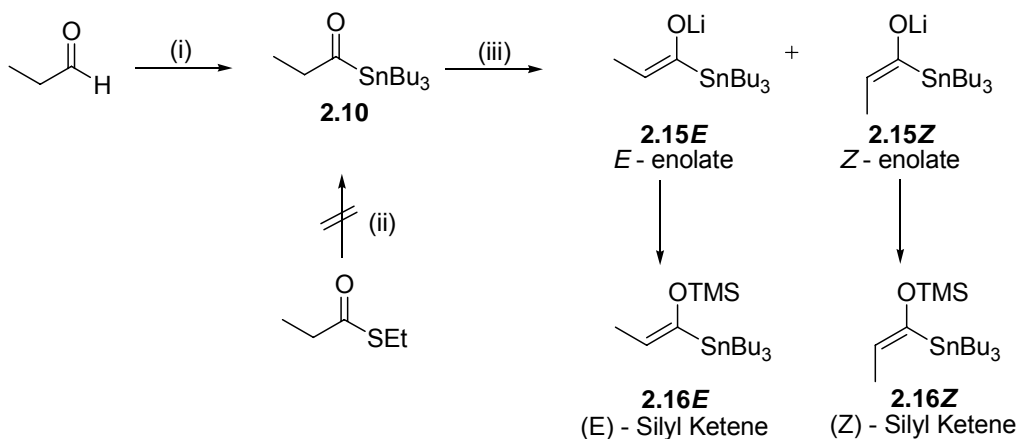
Scheme 2.3   Attempted stereoselective generation of vinyl stannane **2.16E** *via* acyl stannane **2.10**.

Reagents and yields: (i) Mg, Bu$_3$SnCl, ether, reflux; then purification *via* distillation, 54%; (ii) LDA, Bu$_3$SnH, THF; then *S*-ethyl thiopropionate (0.5 equiv), -78°C → -23°C; (iii) LDA (1.1 equiv), THF/45% DMPU; then TMSCl.

Rapid access to the acyl stannane material (**2.10**) and control over the ketene stereochemistry were anticipated to compensate for the potential synthetic difficulty in dealing with such a reactive species. In practice however, the acyl stannane **2.10** proved to be difficult to manipulate, readily decomposing during attempts to purify it, due to a noted reactivity to molecular oxygen and light as has been previously observed.[53,57-59] Efforts to achieve acceptable synthetic yields *via* either Cannizzaro reaction of a stannyl Grignard[57] or nucleophilic attack of tributylstannyl lithium on S-ethyl thiopropionate[53,57] were hindered by the difficulty in purification of the crude mixtures. Analysis of the acyl stannane material, obtained following purification *via* either chromatography under an inert atmosphere or aqueous workup, indicated the formation of significant quantities of tributylstannylpropionate. A mass ion at *m/z* 307 observed *via* LRMS was attributed to the loss of a butyl group from EtC(O)OSnBu$_3$, the product arising from the oxidation of the acyl stannane carbonyl-tin bond.

Additionally, preliminary investigations of the enolisation-silyl protection step indicated that this methodology was not sufficient to deliver the desired isomer **2.16E** with an acceptable level of stereocontrol. Following the procedure of Verlhac,[56] reaction of purified acyl stannane **2.10** with LDA in THF at -78°C, with *in-situ* quenching of the resultant enolate with TMSCl, gave after careful distillation (b.p ~90-100°C / 0.05 mm Hg), a 78:12 mixture of **2.16Z**:**2.16E** silyl ketenes.

The use of a dipolar aprotic solvent, through the inclusion of 45% DMPU/THF, was observed to generate the desired **2.16E** silyl ketene almost exclusively (10:90) as anticipated. However, low yields and extensive decomposition upon distillation (b.p. ~115°C / 0.05 mm Hg) hindered preparation of significant quantities. A number of bases (LDA, LiHMDS, NaHMDS) and solvent systems (THF; 45% DMPU / THF; 20% HMPA / THF) were attempted but the *Z*-isomer predominated upon attempted purification. Attempts to quench with TBSCl resulted in further reduced yields.

Exploratory attempts at palladium-mediated cross couplings of the acyl stannane **2.10** or the stannyl-silylketene acetal mixture (**2.16E/Z**) with **2.9** were also unsuccessful under a number of standard conditions yielding no evidence of the anticipated coupling adducts (**Scheme 2.4**).[18]
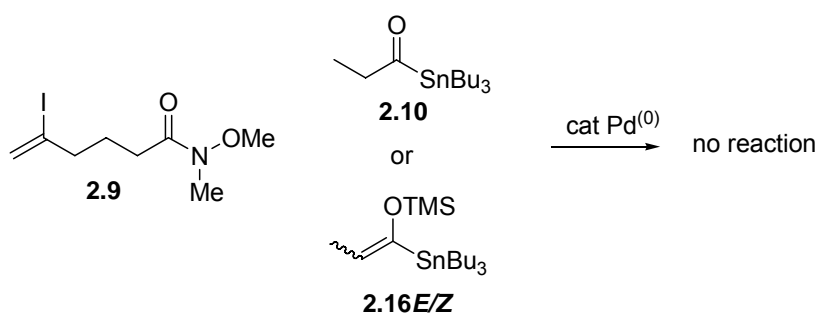
Scheme 2.4   Attempted Stille coupling of acyl stannanes equivalents with vinyl iodide **2.9**.

The acyl stannane intermediate **2.10** was shown to be a competent coupling partner with the preparation of two α,β-diketo structures **2.17** and **2.18** under palladium-mediated coupling conditions (**Scheme 2.5**).[57,60,61]
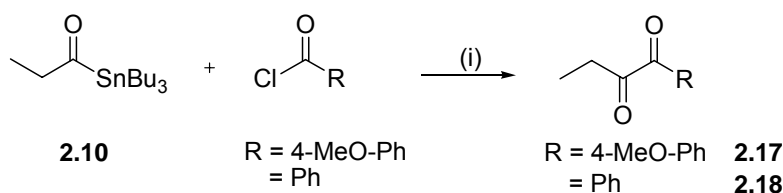
Scheme 2.5   α,β-Diketone formation *via* Stille coupling.

Reagents and yields: (i) Pd(PPh$_3$)$_2$Cl$_2$, toluene, 100°C; **2.17** 51%; **2.18** 66%.

The synthetic difficulty of manipulating the sensitive acyl stannane **2.10**, the poor *E/Z*-stereocontrol observed for the formation of the silyl ketenes and silyl acetals and the absence of discernable coupling product with the vinyl iodide **2.9** encouraged investigation of an alternative strategy to provide access to the diene system **1.70**.

2.5.2 Route B: Alkene α-Metallation

The difficulties in implementing an enolisation strategy for the preparation of the desired vinyl stannane species **2.8** were the result of the need to prepare and manipulate the sensitive acyl stannane material **2.10** and **2.16E** at the commencement of the synthesis. A deprotonation or hydrometallation strategy would offer the advantage of allowing the preparation of reactive reagents *in-situ* without isolation, or preparation of compounds more amenable to standard synthetic manipulation. The lack of extensive research utilising acyl stannanes in synthesis perhaps reflects the difficulties inherent in using these unstable intermediates.

α-Ethoxyethenyllithium (**2.19**) and its methoxy-analogue, by contrast, have received extensive use as nucleophilic acylating agents, reacting with alkyl halides and carbonyl compounds.[62] The lithiated species are usually prepared by metallation of commercially available alkoxyalkenes using *t*-BuLi and TMEDA in pentane at -30°C or *n*-BuLi/*t*-BuOK,[63-65] but the most convenient procedure devised by Baldwin *et al.* simply uses *t*-BuLi in pentane/THF (-65°C → 0°C).[62] The observed α-metallation can be understood as pre-coordination of the lithiating reagent by the vinyl oxygen, directing deprotonation to occur at the adjacent kinetically more acidic α-vinyl position, where the anion is stabilised through inductive effects.[66] Transmetallation of this species to cerium, copper, zinc or alkyltin enables an expanded manifold of reactions including additions to hindered carbonyls,[67] conjugate addition to enones[68] and Negishi (Zn)[69] and Stille (Sn)[70] cross-coupling reactions (**Figure 2.10**).
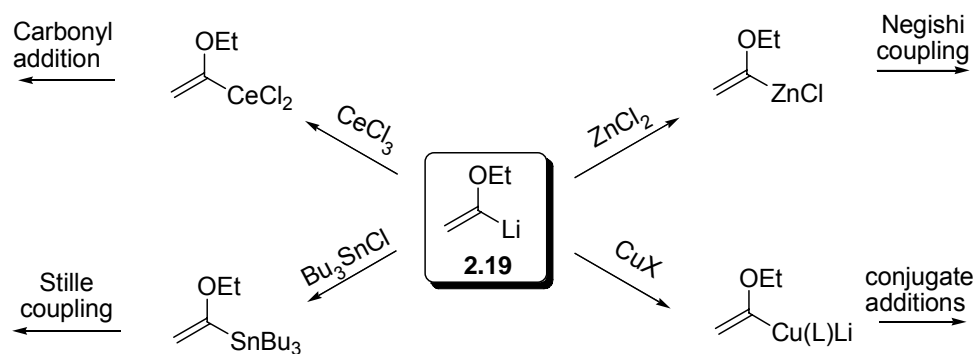
Figure 2.10   Synthetic variants *via* transmetallation of α-ethoxyethenyllithium.

However, despite the varied chemistry of α-alkoxyethenyl metal derivatives, longer chain homologues have not been extensively reported in the literature.[71] This may be due to the failure of β-alkyl-substituted acyclic enol ethers to undergo clean lithiation under generally applicable

conditions[72] and, additionally, the difficulty associated with establishing the desired *E*/*Z* ratio in the enol-ether substrate.

Gould *et al.* reported that 1,3-dibutoxypropene (**2.20**) undergoes regioselective vinylic α-metallation in preference to the allylic deprotonation.[73] Alkylation with primary alkyl bromides and iodides proceeded with retention of stereochemistry as determined by deuterium quenching studies (**Figure 2.11**). However, the synthetic route used to prepare the vinyl enol-ether generated an isomeric mixture of alkenes that could only be adequately separated *via* HPLC.
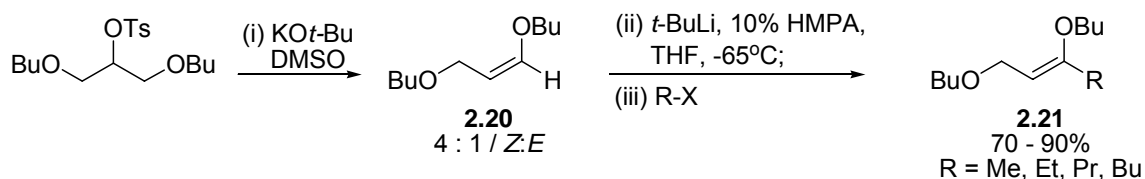
Figure 2.11   Retention of stereochemistry demonstrated in α-alkoxy,α-lithio derivatives.

Very few synthetic routes to the required *Z*-enol ether (**2.11**) have been reported. Those utilising an E1cB mechanism of a suitable leaving group often result in the generation of *E/Z* isomeric mixtures as observed by Gould. The formation of the *E*-isomer is usually favoured due to minimisation of steric interactions in the transition state, however internal coordination can result in preferential *Z*-isomer formation.[74]

The controlled *syn*-hydrogenation of alkyne **2.12** over a heterogeneous catalyst[75] or the isomerisation of a terminal allylic ether (**2.22**) to an internal propenyl ether under basic or transition metal catalysed conditions[76] also present plausible stereoselective routes to the preparation of *Z*-enol ether **2.11** (**Figure 2.12**)
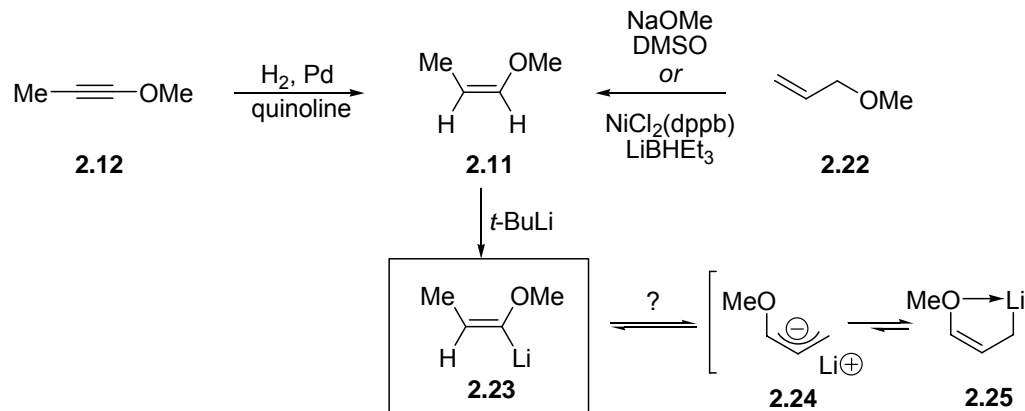
Figure 2.12   Preparation of (*Z*)-1-methoxypropene (**2.11**) *via* reduction or isomerisation.

However, competitive reactions such as the isomerisations of 1-alkoxyalkynes to terminal allylic alcohols under heterogeneous catalysis and the formation of π-allyl complexes (**2.24**) and stabilised α,β-enol-γ-metallocycle intermediates (**2.25**) may complicate such a synthetic preparation.[9,77] It is pertinent to note that literature examples of alkyl-lithium mediated deprotonation of long chain homologues of alkoxy-ethenes to form α-metallated vinyl ethers are of a carbocyclic or allenic nature in which the π-allyl metallocyclic structure **2.25** would be unable to form due to steric and torsional constraints.[78] As such, it is uncertain whether α-metallation of *(Z)*-propenyl-ethers of non-carbocyclic nature is feasible. Furthermore, the separation of product from starting materials and of the potential for *E/Z*-isomers rendered such approaches to **2.23** synthetically problematic.

2.5.3   Route C: Alkyne Hydrofunctionalisation

Difficulties in preparing stereodefined alkenyl-metal or alkenyl halide species *via* selective deprotonation of alkenes have led to investigation into synthetically equivalent regio- and stereoselective hydrometallation-transmetallation sequences. Hydrometallation, involving the *syn*- or *anti*-addition of a metal hydride species across an alkyne bond results in a vinyl-metalloid species (**2.26**) (**Figure 2.13**).
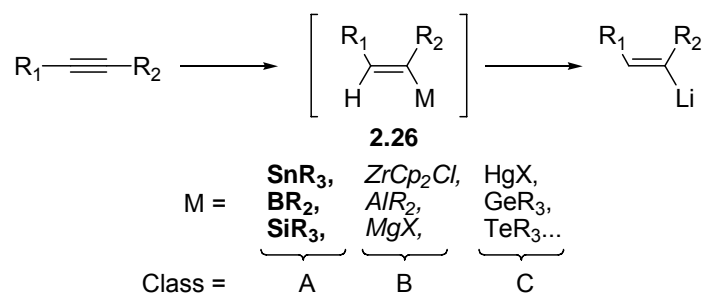
Figure 2.13   Vinyl metalloid generation *via* hydrometallation.

The vinyl organometallic species **2.26** can be broadly divided into three classes:

Class A (Sn, B, Si):   Primary methods and species for alkyne functionalisation that have been utilised extensively in organic synthesis and natural product synthesis. These functionalised vinyl-metalloid intermediates are often amenable to isolation and purification and have been extensively reviewed.[58,79-81]

Class B (Zr, Al, Mg): Non-isolable intermediates that are coupled or converted *in-situ via* transmetallation. Excellent regio- and stereo-selectivity can be achieved with the utilisation of heteroatom coordination or steric effects.[82,83]

Class C (Hg, Ge, Te): Less frequently prepared vinyl organometallic species, due to replication of Class A and B properties, or toxicity issues, although some exhibit novel capabilities that have been used synthetically.[84-86]

Vinyl organostannanes have been extensively utilised due to their ease of synthesis, purification, functional group tolerance and for the ability to access additional reactivity manifolds *via* transmetallation, as discussed in **Section 2.4**.

However, in contrast to terminal alkynes, where the regioselectivity, stereochemistry and mechanisms of hydrostannylation are often well investigated, internal alkynes have received far less attention. The issues of stereochemistry and the product distribution of internal alkynes are poorly documented despite the importance of tri-substituted olefin structures to synthetic chemistry.

Vinyl organostannanes can be prepared *via* three synthetic protocols, which result in distinct regio- and stereochemical product distributions. The nature of the product distributions reflects the dominant reaction mechanism through which hydrometallation occurs.

2.5.3.1   Radical Hydrostannylation

The most prominent method for the addition of an alkyltin hydride to an alkyne is the radical-induced process. The hydrostannylation of alkynes, alkenes and allenes under free-radical conditions has been widely studied and gives, in general, a mixture of stereoisomers with regiochemistry controlled by the relative stability of the two possible intermediate β-stannyl radicals (**Figure 2.14**).[87-89] Excluding known systems such as enynes, enynols and propargyl alcohols, a strong regiochemical preference is observed for the formation of the β-stannyl adduct **2.27β-*E*** due to the stability of the *E*-vinyl radical.[90,91] Stereoselectivity is often a significant problem however, since the initially formed kinetic product is equilibrated by further addition - elimination processes under the reaction conditions.
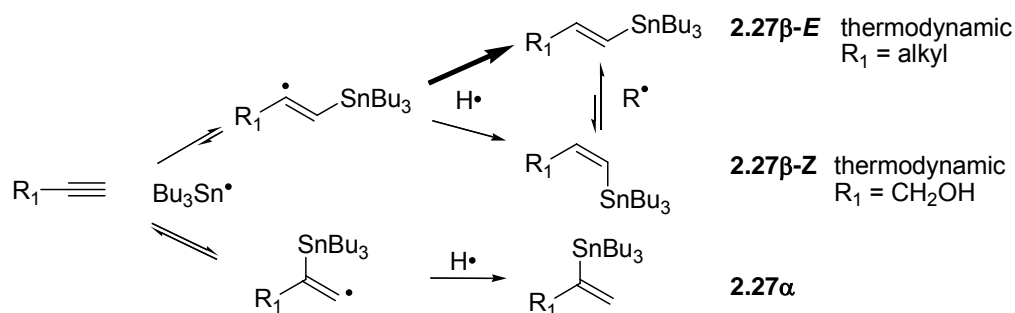
Figure 2.14   Product distributions under radical conditions.

Radical hydrostannylation of internal alkynes suffer from poor selectivities, with complex systems often giving statistical mixtures based on substituent steric effects, electronic effects and intramolecular heteroatom coordination.

2.5.3.2   Transition Metal-Catalysed Hydrostannylation

The transition metal-catalysed hydrostannylation of alkynes is a field of continuing development.[92] Although a definitive mechanism has not been elucidated, a general catalytic cycle based upon an oxidative addition/hydrometallation/reductive elimination sequence has been proposed that endeavours to rationalise the existing literature data for the hydrostannylation of sterically differentiated alkynes (**Figure 2.15**).[93]
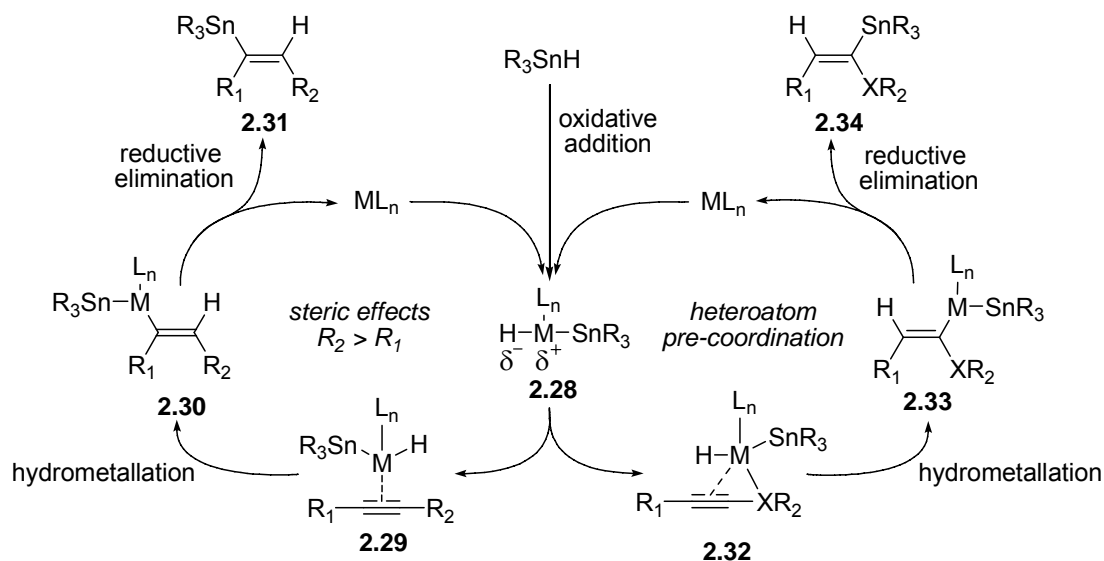
Figure 2.15   Proposed transition metal-catalysed hydrostannylation of alkynes utilising steric or coordination effects.

Oxidative addition of R_3SnH to the transition metal centre (ML_n) generates the metal-hydrido complex **2.28**. Coordination to the π-system of the alkyne (**2.29**), and subsequent hydrometallation affords the vinyl metallated species **2.30**, which furnishes the organostannane product **2.31** *via* a reductive elimination. The proposed mechanism correctly predicts the observed *syn*-addition to generate *E*-vinyl stannanes, and the relative influence of R_1 and R_2 due to steric effects (**Table 2.1** - *entry 1 vs 5*).

Electronic effects such as heteroatom coordination by neighbouring groups (propargyl alcohols and amines), conjugation and polarizing functional groups can dominate the regiochemistry of hydrostannylation.[94,95] Pre-coordination of the transition metal centre **2.28** by the heteroatom (XR_2) in a putative metallacycle (**2.32**) favours the generation of adducts with the stannane proximal to the coordinating functionality (**2.34**) *(entry 6 v 7)*.

Table 2.1   Observed regioselectivity of the transition metal-catalysed hydrostannylation of terminal alkynes due to steric and coordination effects.
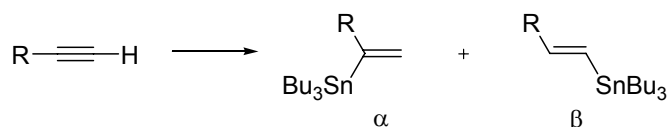
Entry	R	α:β[a]	Yield (%)[b]	Reference
1	$(CH_2)_2CH_3$	1 : 2.2	-	95
2	CH_2OH	1.3 : 1	95	95
3	$(CH_2)_3CH_2OH$	1 : 3	95	95
4	$(CH_2)_2CH_2Cl$	1 : 1.4	84	96
5	*t*-Bu	1 : 99	59	96
6	Ph	1 : 1.2	82	97
7	CH_2OPh	10 : 1	85	98
8	CO_2Me	100 : 0	94	98
9[c]	CH_2OH	8.1 : 1	94	99

Notes: (a) Product ratio determined by ^{1}H NMR; (b) Reaction conducted with $Pd(PPh_3)_2Cl_2$ (5 mol %), Bu_3SnH (1.1 equiv), values refer to isolated yields; (c) $Mo(CO)_3(t\text{-BuNC})_3$ catalyst, with Bu_3SnH (3 equiv).

Palladium and molybdenum catalysts, such as $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$ and $Mo(allyl)(CO)_2(MeCN)_2Br$, display good *syn*-stereoselectivity but poor regioselectivity for addition to terminal and internal alkynes.[100] Significant use has been made of steric or electronic control elements such as propargyl alcohol *(entry 1 vs 2)*,[98] fluorination, conjugation[101] or aromatic groups *(entry 4 vs 7)*[102] to achieve high regiocontrol. Recently, $Mo(t\text{-BuNC})_3CO_3$ has

been developed as a catalyst that delivers good regioselectivity (>90:10) for α-vinyl stannanes adjacent to propargyl alcohol functionality *(entry 9)*.[99]

The regiochemical preferences displayed for the palladium-catalysed hydrostannylation of terminal alkynes (α:β ~ 1:2)[95] is in contrast to the strong intrinsic preference for β-regiochemistry observed for hydroboration,[103] hydrozirconation[104] and free radical hydrostannylation. Two exceptions to these observations are the use of Lewis-acidic ZrCl₄, which gives exclusive *Z*-β-stannanes,[105] and the preparation of *E*-β-stannanes from bromoalkynes utilising a hydrostannylation - debromination pathway in the presence of excess tin hydride.[98]

Pertinent to the preparation of α-methoxy-stannylpropene **2.8** is the work of Kocieński *et al.* who demonstrated that *syn*-addition is maintained during palladium-catalysed hydrostannylation of internal alkoxy-alkynes (**2.35**) and that the regiochemistry is strongly influenced by steric effects of the R₁ and R₂ substituents (**Figure 2.16**).[106] Increasing the steric size of R₂ increased the proportion of **2.36α**; while conversely increasing the steric demand of R₁ lead to an increase in the amount of the regioisomer **2.36β** generated.

R₁	R₂	2.36α	2.36βᵃ	%ᵇ
OBn	*n*-Bu	1.8	1	46
OBn	*s*-Bu	5.2	1	57
OBn	*t*-Bu	100	1	71
1-menthyl	Me	1	3	23

(a) destroyed *via* Al₂O₃ chromatography or Kugelrohr distillation;

(b) yield of isolated pure **2.36α**.
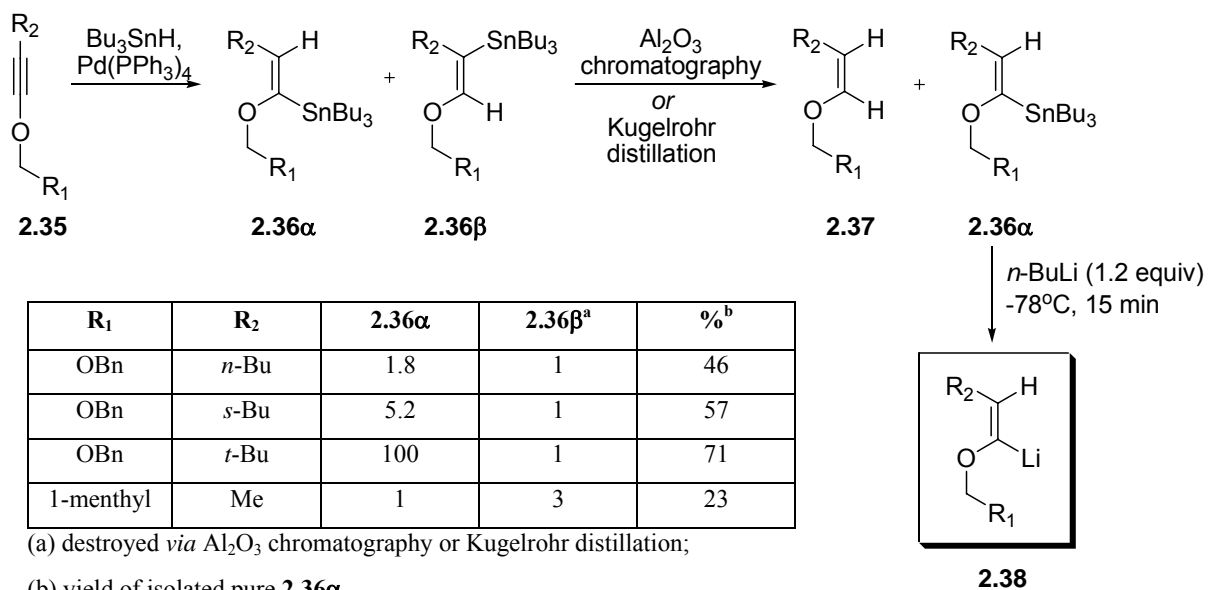
Figure 2.16   Hydrostannylation of internal 1-alkoxyalkynes.

Subsequent transmetallation of the α-alkoxyalkenylstannane **2.36α** proceeded regio- and stereoselectively in quantitative yield to give α-alkoxyalkenyllithium **2.38**. This hydrostannylation - transmetallation protocol overcomes the problems associated with the

lithium-based deprotonation of non-cyclic long-chain homologues of enol ethers as discussed previously.[107]

2.5.3.3   Metallostannylation

Free-radical or transition metal-catalysed (Pd, Mo) hydrostannylation results predominantly in regio- and stereo-defined β-vinyl stannanes from alkyl alkynes. The development of alkyne metallometallations, such as stannylcupration (Sn-Cu),[108-110] silastannylation (Sn-Si),[111] and others (-Zn, -Al, -Sn, -Mn, -B, -Mg, -Ge)[109,112] have allowed access to the less readily available α-vinyl stannanes in a stereospecific and regioselective manner.

Stannylcupration and silastannylation have been the most extensively investigated, with a number of natural product syntheses using α-stannyl species generated *via* stannylcupration.[113] Silastannylation shows potential to allow differential coupling protocols to occur based on sequential Stille – Hiyama coupling.

2.5.3.4   Preparation of 1-Methoxypropyne

From the above discussion, the most favourable route to the regio- and stereo-defined 1-alkoxy-1-functionalised-propenes **2.6** and **2.8** required the controlled hydrometallation or metallometalation of an appropriately substituted 1-alkoxypropyne.

1-Methoxypropyne (**2.12**) was chosen as a suitable alkyne source due to consideration of factors such as steric constraints, ease of hydrolysis and spectroscopic identification. Synthetic routes to the preparation of 1-alkoxyalkynes have been described, commonly employing base induced eliminations from haloalkenyl ethers, dihaloethers and haloacetals to generate the alkyne functional group (**Figure 2.17**).[114,115]
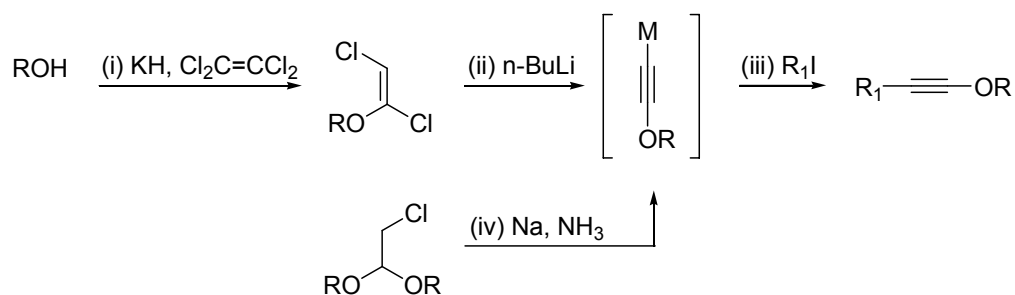
Figure 2.17   Elimination routes to 1-alkoxyalkynes.

These protocols (**Figure 2.17**) are most suited to the preparation of higher R and R_1 homologues of **2.12** where the desired alkyne product can be efficiently distilled from the reaction solvent and excess alkyl halide (R_1-I). The separation of **2.12** (b.p. 65.7-66.3°C / 760 mmHg)[116] from the reaction solvent and excess iodomethane was anticipated to be problematic.

The reaction sequence detailed by Nooi *et al.* provides a solution to this issue (**Scheme 2.6**). The final step to generate **2.12** involves the controlled distillation of the volatile alkyne from a heterogeneous mixture comprised of bromo-alkene **2.39Z** and solid potassium hydroxide.[116] Using this method, pure 1-methoxypropyne (**2.12**) was generated in four steps from propionaldehyde in 51% yield on a 1.5 mole scale. A noted side product was the formation of methoxy-allene **2.40** arising from the anti-periplanar elimination of hydrogen bromide from rotationally restricted 2-bromo-1-methoxypropene **2.39E**.
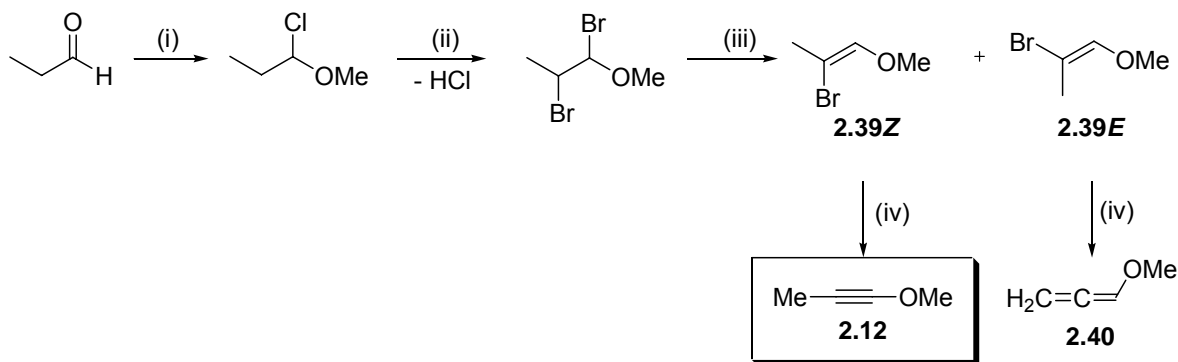
Scheme 2.6   Preparation of 1-Methoxypropyne (**2.12**).

Reagents and yields: (i) 1 equiv MeOH, excess anhyd. HCl, -10°C; (ii) 1 equiv Br_2, rt; (iii) *N,N*-diethylaniline, reflux; distillation to separate **2.39Z** and **2.39E**; (iv) 5 equiv KOH, 51% (four steps).

2.5.4   Hydrostannylation Studies

Attempts to prepare 1-methoxy-1-stannylpropene (**2.8**) in a stereo and regiocontrolled fashion from 1-methoxypropyne (**2.12**) led to the investigation of a number of hydrostannylation reactions (**Table 2.2**).

Table 2.2   Hydrostannylation of **2.12**.

	2.8	2.41	2.42	2.43
^{1}H NMR [δ_{Ha}]	4.63	5.26	5.62	6.41
Coupling	multiplet	triplet of quartets	triplet	triplet
		J_{H-H} = 6.5 Hz	J = 1.8 Hz	
		$^3J_{Sn-H}$ = 46.5 Hz	$^3J_{Sn-H}$ = 33.0 Hz	$^3J_{Sn-H}$ = 45.1 Hz
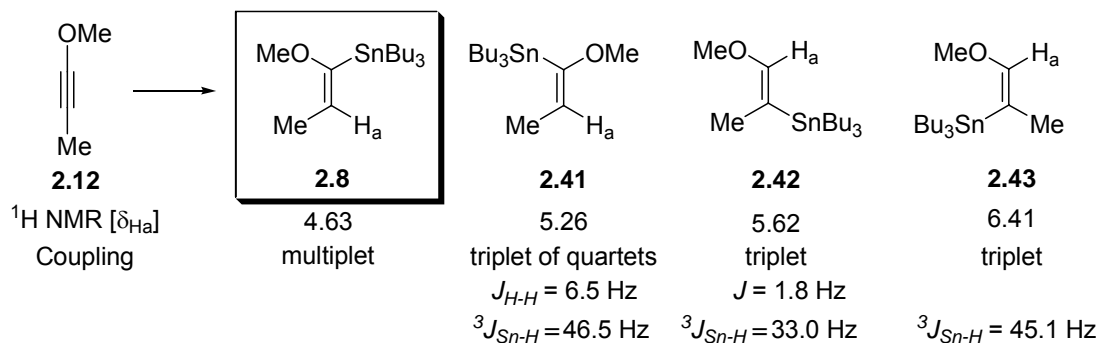
Entry	Reagent and Conditions	Product Distribution Ratios^a

Entry	Reagent and Conditions	2.8	2.41	2.42	2.43
1	Bu$_3$SnH, AIBN, toluene, 80°C	21	36	13	30
2	Bu$_3$SnH, Et$_3$B, toluene, rt	trace	66	trace	34
3	Bu$_3$SnH, Pd(AsPh$_3$)$_2$Cl$_2$, THF, rt^b	42	0	32	26
4	Bu$_3$SnH, Pd(CH$_3$CN)$_2$Cl$_2$, THF, rt	trace	0	trace	trace
5	Bu$_3$SnH, Pd(PPh$_3$)$_4$, THF, rt	24	0	76	0
6	Bu$_3$SnH, Pd(PPh$_3$)$_2$Cl$_2$, THF, rt	30	0	70	0
7	Bu$_3$SnH, Pd(PPh$_3$)$_2$Cl$_2$, THF, rt^c	3	trace	97	0
8	Bu$_3$Sn(Bu)Cu(CN)Li$_2$, THF, -78°C	0	0	100	0
9	Bu$_3$Sn(Bu)Cu(CN)Li$_2$, THF/MeOH, -78°C	23	0	77	0

Notes: (a) product distribution assessed *via* ^{1}H NMR integration of characteristic vinyl proton signals; (b) ~10% conversion; (c) addition of 1 equiv. of Bu$_3$SnH over 30 min on 1 mmol scale.

2.5.4.1   Radical Hydrostannylation

Free-radical hydrostannylation of **2.12** with tributyltin hydride using thermal initiation (AIBN)[117,118] resulted in the generation of all four possible vinyl stannanes with little stereo- or regio-control *(entry 1)*. In contrast, low temperature initiation (Et$_3$B/O$_2$)[89,119] provided the products **2.41** and **2.43**, arising from *trans* addition, with only trace amounts of isomerisation *(entry 2)*.

The kinetic preference for **2.41** over **2.43** (2:1) presumably reflects either the more rapid rate of addition proximal to the methoxy heteroatom or alternatively, that the incipient alkenyl radical is favourably stabilised adjacent to the alkyl group relative to the methoxy group. A *trans* mechanism for the tributyltin radical addition can be inferred from the kinetic products *(entry 2)*, which degrade under the thermal reaction conditions *(entry 1)*. It is apparent that neither the methoxy nor methyl group exerts a significant influence to generate a thermodynamically favoured product.

2.5.4.2   Palladium-catalysed Hydrostannylation

Palladium-catalysed hydrostannylations were conducted on a 1 millimolar scale with the dropwise addition of tributyltin hydride to a mixture of the alkyne **2.12** and a palladium catalyst in THF at room temperature.[98] Solutions containing $Pd(AsPh_3)_2Cl_2$ and $Pd(CH_3CN)_2Cl_2$ as catalysts were observed to darken immediately, and hydrogen generation was observed from the solutions *(entry 3 and 4)*. ^{1}H NMR spectroscopy of sample aliquots indicated poor conversion to the vinyl stannane adducts in agreement with the rapid catalyst destruction. Trialkyltin hydrides have been observed to decompose under palladium catalysis to generate hydrogen and hexaalkylditins products with an accompanying darkening of the solution as palladium metal precipitates (**Figure 2.18**).[120,121]

$$2\ Bu_3SnH \xrightarrow[\quad Pd(s) \quad]{\quad Pd^{(0)} \quad} (Bu_3Sn)_2\ +\ H_2$$
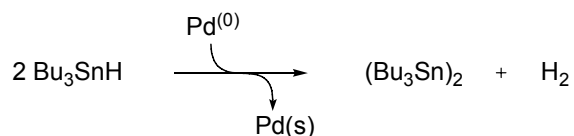
Figure 2.18   Trialkyltin hydride decomposition under palladium catalysis.

The use of $Pd(PPh_3)_4$ or $Pd(PPh_3)_2Cl_2$ gave yellow solutions and clean conversion to the vinyl stannanes **2.8** and **2.42** in ratios of 24:76 and 30:70 respectively *(entry 5 and 6)*. Interestingly, slow addition of the hydride (~30 min for the addition of 162 μL) resulted in a remarkable increase in regioselectivity, yielding **2.42** almost exclusively *(entry 7)*. The preference for **2.42** formation is perhaps a consequence of polarisation of the alkyne ether or of internal pre-coordination of the palladium catalyst to the ether oxygen prior to hydrostannylation (see **Figure 2.15**) as the methyl and methyl ester substituents could be anticipated to display similar steric properties. These results are similar to those obtained by Guibé,[98] Lébl,[122] and Kocieński[106] on related alkoxyalkynes.

2.5.4.3   Stannylcupration

Stannylcupration of terminal alkynes has been widely applied to the preparation of vinyl stannanes with high regio- and stereoselectivity; however internal alkynes that do not possess mesomeric, inductive or coordination effects have not been extensively investigated.[94,123] Oehlschlager *et al.* investigated the stannylcupration of ethoxy-acetylene (**2.44**) under both thermodynamic and kinetic quenching conditions, utilising ^1H and ^{13}C NMR spectroscopy to identify the reaction intermediates.[124] The studies concluded that the observed regiochemistry of the stannylcupration adducts was a function of the reaction conditions. Under kinetic control, achieved by inclusion of MeOH in the solvent, higher **2.45** and lower order **2.46** stannylcuprates generate the vinyl copper species **2.47α**, and its subsequent product **2.48α**. Under thermodynamic control where the vinyl copper species were allowed to equilibrate before the addition of MeOH, a β-vinyl stannane **2.48β** was obtained possibly due to a favourable intramolecular interaction between the ether oxygen and the copper species (**2.47β**) (**Figure 2.19**).
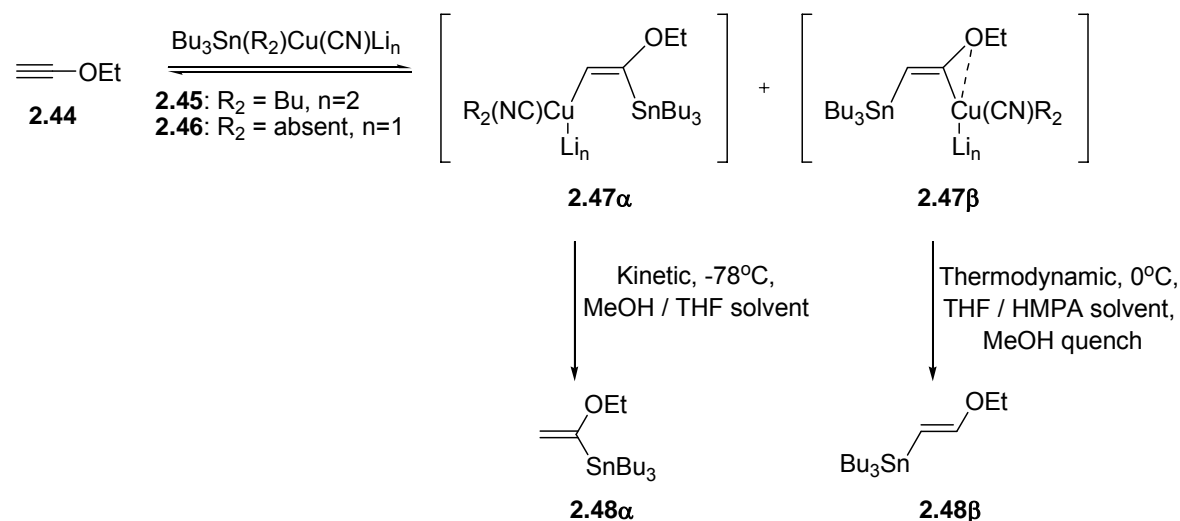
Figure 2.19   Stannylcupration mechanism proposed by Oehlschlager *et al*.

In agreement with Oehlschlager's proposals for the terminal stannylcupration of alkoxylacetylenes, the reaction of **2.12**, under thermodynamic conditions led exclusively to the generation of β-vinyl stannane **2.42** *(Entry 8)*. Reactions conducted under kinetic conditions using either **2.45** or **2.46** resulted in a mixture of the regioisomers **2.8** and **2.42** s *(entry 9)*. It is apparent that although the methyl group is relatively small, it is still able to exert a considerable steric (and possibly electronic) effect.

The failure to achieve the desired *E*-α-vinyl stannyl ether **2.8** *via* free-radical, palladium-catalysed hydrostannylation or stannylcupration methodology lead to the consideration of other synthetic methodologies.[125-127]

2.5.5   Alkyne Hydrohalogenation

Fortunately, a solution to the impasse encountered when attempting to prepare the regio- and stereodefined α–stannylvinyl ether **2.8** was presented with a publication by Jin and Yu.[128] They reported that a highly stereospecific synthesis of α-halovinyl ethers (**2.49**) can be achieved when alkoxyalkynes were exposed to halo-trimethylsilanes at low temperature (**Figure 2.20**).
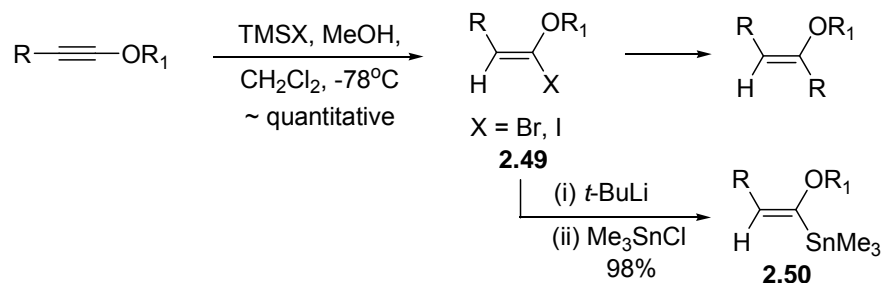
Figure 2.20   Hydrohalogenation of 1-alkoxyalkynes.

The α-halo vinyl ethers (**2.49**) could engage in Stille, Sonagashira and carbonylation reactions in high yield. Furthermore, the reaction between the α-halo vinyl ether **2.49** and *t*-BuLi afforded α-alkoxyl-vinyl lithium species quantitatively, with the retention of stereochemistry. The generated α-alkoxyl-vinyl lithium could engage in alkylation, acylation, conjugate addition reactions and importantly, transmetallation to α-stannyl vinyl ethers (**2.50**).[128-130]

Using the protocol of Yu and Jin, iodotrimethylsilane[131] was added slowly to a solution of 1-methoxypropyne and methanol in dichloromethane at -78°C to successfully deliver the desired 1-iodo-1-propenyl methyl ether in quantitative yield. The formation of a pink colouration in CDCl₃ indicated that the vinyl iodide species **2.6** was relatively unstable with respect to exposure to acid, light or atmospheric moisture. Removal of the dichloromethane solvent under an inert atmosphere and replacement with anhydrous diethyl ether allowed the low temperature (-98°C) lithium-halogen exchange to generate the α-alkoxyl-vinyl lithium **2.23** *in-situ*.[132] This species could be trapped with the slow addition of Bu₃SnCl to generate the desired *E*-α–stannane vinyl

ether **2.8** in high yield or transmetallated (*vide infra*) to allow subsequent coupling reactions to be performed *in-situ* (**Scheme 2.7**).
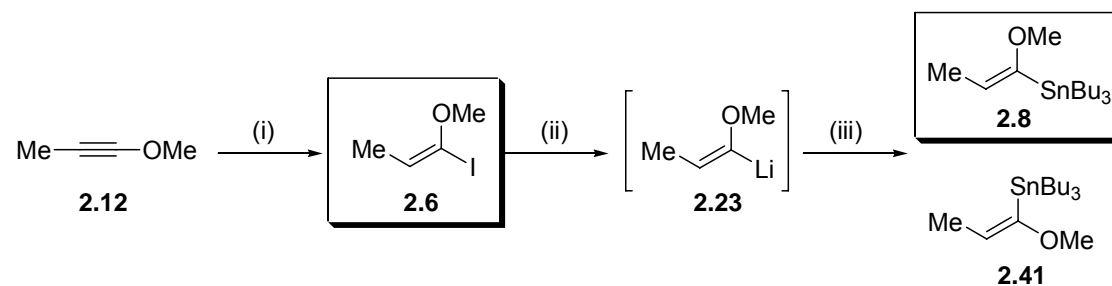
Scheme 2.7   Preparation of vinyl iodide **2.6** and vinyl stannane **2.8**.

Reagents and yields: (i) MeOH (0.99 equiv), TMSI (0.99 equiv), CH_2Cl_2, -78°C → rt; then evaporation of solvent [23°C / 12 mmHg]; (ii) *t*-BuLi, diethyl ether, -98°C → -78°C, 30 min; (iii) Bu$_3$SnCl, **2.8** 69%, **2.41** 17%.

Although a small amount of the *Z*-α–stannane vinyl ether **2.41** was observed, excellent regiocontrol and stereocontrol was achievable with precise control of experimental conditions (particularly the internal temperature profile). The vinyl tin species **2.8** and **2.41** were isolated after careful flash column chromatography in 69% and 17% yield respectively. The use of basified silica, through the addition of triethylamine to both the eluting solvent and the silica slurry, was essential to minimise decomposition *via* proto-destannylation.[59,112]

2.5.6   Preparation of the α-Alkoxy-ethene Coupling Partner

As discussed in **Section 2.5.2**, the α-lithiation of 1-alkoxy-ethylene has been extensively utilised in synthesis. Low temperature deprotonation of commercially available ethoxy vinyl ether, followed by quenching of the lithio-anion **2.19** with tributyltin chloride generated the ethoxy stannane **2.51**, in high yield. Alternatively, the *in-situ* transmetallation with zinc chloride allowed preparation of the vinyl zinc species **2.52** (**Scheme 2.8**).[107,133]
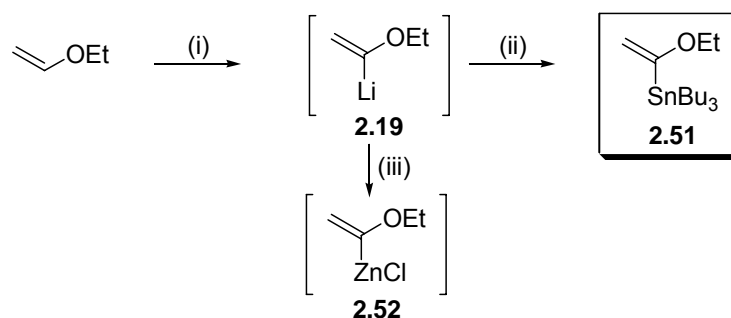
Scheme 2.8   Preparation of ethoxy vinyl stannane **2.51** required for the florlide synthesis.

Reagents and yields: (i) *t*-BuLi, ether, -98°C → -30°C, 1 h; (ii) Bu$_3$SnCl, -78°C → rt, 87%; (iii) ZnCl$_2$, ether.

2.6   Synthetic route to 2.7 and 2.9

The synthesis of the α-functionalised vinyl stannane **2.7** and vinyl iodide **2.9** required the regioselective hydrostannylation or hydroiodination of a terminal alkyne, the methods for which were reviewed in **Section 2.5.3**. Preparation of the common intermediate 5-hexyn-1-ol (**2.53**), was performed *via* the method of Brandsma.[115] Whilst numerous methods have been detailed for the functionalisation of terminal alkynes, it was important to investigate which protocols gave the best regiocontrol, stereocontrol and isolated yields, and whether the functionality introduced could survive subsequent synthetic manipulation. Towards this goal, two routes were investigated (**Scheme 2.9**).

Route A features an initial alkyne functionalisation step followed by oxidation of the terminal alcohol to effect conversion to the desired coupling partner, *N*-methoxy-*N*-methyl-5-tributylstannyl-5-hexenamide **2.7** or *N*-methoxy-*N*-methyl-5-iodo-5-hexenamide **2.9**. *Route B* involves the initial oxidation and amide formation, followed by α-functionalisation to generate **2.7** or **2.9** (**Scheme 2.19**).
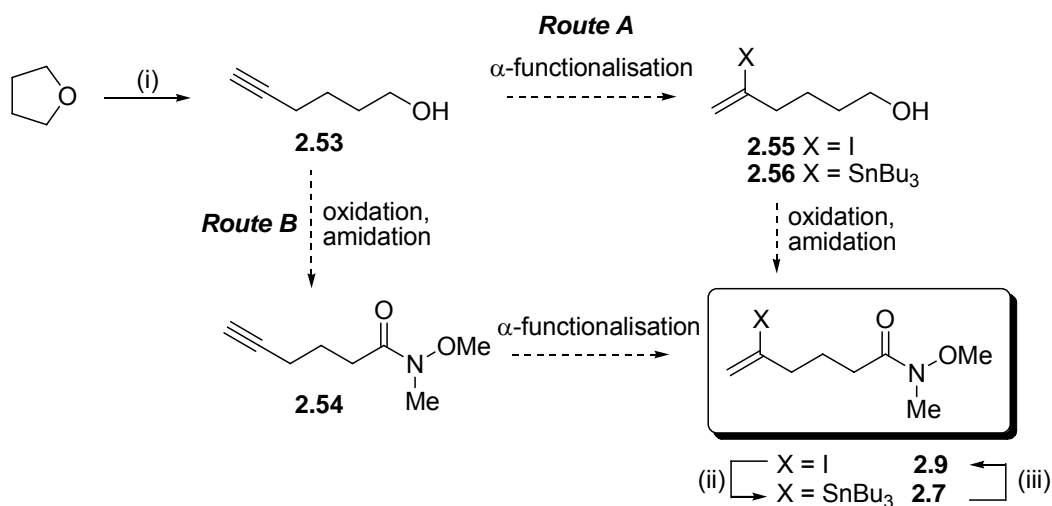
Scheme 2.9   Complementary synthetic routes to **2.7** and **2.9**.

Reagents and yields: (i) see ref. 115; *(a)* anhyd. HBr; *(b)* DHP, p-TsOH (cat); *(c)* lithium acetylide, NH$_3$; *(d)* HCl (cat), EtOH, reflux; 4 steps 87%; (ii) (Bu$_3$Sn)$_2$, Pd(PPh$_3$)$_4$, DMF; (iii) I$_2$, CH$_2$Cl$_2$.

2.6.1   ROUTE A

2.6.1.1   Preparation of *N*-Methoxy-*N*-methyl-5-iodo-5-hexenamide 2.9

The preparation of **2.55** from 5-hexyn-1-ol (**2.53**) had previously been reported by Weinreb *et al.* utilising the hydroiodination protocol of Ishii.[134,135] Treatment of **2.53** with anhydrous hydroiodic acid in MeCN, generated *via* the reaction of TMSCl, NaI and H_2O, was reported to give **2.55** in 72% yield. In the author's hands, however, a mixture of the desired product **2.55**, variable amounts of the diiodo compound **2.57** and the double bond isomer **2.58** (~10-15%) were isolated (**Scheme 2.10**).
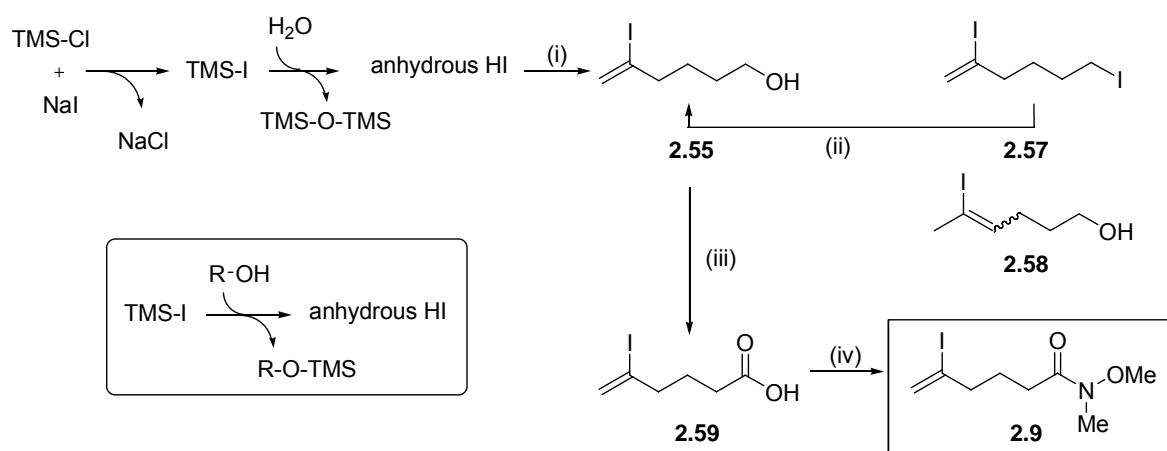
Scheme 2.10   Preparation of **2.9**.

Reagents and yields: (i) NaI (2.2 equiv), TMSCl (2.2 equiv), H_2O (1.1 equiv), 5-hexyn-ol (1 equiv), MeCN, rt, 2 h; (ii) LiOH (5 equiv), H_2O/dioxane (1:1) (83%); (iii) Jones' reagent (1.2 equiv), acetone, 0°C (87%); (iv) *(a)* (COCl)$_2$ (1.2 equiv), CH_2Cl_2, cat DMF, 0°C; *(b)* N(Me)OMe.HCl (1.05 equiv), pyridine (2.2 equiv), CH_2Cl_2 (98%).

The diiodohexene **2.57** could be readily isolated *via* column chromatography and selectively hydrolysed to **2.55** under basic conditions.[136] However **2.55** and **2.58** were unable to be separated *via* chromatography or distillation. Examination of the original report's supplementary information revealed that their isolated product **2.55**, was also contaminated with ~15% of **2.58**.[134] Efforts to improve the yield of **2.55** whilst minimising the formation of **2.57** and **2.58** were uniformly unsuccessful. Limiting the amount of HI reduced the isolated yield of **2.55** to ~20-30% without eliminating **2.58**, and shorter reaction times resulted in the return of starting material. It was found that the hydroiodination reaction proceeded in the absence of added water, and even with the addition of 4Å molecular sieves, presumably *via* participation of the alcohol functional group forming a silyl ether to liberate HI (**Scheme 2.10** - *inset*). The di-iodo species

2.57 could be generated exclusively in 84% yield when the reaction was run overnight with 3 equivalents of HI.

Protecting group strategies for the alcohol functional group were limited due to ability of HI to act as an ether and silyl cleaving agent.[137] Hydroiodination of various derivatives (acetyl-protected, 5-hexynoic acid and 5-hexynoate methyl ester) were unsuccessful in generating the desired material in synthetically useful yields. Alternative hydrohalogenative protocols have reported diminished yields (36-55%) or the significant formation of isomerised 2-alkenyl halides (10-25%) when performed on alkynols.[135,138]

Optimised conditions were developed which provided access to 5-iodo-hex-5-ene-1-ol (**2.55**) in 36-40 % yield (contaminated with ~2-5 % 5-iodo-hex-4-ene-1-ol **2.58** when 2 equivalents of anhydrous HI were used and the reaction time was restricted to 1 hour at ambient temperature.

Oxidation of the vinyl iodide **2.55** was performed smoothly with Jones' reagent,[139] to yield the acid **2.59**, which was converted to the Weinreb amide **2.9** using standard conditions.[140] Alternatively, the crude hydroiodination material could be oxidised and isolated by subsequent base/acid extraction without chromatography to give the purified acid **2.59** (64%, two steps).

2.6.1.2   Preparation of *N*-Methoxy-*N*-methyl -5-tributylstannyl-5-hexenamide 2.7

Access to the vinyl stannane equivalent **2.7** was desirable to allow for the full investigation of the Stille cross-coupling reaction. Palladium-catalysed hydrostannylation of **2.53** gave good stereocontrol (*syn*-addition) but poor regiocontrol. Superior regioselectivity for the desired α-adduct **2.56** was observed with stannylcupration protocols (**Table 2.3**).

Table 2.3   Hydrostannylation studies of **2.53**.
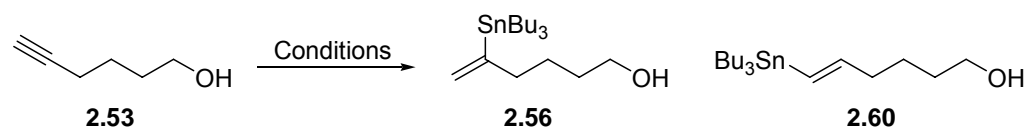
	Reagent and Conditions	**2.56^a**	**2.60**
1	PdCl$_2$(PPh$_3$)$_2$, Bu$_3$SnH, THF	31 %	57%
2	Bu$_3$Sn.Cu.SMe$_2$, THF, -48°C^{b,c}	45%	11%
3	Bu$_3$Sn(Bu)Cu(CN)Li$_2$, THF, -78°C^d	73%	15%

Notes: (a) refers to chromatographically pure isolated yields; (b) required the used of freshly prepared CuBr.Me$_2$S; (c) stirred at -78°C, alkyne added in THF/MeOH, stirred at -63°C / 6 h; (d) stirred at -78°C / 2 h and quenched with the addition of MeOH.

Guibe *et al.* reported that the palladium-catalysed hydrostannylation of alkynyl alcohols displays diminished α-regioselectivity for elongated carbon chains (n = 5-7). The increased geometric and torsional constraints associated with forming the larger palladacycle-heteroatom chelate ring (**Figure 2.15 - 2.32)** was postulated to be responsible for the reduced α-regioselectivity compared to small chain lengths.[98]

Stannylcupration was successfully achieved using both the higher order stannylcuprate (Bu$_3$Sn(Bu)Cu(CN)Li$_2$) (**2.45**), and lower order stannyl copper reagents (Bu$_3$Sn.Cu.SMe$_2$) (**2.61**). Piers has reported that the stannylcupration of **2.53** and 1-chlorohex-5-yne with Me$_3$Sn.CuSMe$_2$ proceeded regioselectively at the α-position in high yield (85% and 80% respectively, with regioisomeric material observed in ~2-10% yield).[141-144] The tributyltin analogue **2.61** was observed to react under the stated conditions to give a crude mixture containing **2.53**, **2.56** and **2.60** in a ratio of 11:78:11. Column chromatography on basified silica gave **2.56** in an isolated yield of 45% *(entry 2)*.

Barbero reported that many of the limitations of lower order stannyl copper species such as **2.61** could be overcome with the use of higher order stannylcuprates which display greater reactivity and stability.[145] Dominguez reported that the reaction of **2.53** with Bu$_3$Sn(Bu)Cu(CN)Li$_2$ (**2.45**) gave an 62% isolated yield of **2.56**, but did not comment on the generation of isomeric **2.60**.[34] In the author's hands, the addition of stannyl cuprate **2.45** to a solution of **2.53** in THF at -78°C, which was then allowed to stir at -78°C for 2 hours and quenched with the addition of excess MeOH, generated a 5:1 regioselective mixture of **2.56**:**2.60**. Following column chromatography, the α- and β-vinyl stannanes were isolated as pure colourless liquids in 73% and 15% yield respectively *(entry 3)*.

Although it was shown that the use of stannylcuprates provide a convenient access to 5-tributylstannylhex-5-ene-1-ol (**2.56**) and that such vinyl stannanes are amenable to further functional group manipulation,[34,146] including the conversion to isomerically pure 5-iodo-hex-5-ene-1-ol (**2.55**), further synthetic manipulation was not pursued, due to the success of stannylation of the Weinreb's amide hexyne **2.54**, (*vide infra*).

2.6.2   ROUTE B

2.6.2.1   Preparation of *N*-Methoxy-*N*-methyl-5-iodo-5-hexenamide 2.9

In parallel with the functionalisation reactions of 5-hexyn-1-ol, studies were conducted on the alkyne amide **2.54**, using similar hydroiodination and hydrostannylation conditions.

Alkyne amide **2.54** was readily prepared in high yield, *via* a two step oxidation–amide formation protocol (**Scheme 2.11**). Hydroiodination of **2.54** using the conditions of Yu and Jin, when conducted with 3 equivalents of TMSI-MeOH, resulted in a crude 76:24 mixture of **2.9**:**2.54**. Careful Kugelrohr distillation (95-100°C/0.2 mmHg) yielded the iodide **2.9** in 100% yield (b.r.s.m.) and **2.54**, which could be recycled. The alternative procedure of Ishii, using TMSI generated *via* the reaction of TMS-Cl and NaI in acetonitrile, yielded isomerically impure **2.9** in an isolated yield of 38%.
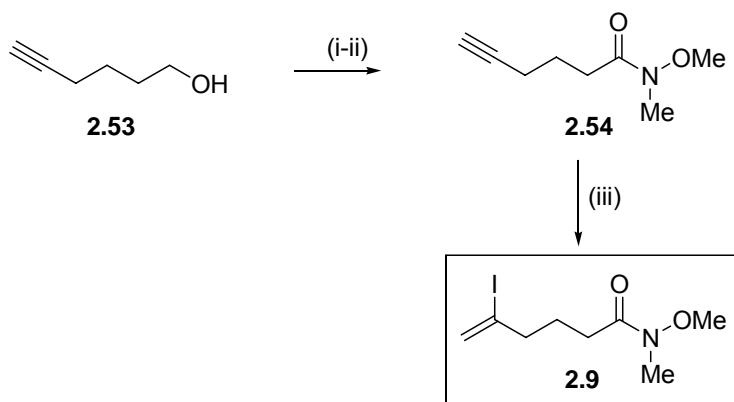
Scheme 2.11 Preparation of vinyl iodide **2.9**.

Reagents and yields: (i) Jones' reagent (1.2 equiv), acetone, 0°C, distillation, 99%; (ii) *(a)* (COCl)$_2$ (1.2 equiv), CH$_2$Cl$_2$, cat. DMF, 0°C; *(b)* HN(Me)OMe.HCl (1.05 equiv), pyridine (2.2 equiv), CH$_2$Cl$_2$ (98%); (iii) TMSI (3 equiv), MeOH (3 equiv), CH$_2$Cl$_2$, -78°C, Kugelrohr distillation, **2.9** 76% (100% b.r.s.m.).

2.6.2.2 Preparation of *N*-Methoxy-*N*-methyl -5-tributylstannyl-5-hexenamide 2.7

Hydrostannylation of **2.54** was conducted using the protocols previously discussed **(Table 2.4)**.

Table 2.4 Hydrostannylation studies of alkyne **2.55**.

	Reagent and Conditions	2.7[a]	2.62
1	PdCl$_2$(PPh$_3$)$_2$, Bu$_3$SnH, THF[b]	31	57
2	Bu$_3$Sn.Cu.SMe$_2$	32	10
3	Bu$_3$Sn(Bu)Cu(CN)Li$_2$, THF, -78°C	61	20

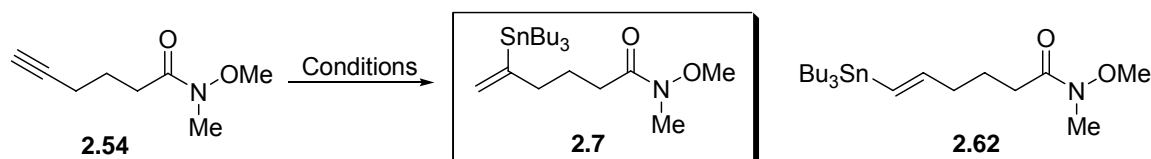(a) All yields refer to isolated chromatographically pure yields; (b) Ratio of products assessed by ^{1}H NMR integration, not isolated.

The palladium-catalysed addition of tributyltin hydride displayed a regiochemical preference for the distal stannylation product **2.62** (entry 1), which was independent of the rate of hydride addition.

Attempted stannylcupration utilising the lower order stannyl-cuprate Bu$_3$Sn.Cu.SMe$_2$ (**2.61**) gave a crude mixture comprised of **2.54**, **2.7** and **2.62** in a ratio of 13:71:16. Chromatography gave isomerically pure **2.7** in an isolated yield of 32%. Castano *et al.* have reported that purification of stannane mixtures can be achieved by brief treatment of the crude mixtures with *p*-TsOH, which leads to the selective proto-destannylation of the more labile terminal vinyl stannane derivative.[147] However, complete destannylation to yield the terminal alkene was observed when this treatment was applied.

The use of the higher order stannylcuprate Bu$_3$Sn(Bu)Cu(CN)Li$_2$ (**2.45**) resulted in a mixture of **2.7** and **2.62** in a ratio of 88:12. Chromatography on basified silica gave an isolated yield of 61% of **2.7** and an inseparable mixture comprised of **2.7** and **2.62.**

These results are in agreement with the previous synthetic studies by Piers[143] and Oehlschlager,[124,148] which indicated that internal stannanes are formed preferentially under thermodynamic conditions for both higher and lower order cuprates.

2.7   Summary of Coupling Fragment Preparation

Synthetic generation of *E*-1-methoxy-1-iodopropene **2.6** was achieved from 1-methoxypropyne (**2.12**) under the conditions of Yu and Jin, with subsequent halogen-metal exchange allowing the isolation of *E*-1-methoxy-1-tributylstannylpropene **2.8** in excellent yield. Also of synthetic interest was the exclusive generation of the isomer **2.42** using palladium-catalysed hydrostannylation and stannylcupration techniques. These two complementary techniques allow stereoselective access to the two regioisomeric *trans*-alkoxy-vinyl stannane adducts **2.8** and **2.42**.

The vinyl iodide species **2.9** was obtained in excellent yield using a hydroiodination protocol. The analogous vinyl stannane amide **2.7** was prepared, utilising stannylcupration methodology, in good yield.

The successful synthesis of complementary reactive partners **2.6/2.7** and **2.8/2.9** allowed investigations into the palladium-mediated cross-coupling reaction to proceed.
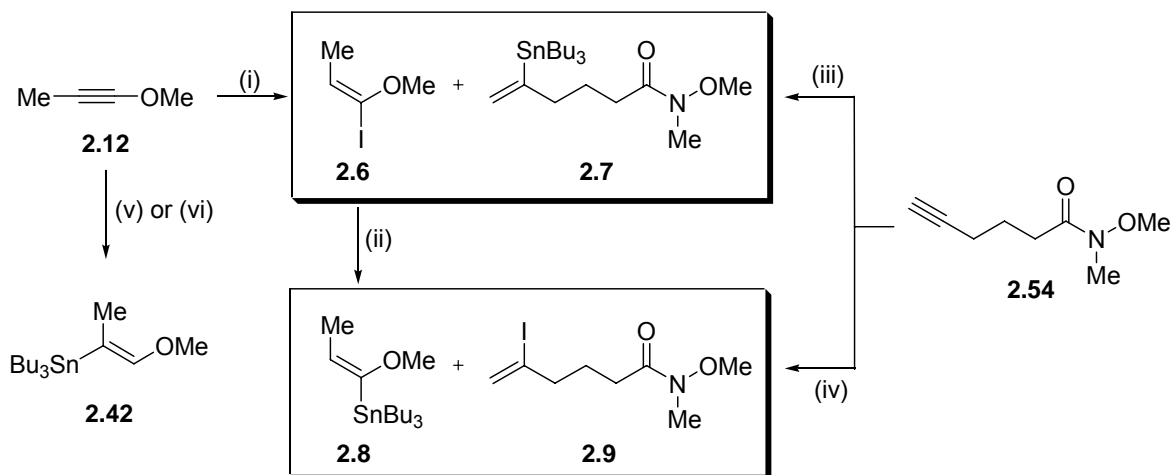
Scheme 2.12 Summary of optimised routes to the preparation of coupling fragments **2.6**, **2.8**, **2.9** and **2.7**.

Reagents and yields: (i) TMSI (1 equiv), MeOH (1 equiv), CH$_2$Cl$_2$, -78°C → 0°C, quantitative; (ii) (i) *n*-BuLi, ether, -100°C → -50°C; Bu$_3$SnCl, 87% (from **2.12**); (iii) Bu$_3$Sn(Bu)Cu(CN)Li$_2$, THF-MeOH, -78°C, 61%; (iv) TMSI (3 equiv), MeOH (3 equiv), CH$_2$Cl$_2$, -78°C → 23°C, 76%; (v) Bu$_3$SnH, Pd(PPh$_3$)$_2$Cl$_2$, THF, rt, 96%; (vi) Bu$_3$Sn(Bu)Cu(CN)Li$_2$, THF, -78°C, 99%.

2.8   Fragment Coupling Reactions

2.8.1   Preparation of Dienes *via* Stille Coupling

Successful synthesis of the complementary partners **2.6/2.7** and **2.8/2.9** allowed investigation of the transition metal-mediated coupling to form the diene system of amide **1.70**. A large number of coupling conditions have been utilised to maximise yields in the occasionally capricious Stille reaction.[18,32,149] A number of the more promising palladium catalyst and solvent systems were surveyed (**Table 2.5**).
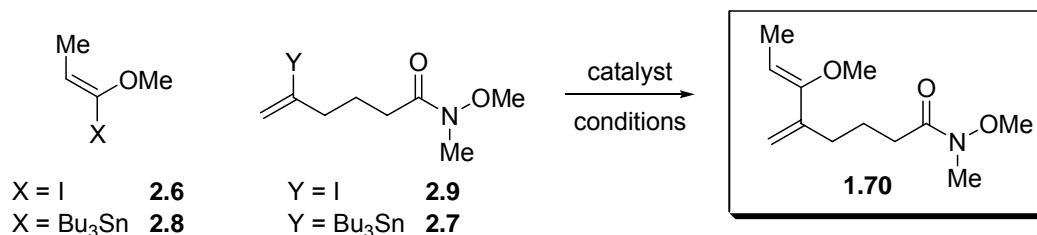
Table 2.5   Stille coupling of vinyl alkene fragments to form **1.70**.

Entry	Reagents	Catalyst	Conditions[a]	Results[b]
1	**2.6/2.7**	Pd$_2$(dba)$_3$, CuI, AsPh$_3$	NMP, 50°C	n.r[c]
2	**2.8/2.9**	PdCl$_2$(PPh$_3$)$_2$	THF, 40°C	23%[d,e]
3	**2.8/2.9**	Pd (PPh$_3$)$_4$	THF, 40°C	n.r
4	**2.8/2.9**	Pd(PPh$_3$)$_4$	Benzene, 80°C	n.r[d]
5	**2.8/2.9**	Pd(PPh$_3$)$_2$Cl$_2$	DMF, 80°C	24%
6	**2.8/2.9**	Pd(MeCN)$_2$Cl$_2$	DMF, 54°C	10%
7	**2.8/2.9**	Pd$_2$(dba)$_3$, CuI, AsPh$_3$	NMP, 54°C	71%[e]
8	**2.8/2.9**	Pd$_2$(dba)$_3$, CuI, AsPh$_3$	DMF, 54°C	73%
9	**2.8/2.9**	Pd$_2$(dba)$_3$, P^{t}Bu$_3$	DMF, 54°C	42%[e]
10	**2.8/2.9**	Pd$_2$(dba)$_3$, P^{t}Bu$_3$	NMP, 54°C	32%[e]

Note (a) Reactions were performed on 0.25 mmol scale with **2.9/2.7** (1 equiv), **2.6/2.8** (1.1 equiv) and catalyst loadings of 5 mol % (Pd); 20 mol % AsPh$_3$ or P^{t}Bu$_3$; and 20 mol % CuI where relevant. All reactions were subjected to six successive freeze-pump-thaw cycles, protected from light in aluminium foil and stirred under dry Ar for 12 h at the stated temperature; (b) Progress of the reaction was monitored *via* ^{1}H NMR spectroscopy of sample aliquots. Yields refer to chromatographically pure isolated material. (c) Decomposition of **2.6**. (d) Decomposition of **2.9** yielding a terminal olefin. (e) Conversion based on ^{1}H NMR integration of olefinic proton ratios [**2.9**:**1.70**].

It readily became apparent that the vinyl iodide **2.6** was unstable to the conditions required for coupling. The vinyl stannane **2.7** was quantitatively re-isolated from the reaction mixture *(entry 1)*. Consequently, focus was turned to **2.8** and **2.9** as coupling partners.

Of the reaction conditions investigated, non-polar or ethereal solvents resulted in poor conversion rates and the decomposition of the vinyl iodide **2.9** to a terminal olefin *(entries 2-4)*. The conditions described by Farina, utilising polar coordinating solvents (NMP or DMF), with ligands of lower denticity (As(PPh)$_3$ or TFP) and CuI as a co-catalyst, resulted in clean conversion to the required diene system with no observed decomposition products.[32,33] The reaction in DMF was observed to proceed to completion, allowing the isolation of the desired diene **1.70** in 73% yield after column chromatography *(entry 8)*. The Stille coupling of fragments **2.8** and **2.9** was found to be reproducible on a 5 millimole scale giving 58-73% yield of the diene system **1.70**. Importantly, the reaction proceeded with complete retention of stereochemistry, with no isomerisation of either vinyl moiety detectable *via* ^{1}H NMR spectroscopy.

Application of the optimised coupling conditions to the cross-coupling of **2.51** and **2.9** resulted in efficient coupling to generate **1.81** in 63% yield (**Scheme 2.13**).
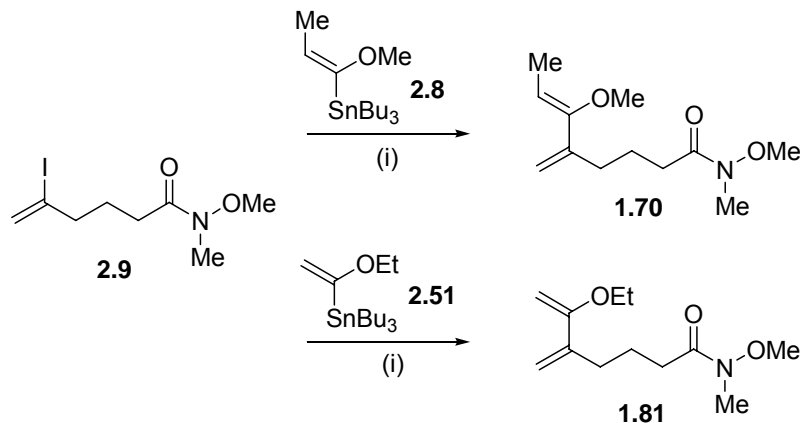
Scheme 2.14 Preparation of dienes **1.70** and **1.81** using Stille coupling.

Reagents and yields: (i) **2.9** (0.8 equiv), **2.8** or **2.51** (1 equiv), Pd$_2$(dba)$_3$ 5 mol %, AsPh$_3$ 20 mol %, CuI 20 mol %, DMF, 65°C, 12 h, **1.70** 73%, **1.81** 63%.

An important aspect of the handling and purification of these diene compounds was the necessity to perform extractions and column chromatography under neutral or mildly basic conditions. Trace quantities of acid resulted in the decomposition of the methyl and ethyl-enol ethers to the parent ketone structures (**Figure 2.21**).
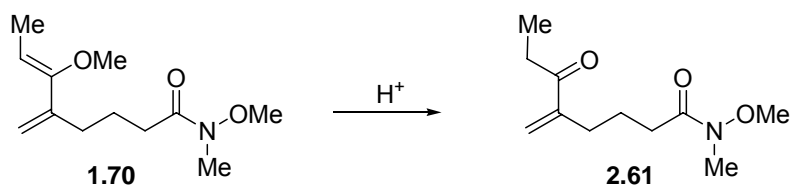
Figure 2.21   Acid catalysed decomposition of the enol-ether moiety.

To avoid decomposition, it was found beneficial to quench reactions with an aqueous solution comprised of (10:1) saturated ammonium chloride and saturated sodium bicarbonate. Flash column chromatography was performed on triethylamine-basified silica gel, with the inclusion of 1% triethylamine in the eluant.

2.8.2   Preparation of Dienes *via* Negishi Coupling

The preparation of the vinyl organozinc species **2.52**, **2.64** and **2.65** was achieved *via* the *in-situ* transmetallation of the respective vinyl magnesium or vinyl lithium species with anhydrous $ZnCl_2$ in ether.[130,150,151] Palladium-catalysed cross-coupling of these vinyl zinc species with vinyl iodide **2.9** resulted in excellent yields for all three organo-zinc species (**Scheme 2.14**).
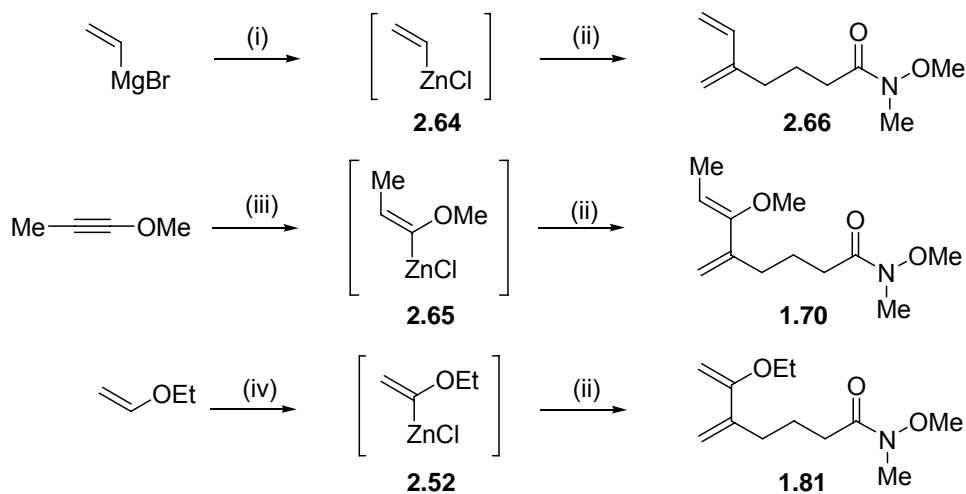
Scheme 2.14   Preparation of dienes **1.70**, **1.81** and **2.66** *via* Negishi coupling.

Reagents and yields : (i) $ZnCl_2$, THF; (ii) Pd(PPh₃)₄ 5 mol %, THF, **2.9**, rt, 12 h; (iii) *(a)* TMSI, MeOH, CH₂Cl₂, -78°C → rt, 1 h; *(b)* *n*-BuLi, -90°C →-25°C; *(c)* $ZnCl_2$, THF; (iv) *(a)* *t*-BuLi, -98°C, 30 min; *(b)* $ZnCl_2$, THF; **2.66** 77%, **1.70** 100%, **1.81** 95%.

Notable in this reaction sequence is the complete chemoselectivity of the organozinc reagents, neither undergoing nucleophilic attack at the amide functionality, nor deprotonating the acidic α-

carbonyl proton. Excellent stereoselectivity was observed in the preparation of **1.70**, with no products arising from isomerisation of any of the *in-situ* intermediates.

The utility of the Negishi coupling is further enhanced by the ability to use excess zinc coupling reagent to ensure complete consumption of the vinyl iodide **2.9**. A simplified work-up involving concentration of the reaction mixture under rotary evaporation to form a thick oil and extraction through a short plug of alumina gave the pure diene in high yield. In contrast, the reaction mixtures derived from Stille couplings require the use of extractive work-up and extensive column chromatography to remove tin by-products.

The multiple consecutive transmetallations achieved in the preparation of **1.70** is striking. A regio- and stereoselective hydroiodination *(i)*, lithium-halogen exchange *(ii)*, transmetallation to zinc *(iii)* and then participation in the palladium-catalysed coupling cycle *(iv)* to effect coupling with vinyl iodide **2.9** *(v)* is achieved in excellent yield with complete retention of stereochemistry in a single reaction vessel (**Figure 2.22**).
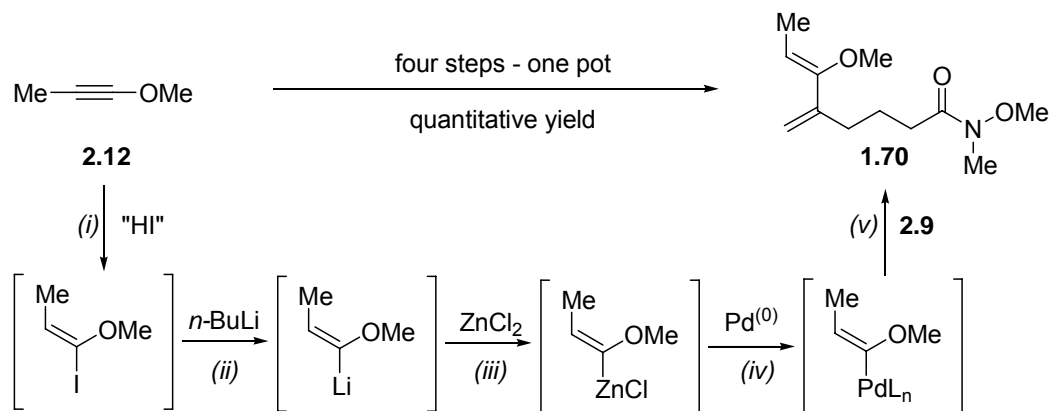
Figure 2.22   One pot generation of the diene moiety *via* Negishi coupling.

2.9   *Preparation of the Diels-Alder Trienone Precursors*

The prepared diene amide systems **1.70**, **1.81** and **2.66** were readily converted to Diels-Alder precursor trienones **1.69**, **1.80** and **2.67** in a single step upon reaction with excess vinyl magnesium bromide in THF at room temperature (**Scheme 2.15**).
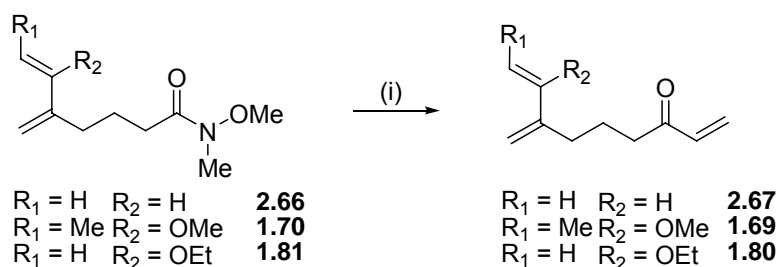
Scheme 2.15   Preparation of Diels-Alder precursors.

Reagents and yields: (i) vinyl magnesium bromide (2 equiv), THF, rt, 12 h, 95-98%.

N-Methoxy-*N*-methyl-amides (Weinreb amides) form stable metal chelating tetrahedral intermediates (**2.68**) upon reaction with an organometallic reagent which prevent subsequent addition to the nucleophilic carbonyl centre (**Figure 2.23**). Upon aqueous work-up, collapse of the tetrahedral intermediate delivers a ketone product, even in the presence of excess organometallic reagent.[140]
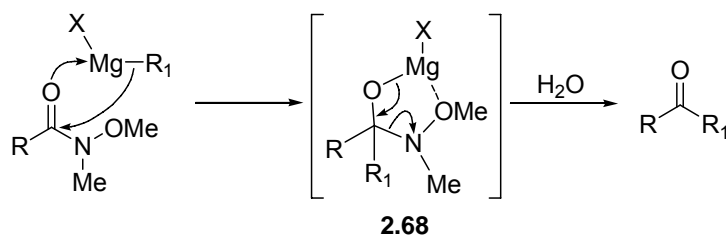
Figure 2.23   Proposed chelate intermediate responsible for mono-alklation.

The triene systems **1.69**, **1.80** and **2.67** were sensitive to acid catalysed hydrolysis and polymerisation reactions when concentrated. However, the isolated triene systems could be stored frozen in benzene without discernable degradation over a period of several months.

2.10   Summary

A concise synthesis of three IMDA triene systems has been developed. This synthesis involved the regio- and stereoselective preparation of vinyl stannane and vinyl iodide species that were coupled utilising Stille and Negishi cross-coupling methodology.

With the successful synthesis of the stereochemically pure Diels-Alder precursors investigation of the intramolecular type II Diels-Alder reaction was pursued. This work is detailed in **Chapter Three**.

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Chapter Three

The Diels-Alder Reaction Directed Towards the Synthesis of Bicyclic Natural Products

3.1   The Diels-Alder Reaction

The [4+2] cycloaddition of a 1,3-diene and an alkene was placed in a synthetic context by the work of Diels and Alder in 1928, who reported the reaction of several dienes and alkenes (**Figure 3.1**).[1] The observed reaction constituted a concerted pericyclic rearrangement with the formation of two carbon σ-bonds and one π-bond. A more detailed mechanistic understanding of the Diels-Alder reaction was achieved with the development of frontier molecular orbital theory (FMO) and the Woodward-Hoffmann rules as they relate to concerted pericyclic reactions.[2-6]
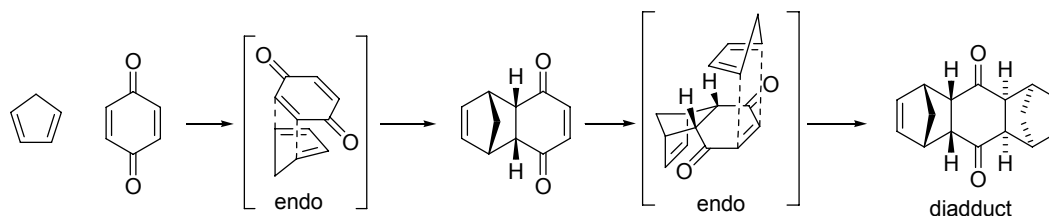

Figure 3.1   [4+2] Cycloaddition of cyclopentadiene and benzoquinone discovered by Diels and Alder.

The synthetic power of the Diels-Alder reaction lies in its ability to allow rapid access to highly functionalised stereodefined cyclohexene structures in a single operation from an acyclic precursor. Up to four contiguous centres and a double bond are created in a single stereospecific operation, in which the relative stereochemical relationships present in the diene and dienophile are conserved. High levels of regioselectivity and diastereoselectivity (*endo vs. exo*) are often possible.[7,8]

Experimentally, the scope of the Diels-Alder reaction has been extended to include intramolecular reactions,[9-11] transannular cyclisations (TADA)[12] and hetero-Diels-Alder reactions. Synthetic efforts to improve the rate and yield have focused on the use of Brönsted and Lewis acid catalysis,[8] high pressure,[13] microwave, ultrasound and salt enhancement.[14,15]

At a strategic level, the application of a Diels-Alder reaction is a powerful tactic to employ as the key step in a synthesis due to its ability to greatly increase molecular complexity.[16] This is evidenced by the extensive employment of Diels-Alder reactions in the synthesis of a wide range of natural products.[7,17-20]

However, despite the enormous potential of the Diels-Alder reaction, isomer control remains as a serious limitation to its effective employment in solving synthetic problems. Efforts have been made to control the regioselectivity, enantioselectivity, and diastereoselectivity of the Diels-Alder reaction employing chiral Lewis acids, chiral auxiliaries, chiral catalysts, Umpulong equivalents and intramolecular reactions, which define the correct geometrical orientation of the diene and dienophile components.

The examples in **Figure 3.2** and **Figure 3.3** illustrate synthetic advances in the use of both the intermolecular and intramolecular Diels-Alder reactions to secure appropriate regiochemical and stereochemical dispositions of functionality, to provide a rigid scaffold for stereoselective elaboration and to form multiply fused bicyclic structures in the pursuit of natural products.
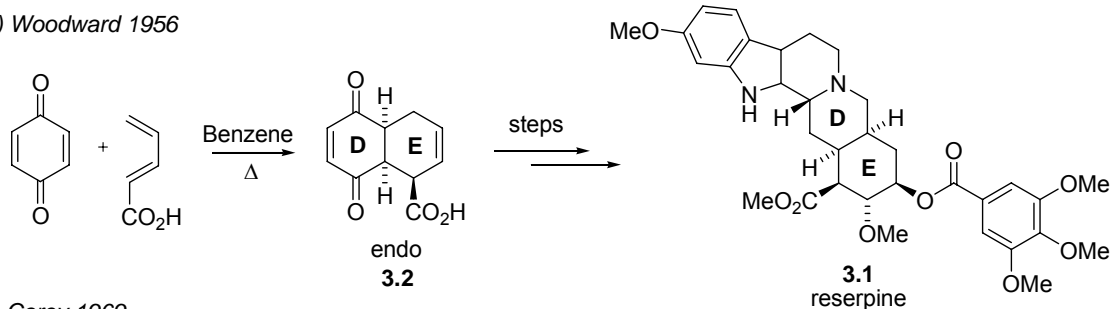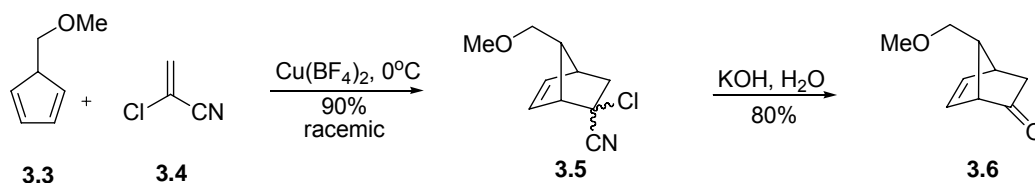
Figure 3.2   Synthetic advances in the application of the intermolecular Diels-Alder reaction to natural product chemistry.

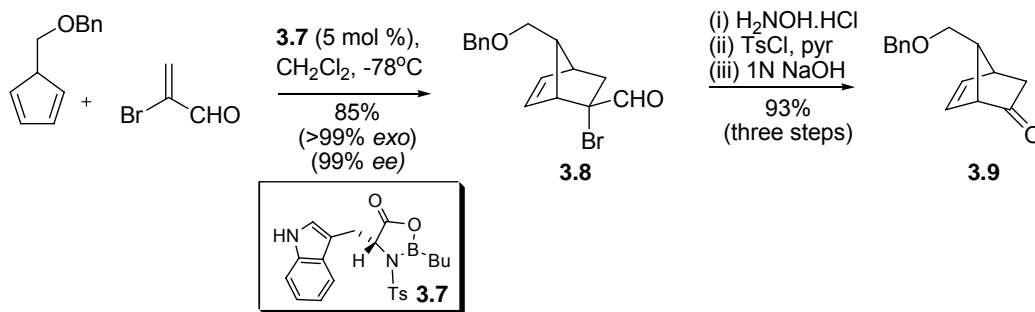In the first example *(A)*, Woodward's 1956 total synthesis of reserpine (**3.1**) opened with a Diels-Alder reaction to form the critical E bicyclic system. The stereochemically pure ester group **3.2**, derived from an *endo*-selective cyclisation, was used as a scaffold for the ensuing synthetic sequence establishing all five stereocentres in the E-ring.[21,22]

Remarkable advances in controlling the absolute stereochemistry of the intermolecular Diels-Alder reaction have been observed in the total syntheses of prostaglandins by the research group of Corey. In the initial approach, *(B)*, a Lewis acid-catalysed Diels-Alder reaction between diene **3.3** and ketene equivalent, 2-chloroacrylonitrile (**3.4**), afforded a racemic mixture of **3.5** with a random *exo/endo* distribution of the dienophile substituents.[23] The (+)-ephedrine salt was used to resolve the mixture to the natural epimer.[24] Successive advances utilising chiral auxiliaries[25] and then asymmetric catalysis,[26,27] such as the chiral oxazaborolidinone catalyst **3.7**, that allows discrimination between the enantiotopic faces of the dienophile, have led to the preparation of adduct **3.8** with a high enantiomeric excess in excellent yield *(C)*. The enantiomerically pure norbornen-2-one adducts **3.6** and **3.9** were advanced to form the natural (+)-prostaglandin $F_2\alpha$ and related prostaglandins.
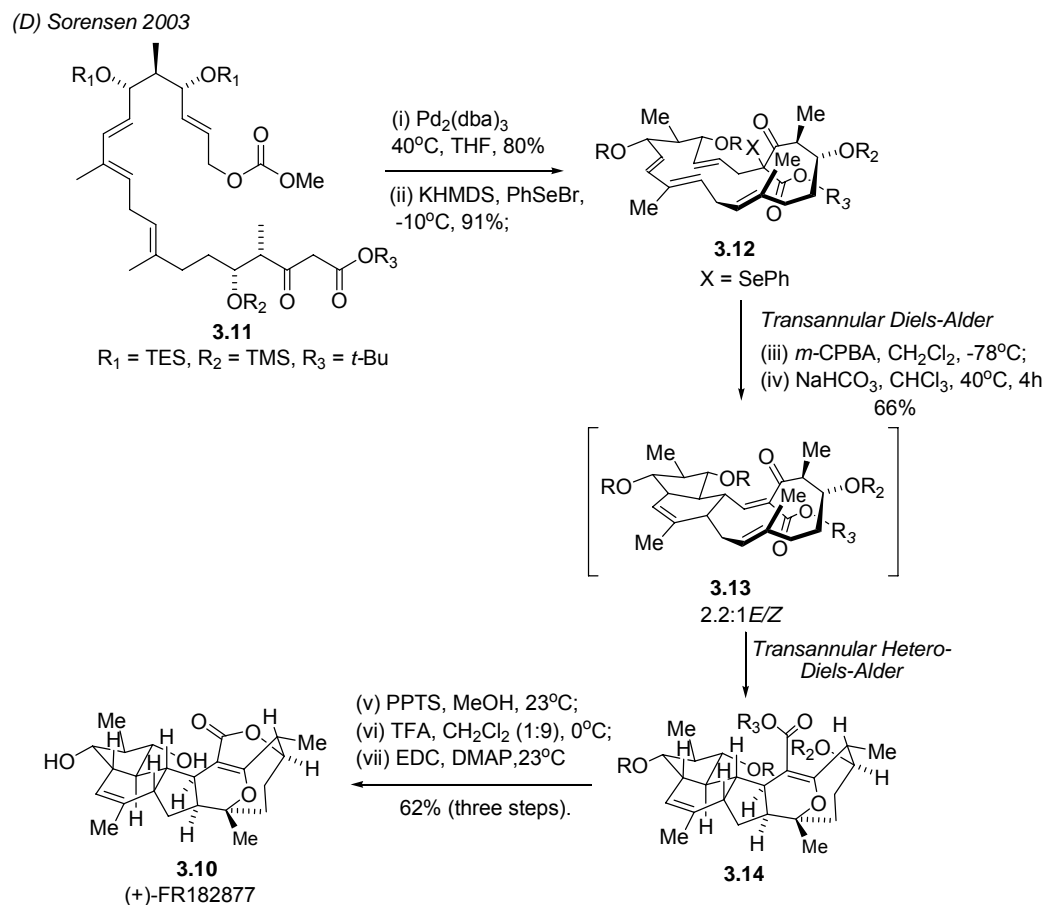

Figure 3.3   Sorensen's application of an IMDA reaction en route to (+)-FR182877.

The recent synthesis of the unnatural epimer of the potent antitumour agent (+)-FR182877 (**3.10**) by Sorensen *et al.* readily demonstrates the powerful ability of the Diels-Alder reaction to form architecturally complex natural products from polyunsaturated macrocycles.[28,29] Based on a biogenetic postulate, a Trost-Tsuji ring closure of **3.11** afforded the tetraene macrocycle **3.12**, from which selenium incorporation and then oxidative-elimination forms the Diels-Alder precursor. A sequential tandem transannular Diels-Alder-transannular hetero-Diels-Alder reaction was observed to proceed under mild conditions to generate the seven new stereocenters and 5 new rings present **3.14**. It was calculated that the desired *E*-isomer **3.13**, arising from deselenation, was converted quantitatively to the (+)-FR182877 carbocyclic skeleton **3.14**. Evans *et al.* reported a similar tandem transannular Diels-Alder reaction to form the natural epimer (-)-FR182877.[30]

3.2   *Intramolecular Diels-Alder Reactions*

The [4+2] pericyclic reaction, as reported by Diels and Alder, was initially investigated in the context of the intermolecular reaction, focusing on the stereospecific and regiospecific union of two separate entities. By contrast, the intramolecular Diels-Alder (IMDA) reaction, where the diene is attached to the dienophile *via* a tether, was not investigated extensively until the 1960s.

The first use of the IMDA reaction in the context of natural product synthesis was reported in 1963, with the preparation of γ-apopicropodophyllin (**3.15**).[31] The cinnamyl phenyl propiolate **3.16**, prepared *via* esterification of the respective *E*-cinnamyl alcohol and acid chloride, when subjected to vigorous conditions resulted in the desired intramolecular cyclisation (**Figure 3.4**).
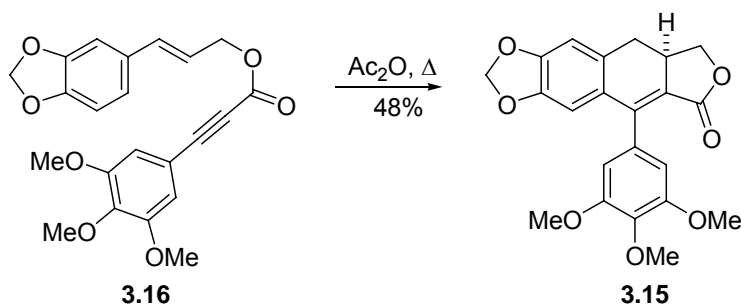

Figure 3.4   The application of an IMDA to form γ-apopicropodophyllin (**3.15**).

3.2.1   Synthetic Advantages of the IMDA Reaction

The synthetic advantages of utilising an intramolecular Diels-Alder reaction arise from the observation that many of the limiting electronic and steric requirements of the intermolecular Diels-Alder reaction, and the chemoselectivity and regioselectivity of the outcomes, can be favourably altered utilising an intramolecularly tethered triene system. The example in **Figure 3.4** illustrates the high regioselectivity achievable in IMDA reactions, primarily due to the torsional and geometric restrictions imposed by the dienophile tether.

The pre-organisation and orientation of the diene and dienophile diminishes the entropy requirements relative to the analogous intermolecular reaction allowing the IMDA reaction to proceed more readily. In addition, by incorporating a stereocenter in the triene precursor, discrimination between the diastereotopic faces of the diene and dienophile can be achieved.

These advantages have led to the extensive use of the IMDA in total synthesis and these applications have been reviewed.[9,11,17,32-36]

3.2.2   Type I and Type II IMDA Reactions

The IMDA reaction can be described as either type I or type II, depending on the position of attachment of the dienophile to the diene (**Figure 3.5**).
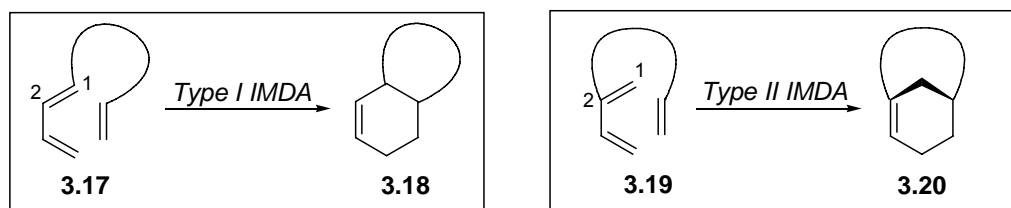
Figure 3.5   Type I and Type II IMDA connectivity and products.

The type I IMDA reaction, involving a C1 terminally connected diene and dienophile system (**3.17**), upon cyclisation forms a *fused* bicyclic ring system (bicyclo[*n*.4.0]alkene) with a connective bond in common (**3.18**). Type I reactions have been utilised to good effect in the preparation of a variety of organic targets and are well documented.[33,34,37-39]

The type II IMDA reaction, which features C2 connectivity (**3.19**) and delivers a *bridged* bicycle (bicyclo[*n*.3.1]alkene) (**3.20**) upon cyclisation, in contrast, has received less synthetic attention.[9]

3.2.3   Regioselectivity

Intermolecular Diels-Alder cyclisations of 2-substituted dienes and dienophiles with electron-withdrawing groups display an intrinsic regiochemical bias favouring the 1,4-disubstituted product (**3.21**) over the 1,3-adduct (**3.22**) *(A)*. This result is commonly interpreted in terms of FMO theory, through the calculated orbital coefficients of the HOMO diene – LUMO dienophile interaction.[40] In contrast, type II IMDA reactions forming small bicyclic rings exhibit a preference for the formation of the *meta*-cycloadduct (**3.23**), in part, due to torsional and geometric strain incurred in meeting the requirements for the effective overlap interaction of the relevant orbitals (**3.25** *vs* **3.26**) and because the *meta*-regioisomer (**3.23**) contains the trans-cycloalkene in the larger ring (**3.27** *vs* **3.28**) *(vide infra) (B)* (**Figure 3.6**).[9]
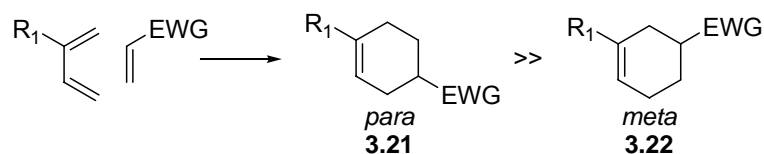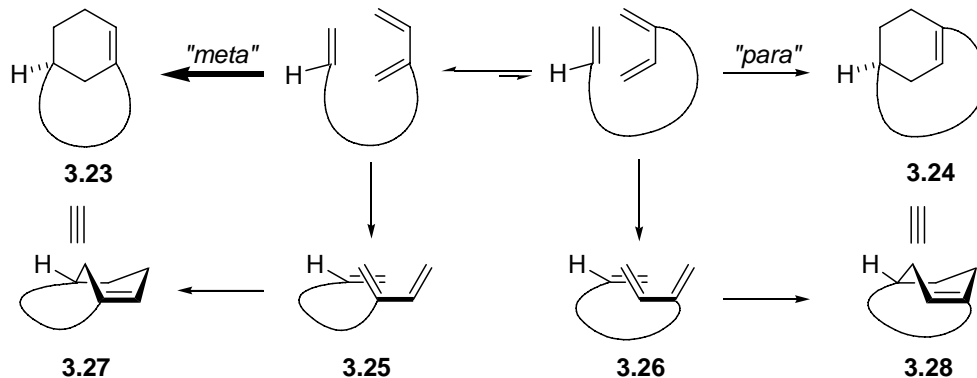
Figure 3.6   Divergent regiocontrol arising with an intramolecular tether.

The difference in energy between the *meta* and *para* isomers **3.23** and **3.24** diminishes as the tether size increases and the IMDA cycloaddition is increasingly influenced by the steric, conformational and electronic factors that affect intermolecular pericyclic reactions. When the tether contains 3-5 atoms, the *meta* regioisomer is the exclusive product of cycloaddition regardless of the dienophile's activation pattern, and the method of cyclisation (thermal or Lewis acid catalysis).[9]

3.2.4   Stereoselectivity

Secondary orbital interactions between the diene and dienophile are attributed as the origins of stereoselectivity in the intermolecular Diels-Alder reaction. These interactions, although typically less than several kcal mol^{-1} in magnitude (**3.29** *vs* **3.30**), result in the predominant formation of the *endo* adduct under kinetic control.[6] Type II IMDA reactions show complete stereoselectivity with cycloaddition taking place from a conformation where the tether occupies the *endo* position (**3.31**) affording an "out"-bridging adduct (**3.32**) as minimisation of torsional strain energy associated with the *exo* ether (**3.34**) dominates contributions from secondary orbital interactions (**Figure 3.7**).

Figure 3.7   Comparison of inter- and intramolecular stereoselectivity.

3.2.5   Bredt's Rule

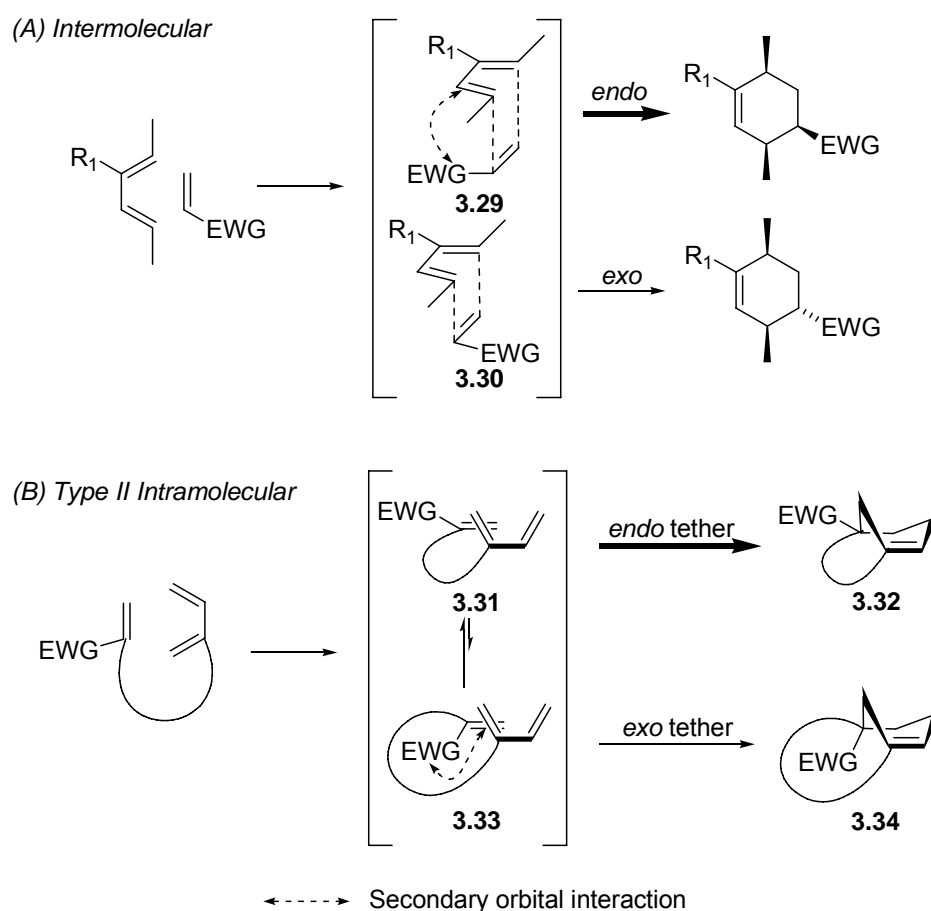An interesting theoretical aspect that has practical implications for the type II IMDA reaction is the observation that incremental contraction of the tether length (n), connecting the diene and dienophile (**3.35**), results in consecutively smaller bicyclo[n.3.1] fused systems with an olefinic bond at the bridgehead carbon (**3.36**) (**Figure 3.8**).
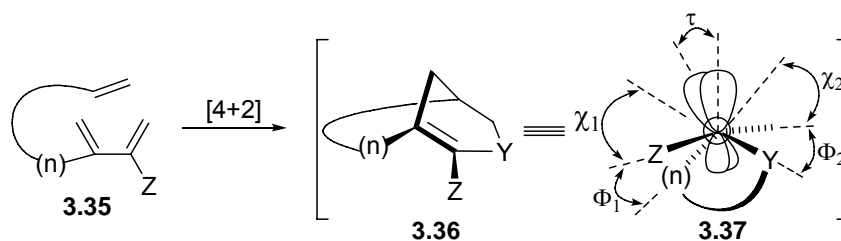
Figure 3.8   IMDA formation of bridgehead olefin bicyclo[n.3.1] systems.

The tether constraint results in conformational distortion of the olefinic sp^2 carbons away from the desired planar geometry giving rise to increased angular (Φ,χ) and torsional (τ) strain energies (**3.37**) and enhancing the chemical reactivity of the olefinic bond.[9,41] Whilst not violating Bredt's rule,[**] a bridgehead olefinic bond within a sufficiently restricted fused bicyclic skeleton can be viewed as representing a potentially strained molecular structure. This may allow more facile ring and bond rearrangement to relieve olefinic and ring strain associated with the double bond.

3.3   *Formation of Bridgehead Olefins via IMDA Reactions*

The type II IMDA and hetero-type II IMDA reactions have been extensively investigated and applied by K. Shea *et al.* to the formation of bridged bicyclic molecules.[9,42]

Significant interest in the use of the IMDA reaction to form bridged bicyclic structures occurred in the wider synthetic community with the discovery of Taxol™ (paclitaxel) **1.7**[43,44] and phomoidrides A and B.[45-47] These natural products possess a bicyclo[5.3.1]undecene and a bicyclo[4.3.1]decene core, respectively. The extensive research endeavours directed towards these natural products serve as a rich and instructive source of routes to bicyclo[n.3.1]carbocycles, and the application of IMDA methodology to form such systems.[48-50]

[**]The empirical observation that carbon double bonds cannot form at the bridgehead of small bicyclic camphane [2.2.1] and pinane [3.1.1] ring systems is formally called Bredt's rule.

Historically, the first examples utilising type II IMDA reactions to generate bridgehead alkene bicyclo[*n*.3.1]carbocyclic skeletons were achieved *via* the high temperature flow pyrolysis of activated and unactivated triene systems (**Figure 3.9**).[9] Some of these molecules had previously been synthesised by pyrolytic elimination of bridgehead substituted ammonium salts,[51] β-lactones,[52] and through intramolecular Wittig reaction[53] during investigations to define the limits of Bredt's rule and predict strain associated with bridgehead double bonds.
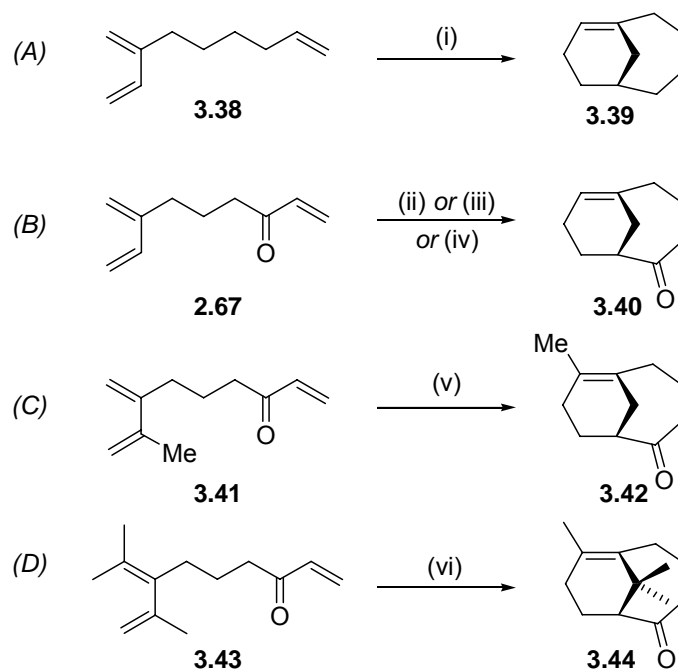
Figure 3.9   Shea's IMDA studies on activated and unactivated triene systems.

Reagents and yields: (i) flow pyrolysis, 455°C, 8s, 760 mmHg, N_2 carrier gas, 55% [GC]; (ii) flow pyrolysis, 398°C, 8s, 85% [GC]; (iii) 201°C, 15 min, 0.04-0.09 M xylene, sealed tube, 57% [GC]; (iv) 140°C, xylene, 30 mol % Proton-sponge®, 20 h, 57%; (v) Et_2AlCl (0.5 equiv), CH_2Cl_2, 15 min, 21°C, 70%, (vi) Et_2AlCl, CH_2Cl_2, 21°C, < 5 min, 70%.

Vigorous conditions were required for the thermally initiated IMDA reaction of unactivated triene systems (**3.38**) (400-500°C, gas phase, atmospheric pressure, with ca. 10-15s contact time) (**Figure 3.9**-*A*).[54] The inclusion of activating substituents on the dienophile (**2.67**) was found to moderate the conditions necessary to achieve cycloaddition, giving increased yields under flow pyrolysis techniques and allowing the use of sealed tube solution-phase thermolysis (*B*).[55,56] The synthetic utility was further extended with the use of Lewis acid catalysts that allowed low temperatures and short reaction times that are compatible with the construction of more highly functionalised bridged bicyclic structures (*C*) and (*D*).[57]

3.3.1   Stereoselective and Regioselective Elaboration of Bridged Bicyclic Olefins

As illustrated in **Figure 3.9**, Shea *et al.* demonstrated that direct cyclisation of an acyclic precursor *via* an IMDA reaction was a feasible synthetic route to the formation of medium-sized rings. Such systems present a significant challenge to other routes of preparation due to high entropic and enthalpic barriers.[58] Furthermore, the conformation restriction imposed by the bridged bicyclic skeleton enables stereoselective and regioselective elaboration to occur.[59]

The synthesis of ledol (**3.45**), a plant derived sesquiterpene, *via* what was termed a bridged-to-fused-ring interchange, illustrates many of these important aspects (**Figure 3.10**).[59,60]
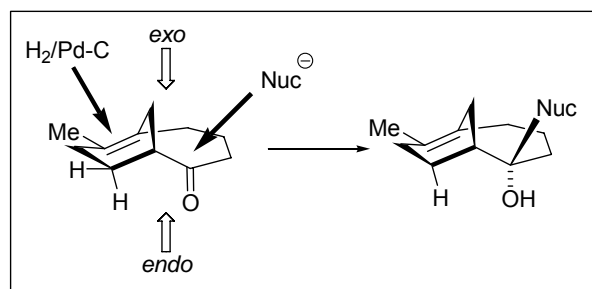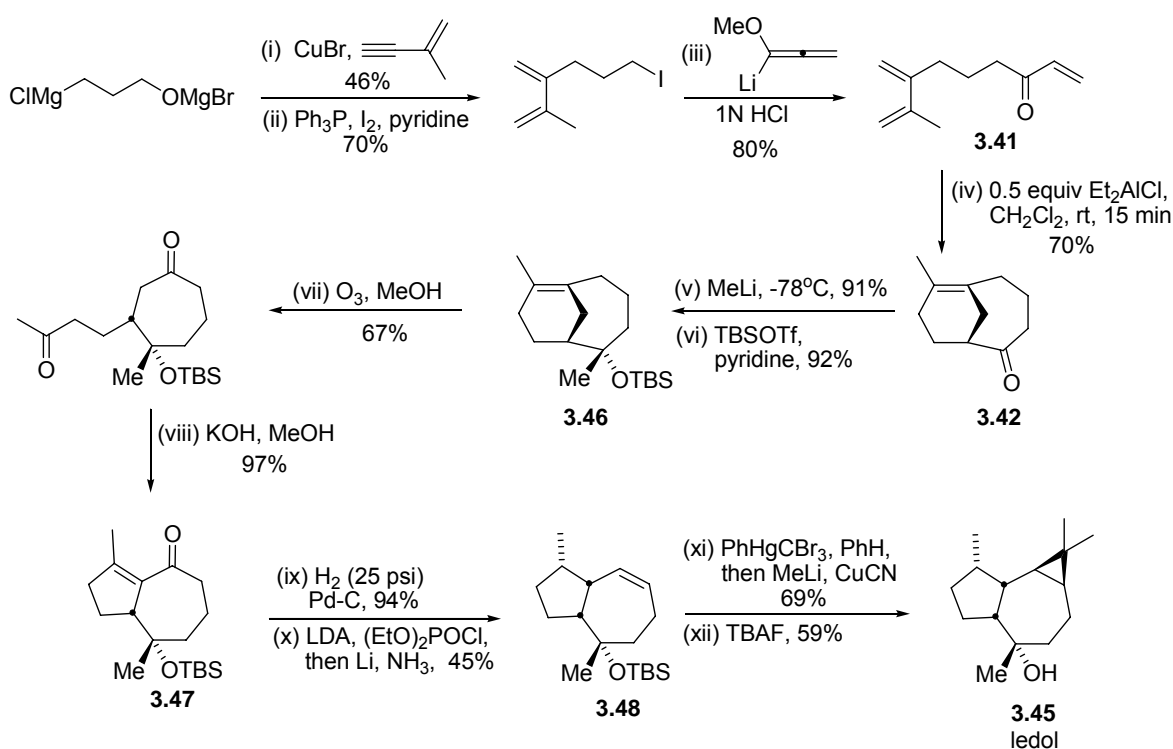

Figure 3.10   Synthesis of ledol utilising an IMDA reaction.

The readily prepared IMDA triene precursor **3.41**, when subjected to the Lewis acid diethylaluminium chloride at room temperature, cyclised rapidly to the corresponding bicyclic ring system **3.42**. Stereoselective control was observed with the addition of MeLi to the carbonyl functional group occurring from the less sterically hindered *exo* face (**Figure 3.10** - *inset*). The conformational bias resulted in the exclusive generation of the tertiary alcohol **3.46**. Ozonolysis of the bridgehead alkene, followed by base-promoted aldol condensation provided the fused bicyclic system **3.47** in high yield. Exclusive addition from the convex face to generate a single diastereomer is again observed in both hydrogenation, to generate the ring fused stereochemistry (**3.48**), and during dibromocyclopropanation with Seyferth's reagent. The synthetic sequence was readily concluded with gem-dimethylation and deprotection of the tertiary alcohol to generate ledol (**3.45**).

Another unique aspect that arises for constrained bicyclic conformations, is the ability to perform regioselective alkylations (**Figure 3.11**).[61]
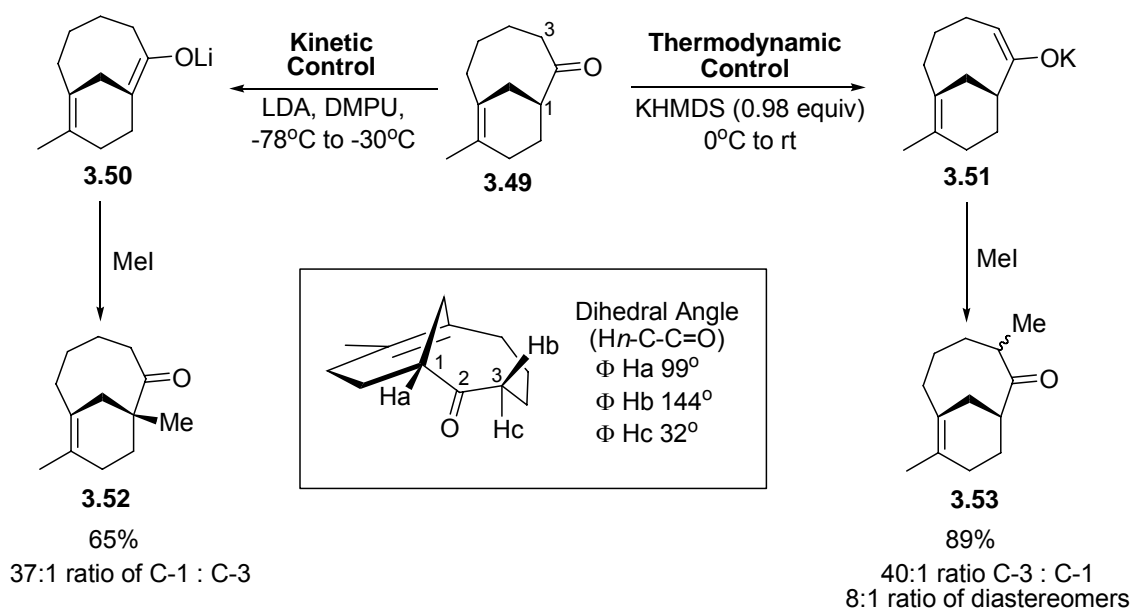
Figure 3.11   Regioselective alkylation of constrained bicyclic systems.

Deprotonation of bicyclo[5.3.1]undecenone **3.49** gives the more highly substituted bridgehead enolate **3.50** under kinetic control, whilst the less substituted enolate **3.51** is achieved under thermodynamic control. The origin of this selectivity can be understood by consideration of both stereoelectronic and strain factors. The stereoelectronic requirement for kinetic deprotonation is optimal with a C-H dihedral angle of 90° relative to the carbonyl sigma plane. In the lowest energy conformation (MM2), the C1-Ha carbon-hydrogen bond is more closely aligned with the

carbonyl π-system, while both the C3 hydrogens bisect the carbonyl π-system (**Figure 3.11** - *inset*). Stereoelectronic factors favour kinetic deprotonation of Ha resulting in the formation of a bridgehead enolate **3.50**. However, enolate **3.50** is expected to be thermodynamically disfavoured due to the strain involved in formation of an additional bridgehead double bond. Under equilibrating thermodynamic control the C2-C3 enolate **3.51** is formed preferentially.

This principle was utilised by Holton *et al.* en route to the synthesis of paclitaxel, where selective bridgehead functionalisation was achieved under kinetic control, even though the C3 hydrogen of **3.54** could be anticipated to be more acidic (**Figure 3.12**).[62,63]
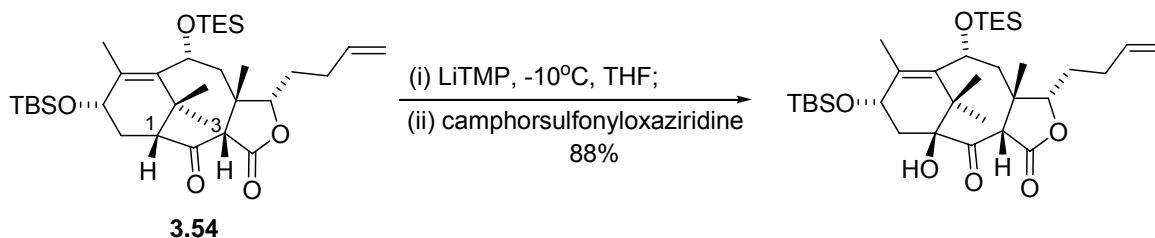
Figure 3.12   Regioselective hydroxylation at the bridgehead position.

The proposed syntheses of the nakafuran and florlide natural products, as illustrated in **Scheme 3.1**, also makes use of these principles to introduce the C3 sidechain which will be elaborated into a furan moiety of the nakafurans and to establish the bridgehead hydroxylation observed in the florlide compounds.
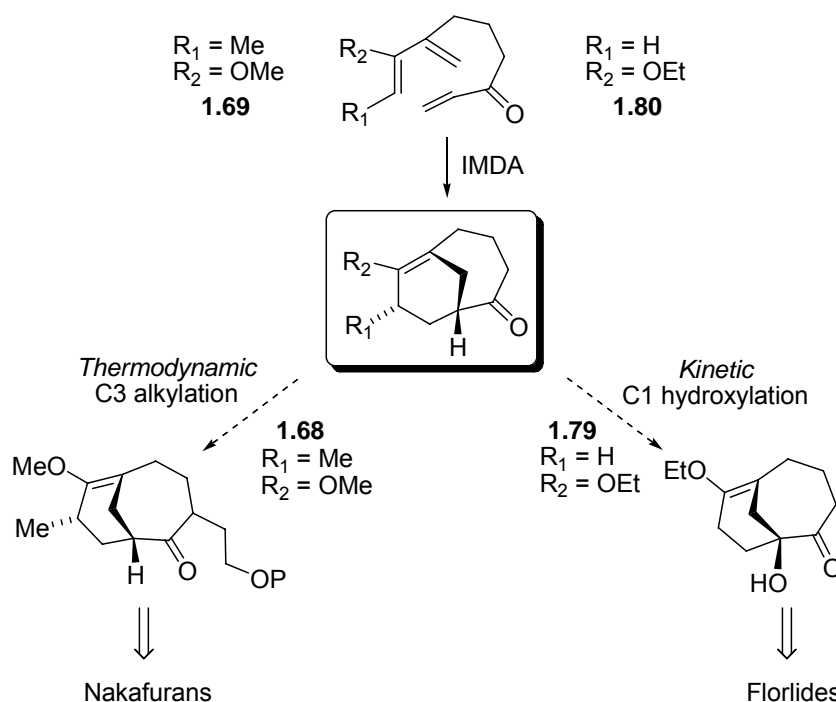
Scheme 3.1   Conformational control leading to selective alkylation and hydroxylation.

3.4   IMDA Reactions Directed Towards the Bicyclo[4.3.1]-decene Core

3.4.1   IMDA Cyclisation of Methoxy-triene 1.69

The initial investigations of the IMDA cyclisation reaction were conducted on methoxy-triene **1.69**, directed towards synthesis of the nakafuran-type family of natural products (**Scheme 3.1**). As illustrated above, Shea's synthesis of ledol and the studies utilising IMDA approaches to the synthesis of the paclitaxel and phomoidride natural products provides a rich source of protocols and methodology to achieve the desired cyclisation.

When the triene **1.69** was subjected to standard Diels-Alder cyclisation conditions (toluene, 0.1 M, reflux, 20 h; or toluene, 0.1 M, 150°C, sealed tube, 20 h), ^{1}H NMR spectroscopy of the crude reaction mixtures indicated that a large amount of decomposition had occurred. Inspection of the ^{1}H NMR spectrum indicated that signals associated with the starting diene system remained but those of the enone dienophile were absent. Silica column chromatography was unable to isolate any discernable cyclised material (**Table 3.1**).

Table 3.1   IMDA cyclisations of triene **1.69**.

Entry	Reaction Conditions[a]	Yield %[b]
1	Toluene (no BHT)	dec.
2	Toluene	35
3	*m*-Xylene	36
4	Benzene	68
5	10 equiv $BF_3.Et_2O$, -78°C, CH_2Cl_2, 60 min.	46
6	1 equiv Et_2AlCl, -78°C to rt, CH_2Cl_2, 90 min.	79

Note (a) Thermal IMDA reactions were conducted on 50 mg at 180°C in sealed tubes at 0.1 M, with ~1 mg BHT, 30 h. (b) Yields are for isolated chromatographically pure material.

When the triene **1.69** was subjected to thermal cyclisation conditions, performed in sealed tubes at 180°C for 30 hours using degassed solvents and in the presence of a crystal of BHT as a radical inhibitor,[59] clean consumption of the starting material was observed with minimal decomposition. A single product (**3.55**) was isolated in good yield as a colourless oil.

In contrast to thermal cyclisations of triene systems, which are known to require temperatures of at least 150°C for a practical rate of cyclisation, Lewis acid catalysis allows the reaction to proceed more readily, often at room temperature or below, and achieve greater control of *endo/exo* selectivity.[11,57,64]

The addition of 10 equivalents of freshly distilled $BF_3.OEt_2$ to the triene system **1.69** in CH_2Cl_2 at –78°C yielded the cyclised product **3.55** in 46% isolated yield, but exhibited significant decomposition.[65,66] Exposure of the triene to 1 equivalent of Et_2AlCl in CH_2Cl_2 at room temperature resulted in the clean conversion to cycloadduct **3.55**, which was isolated in 79% yield after aqueous work-up and silica column chromatography.

However, with clean isolation of the cyclised adduct **3.55**, a significant problem became apparent. Inspection of the ^1H NMR spectrum of the isolated material indicated that the anticipated doublet arising from the $^3J_{HH}$ coupling interaction of the C11 methyl group with the adjacent H-8 proton was absent; instead a singlet was present at δ_H 1.63 which integrated for three hydrogens (**Figure 3.15**). The clean disappearance of the signals associated with the vinylic protons of the starting material and the increased complexity of the ^1H NMR spectrum, attributable to the conformational rigidity of the bicyclic system causing separation of the diastereotopic proton signals, supported the supposition that an IMDA reaction had occurred. Additionally, complete integration of the ^1H NMR spectrum indicated that 18 hydrogen signals were present, identical to the starting material and the anticipated product, which was confirmed by high resolution mass spectroscopy.

A full range of two-dimensional NMR experiments (COSY, HSQC, CIGAR, and 1D NOESY) were performed on the isolated cycloadduct **3.55**. The results of these experiments led to the conclusion that, although the cyclised adduct contained the anticipated bicyclo[4.3.1]decene framework arising from a successful IMDA reaction, the double bond had isomerised from the desired $\Delta^{6,7}$ position (**1.68**) to the $\Delta^{7,8}$ position (**3.55**) (**Figure 3.13**).
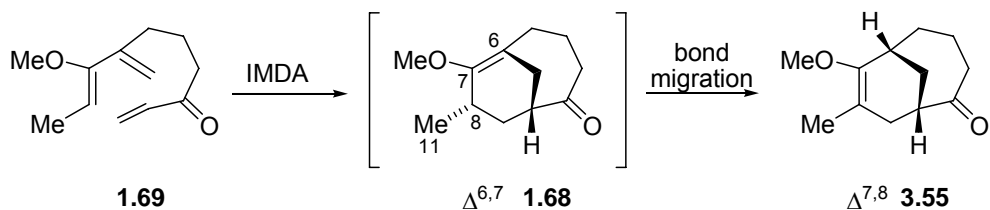
Figure 3.13   IMDA cyclisation of triene **1.69** to give isolated isomerised IMDA adduct **3.55**.

The important correlations observed in the CIGAR and the NOE experiments that allowed elucidation of molecular connectivity are depicted in **Figure 3.14**. The ^{1}H NMR spectrum and chemical assignments based on HSQC J_{CH} coupling and NOE correlations are depicted in **Figure 3.15**.
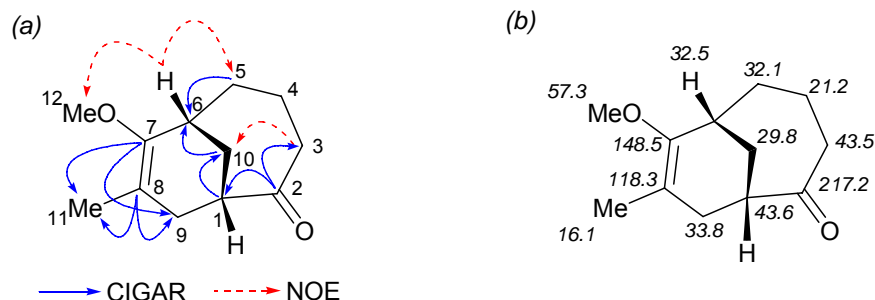
Figure 3.14   *(a)* Important 2D NMR CIGAR and NOE correlations and *(b)* δ_C ^{13}C chemical shift assignment for **3.55**.
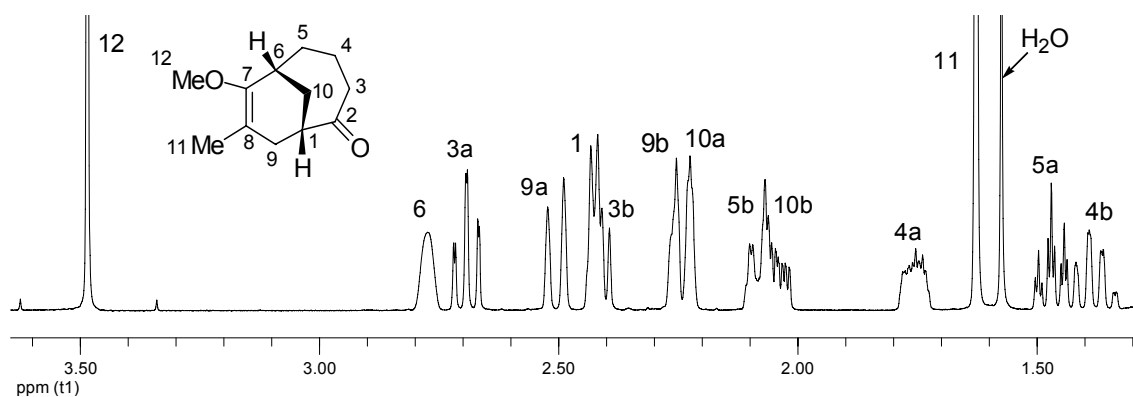
Figure 3.15   500 MHz ^{1}H NMR of **3.55** recorded in CDCl$_3$ with hydrogen assignments.

Specific correlations that support the assignment of the isolated IMDA adduct as the $\Delta^{7,8}$-olefinic adduct **3.55** are:

(i)   COSY correlations from the broad singlet at δ_H 2.76 (H6) to δ_H 1.46 (H5a), δ_H 2.06 (H5b), δ_H 1.62 (H11) and δ_H 2.03 (H10b);

(ii)   an NOE effect from the broad singlet at δ_H 2.76 (H6) to the singlet at δ_H 3.48 (C12 –OMe) and the multiplets at δ_H 2.22 (H10a) and δ_H 2.03 (H10b) and,

(iii)   a strong CIGAR J_{CCH} coupling from δ_C 118.3 (C8) to δ_H 1.62 (H11 – Me) and to the resonances at δ_H 2.50 (H9a) and δ_H 2.24 (H9b), in conjunction with a weak coupling to δ_H 2.42 (H1).

The spectroscopic assignment was supported by cyclopropanation of the isolated cycloadduct **3.55** to give the cyclopropane **3.56**. Acidic hydrolysis of the C7 methyl-ether, with concurrent cationic cyclopropane ring cleavage[67,68] resulted in the preparation of the gem-dimethyl derivative **3.57**. Under the reaction conditions, this diketo-intermediate was observed to undergo an acid-catalysed aldol reaction[69] generating the novel indenone species **3.58**.
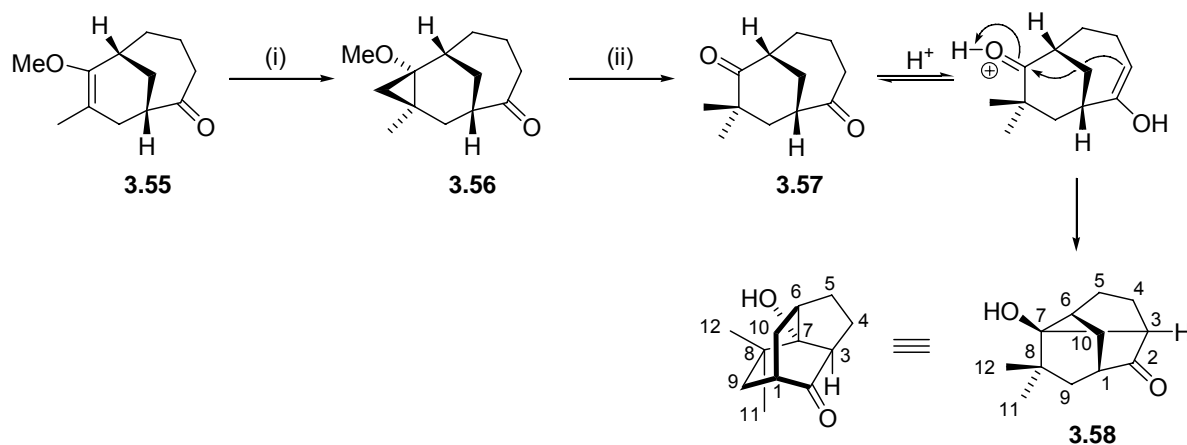
Figure 3.16   Verification of structural assignment of **3.55** through cyclopropyl fragmentation to **3.57** and subsequent intramolecular aldol reaction.

Reagents and yields: (i) ZnEt₂, CH₂I₂, DCE, 40°C, 44 h, 66%; (ii) 10% HCl, EtOH, reflux, quantitative.

The structural assignment of **3.58** was based on extensive 1D and 2D NMR spectroscopic experiments (COSY, HSQC, CIGAR, 1D NOESY and TOSCY) performed in CDCl₃ and in C₆D₆, the presence of an alcohol adsorption in the IR spectrum (3437 cm⁻¹) and HRMS data which indicated a molecular formula of $C_{12}H_{18}O_2$ (194.1315), isomeric with the anticipated diketo species **3.57**. Particularly informative CIGAR correlations and NOE enhancements are depicted in **Figure 3.17**.
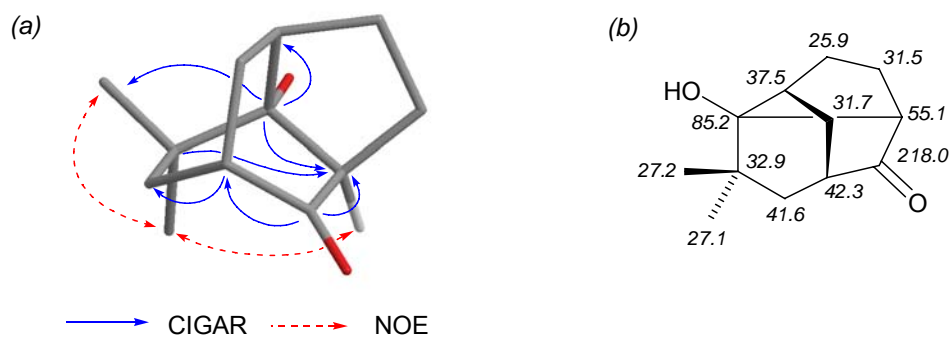
Figure 3.17   *(a)* Important 2D NMR CIGAR correlations and NOE enhancements and *(b)* δ$_C$ ¹³C chemical shift assignment observed for **3.58** (in CDCl₃).

Specific correlations that support the proposed assignment of **3.58** are:

(i)   a strong CIGAR J_{CCH} correlation for the quaternary centre at δ_C 85.2 (C7) to δ_H 2.42 (br doublet, J = 7.2 Hz, C3), δ_H 0.90 (s, 3H, C11), δ_H 1.06 (s, 3H, C12) and δ_H 2.21 (m, C6);

(ii) strong CIGAR J_{CCH} correlations from the quaternary centre at δ_C 32.9 (C8) to δ_H 0.90 (s, C11), δ_H 1.06 (s, C12) and 2.42 (br doublet, J = 7.2 Hz, C3) and,

(iii) an NOE effect observed from the methyl singlet at δ_H 0.90 (s, 3H, C11) to the C3 proton at δ_H 2.42 (distance = 2.931Å).[††]

The observed CIGAR correlation of the two methyl signals at δ_H 0.90 (C11) and δ_H 1.06 (C12) to δ_C 32.9 (C8), support the assignment of **3.56** as the $\Delta^{7,8}$ cyclopropane adduct, and by inference **3.55** as the $\Delta^{7,8}$-olefinic adduct.

3.4.1.1   Bridgehead Olefinic Isomerisation [$\Delta^{6,7}$ to $\Delta^{7,8}$]

It is postulated that following the initial IMDA reaction to generate the desired $\Delta^{6,7}$ bridgehead olefin adduct **1.68**, an olefinic bond isomerisation occurs that relieves the π-bond torsional strain associated with the bridgehead double bond and generates the $\Delta^{7,8}$ adduct **3.55** (**Figure 3.13**).

This observation is in contrast to the extensive work of Shea *et al.* on triene systems which have been observed to undergo IMDA cyclisation leading to bridgehead olefinic adducts under a number of experimental conditions (see **Figure 3.9**).[59] No instances of isomerisation products were reported, although it was noted that trienes such as **2.67** and **3.38** which lack a C7 substituent were quite sensitive to Lewis acids and required thermal cyclisation conditions. The addition of 1,8-bis(dimethylamino)naphthalene (Proton-sponge®), a strong non-nucleophilic hindered base, resulted in a significant improvement in the isolated yield. Furthermore, in many instances the cycloadducts were not purified but taken as crude mixtures into subsequent reaction steps, which may indicate instability upon prolonged standing.

Double bond isomerisation within bicyclo[4.3.1] systems is not without precedence. The research of Phillips *et al.*, which was focused on synthetic routes to paclitaxel analogues,

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[††]Distance from the C11 carbon to C3 proton (MM2 energy minimized; Chem3D, CambridgeSoft Corporation)

encountered a similar example of $\Delta^{6,7} \rightarrow \Delta^{7,8}$ olefin isomerisation during an IMDA reaction (**Figure 3.18**).[65,66]
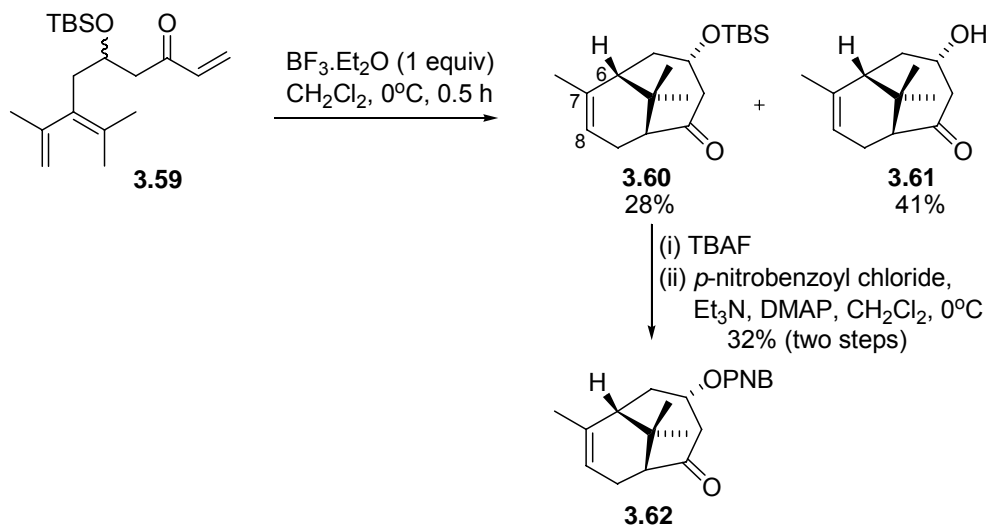
Figure 3.18 $\Delta^{6,7} \rightarrow \Delta^{7,8}$ isomerisation observed by Phillips *et al.*

The reaction of the triene substrate **3.59** with one equivalent of BF$_3$.Et$_2$O as a Lewis acid catalyst resulted in the isolation of a cycloadduct in which the double bond had migrated from the desired $\Delta^{6,7}$ position to the non-bridgehead $\Delta^{7,8}$ position (**3.60**). Partial desilylation was also observed (**3.61**). The assignment was confirmed by X-ray crystallography. The crystalline 4-nitrobenzoate ester **3.62** was prepared and the resulting X-ray structure revealed that the suspected isomerisation had taken place with protonation occurring from the accessible convex face.

Phillips *et al.*, proceeding on the assumption that the isomerisation was most likely caused by an acid-catalysed mechanism, conducted the reaction using freshly purified BF$_3$.Et$_2$O to remove any traces of adventitious moisture, however only the isomerised material was isolated. It was discovered that the addition of excess BF$_3$.Et$_2$O (10 equivalents) at low temperature resulted in the clean cyclisation of the triene **3.59** to the desired olefinic bridgehead adduct **3.63**. The exposure of **3.63** to TBAF, or BF$_3$.Et$_2$O, at ambient temperature resulted in extensive decomposition and the observation of double bond migration (**Figure 3.19**).
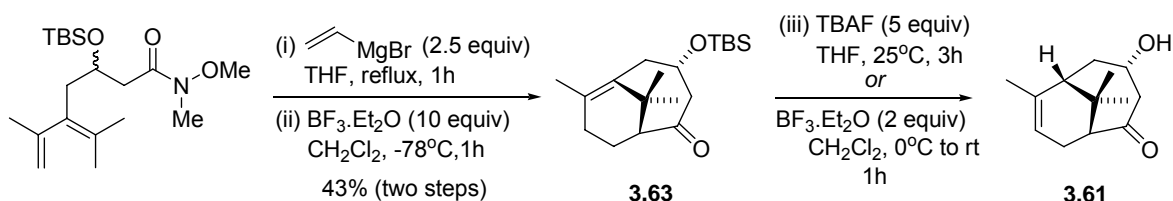
Figure 3.19   Sequential IMDA cyclisation–olefin isomerisation.

The application of high-pressure (19 kbar, 25°C, 24 h) resulted in the 80% conversion of the triene **3.59** to the desired adduct **3.63** (as assessed by ^{1}H NMR spectroscopy). Elevated temperature (16 kbar, 55°C, 64 h) resulted in complete isomerisation to the non-bridgehead $\Delta^{7,8}$ position **3.60**.

3.4.1.2   **Minimisation of Double Bond Isomerisation**

With these results in mind, efforts were made to prepare the Diels-Alder adduct **1.68**, utilising a variety of different Lewis acid catalysts, additives and solvent systems, many of which had proven themselves successful in IMDA reactions directed toward the synthesis of paclitaxel and the core of the phomoidrides.

64 h)

As can be observed in **Table 3.2**, no cyclisation protocols could be found to successfully deliver the desired cycloadduct **1.68**.

The addition of additives such as BHT and Proton-sponge® to the thermally initiated cycloadditions resulted in a noticeable increase in yield, in agreement with the observation of Shea *et al. (entries 1a-1c)*.[59] Experimentation with $BF_3.Et_2O$, using variations of temperature, Lewis acid equivalents and quenching protocols uniformly returned only the $\Delta^{7,8}$ isomerised product **3.55**. The preferential isolation of the non-isomerised $\Delta^{6,7}$ adduct was not observed with the use of excess reagent *(entry 2b)*, as had been the experience of Phillips and co-workers.

The use of alkylaluminium halides as Lewis acid catalysts has been advocated as a way of ensuring anhydrous conditions. This recommendation is based on the dual nature of these aluminium species as both Lewis acids and Brönsted bases. Extensive experimentation with catalytic equivalents employed, reaction time, temperature, and the quenching conditions were conducted on the IMDA precursor **1.69** using Et_2AlCl as a Lewis acid. Quenching studies at variable temperatures indicated that the reaction did not proceed below -10°C, and that greater than 0.2 equivalents of the Lewis acid were required for a reaction to occur. Below these minimum conditions the starting triene could be recovered unchanged despite extended periods. Acidic quenching conditions (sat. aqueous NH_4Cl, 1 M aqueous HCl) improved the isolated yield of the isomerised adduct, whereas quenching with base resulted in the production of a gelatinous precipitate that hindered extraction, presumably accounting for the diminished yield *(entry 3 vs 4)*.

Table 3.2   IMDA cyclisation conditions performed on triene **1.69**.
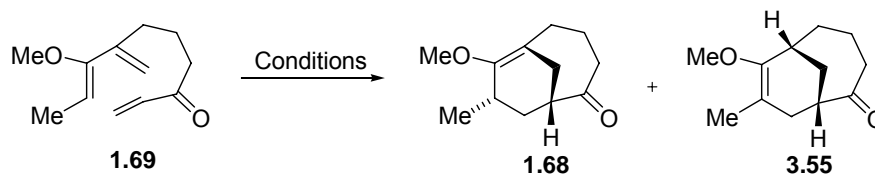
Entry	Reaction Conditions[a]	Results (%)[b]
1a	Thermal (Benzene, 160°C, 20 h)	**3.55** (35)
1b	Thermal (Benzene, 30% Proton-sponge®, 160°C, 20 h)	**3.55** (65)
1c	Thermal (Benzene, BHT, 160°C, 20 h)	**3.55** (68)
2a	BF$_3$.Et$_2$O (1 equiv), -78°C, 30 min, NaHCO$_3$ quench	**3.55** (33)
2b	BF$_3$.Et$_2$O (10 equiv), -78°C, 30 min, NaHCO$_3$ quench	**3.55** (46)
3	Et$_2$AlCl (1 equiv), CH$_2$Cl$_2$, -78°C → rt, NH$_4$Cl quench	**3.55** (79)
4	Et$_2$AlCl (1 equiv), CH$_2$Cl$_2$, -78°C → rt, NaHCO$_3$ quench	**3.55** (51)
5	Et$_2$AlCl (1 equiv), CH$_2$Cl$_2$, 0°C, NaHCO$_3$ quench	C.M.
6a	Et$_2$AlCl (0.5 equiv), CH$_2$Cl$_2$, 0°C, NaHCO$_3$ quench	C.M
6b	Et$_2$AlCl (0.2 equiv), CH$_2$Cl$_2$, 0°C, NaHCO$_3$ quench	S.M.
6c	Et$_2$AlCl (1 equiv), toluene, 0°C, NaHCO$_3$ quench	C.M
7	Et$_2$AlCl (1 equiv), temperature studies, NaHCO$_3$ quench	S.M.[c]
8	SnCl$_4$, CH$_2$Cl$_2$, -78°C, NaHCO$_3$ quench	**3.55** (14)
9	TiCl$_4$, CH$_2$Cl$_2$, -78°C, NaHCO$_3$ quench	Decomposition
10	AlCl$_3$, AlMe$_3$, CH$_2$Cl$_2$, -78°C, NaHCO$_3$ quench	**3.55** (23)
11	ZnCl$_2$, DCE, 40°C	S.M.
11a	ZnCl$_2$, pyridine (10%), DCE, 40°C	S.M.
12	Sc(OTf)$_3$, DCE, 40°C	S.M.
13	TMS-OTf, CH$_2$Cl$_2$, -40°	Decomposition
14	Eu(fod)$_3$, CH$_2$Cl$_2$, 40°C	S.M.
15	Cr(III)(salen)Cl catalyst, DCE, 40°C	S.M.

Note: (a) Reaction performed on 20 mg **1.69**, (dried by high vacuum azeotrope with toluene), at a concentration of 0.01 M, with 1 equiv. of Lewis acid, in anhydrous, deoxygenated solvents unless otherwise stated. (b) Values in parentheses refer to isolated chromatographically pure material; C.M. = complex mixture; S.M. = starting material as assessed by ^{1}H NMR spectroscopy. (c) Only starting material was isolated at temperatures below -10°C.

In a few instances, an unidentified material displaying complex ^{1}H NMR aliphatic resonances at δ_H 1.7-2.8, a doublet at δ_H 1.19 (J = 6.8 Hz) and a singlet at δ_H 3.38 was observed. This compound was tentatively assigned as the desired $\Delta^{6,7}$ adduct **1.68**.

The increased complexity in the aliphatic region was analogous with the $\Delta^{7,8}$ adduct **3.55**, where due to the conformational rigidity of the bicyclic skeleton, resolution of the diastereotopic

protons is observed. Crucially, the presence of a doublet at δ_H 1.12 implied the existence of a J_{HCCH} coupling, such as that anticipated to occur between the adjacent protons upon C8 and C11 of **1.68**. The upfield shift of the doublet (attributed to the C11 methyl group) to δ_H 1.12 for the postulated IMDA adduct **1.68** is in agreement with the methyl group being attached to an sp^3 substituted centre, compared to δ_H 1.71 for the starting material **1.69** and δ_H 1.63 observed for the isomerised adduct **3.55** in which the methyl group is attached to an sp^2 substituted carbon centre.

These ^{1}H NMR resonances were used as diagnostic signals in the assessment of product distributions arising from the cycloaddition reactions. However, this material constituted a minor component of the crude mixture (~ 2-5%) and was unable to be separated from the reaction by-products.

It was apparent that the use of the moderately Lewis acidic diethylaluminium chloride was unable to suppress the double bond isomerisation. Endeavours to obtain the desired cycloadduct consequently focused on two opposing strategies; the use of stronger Lewis acids at low temperature; and the use of milder Lewis acids at elevated temperatures.

The use of strong Lewis acids (SnCl$_4$, TiCl$_4$, and AlCl$_3$-AlMe$_3$) at low temperature (-78°C) resulted in rapid IMDA reactions, delivering the isomer adduct **3.55** as the sole isolated product. Low yields were obtained due to significant decomposition of the enone under the reaction conditions (*entries 8-10*).

Conversely, the use of mild Lewis acids such as the ZnCl$_2$-pyridine mixture used by Fukuyama,[70] the lanthanide catalyst Eu(fod)$_3$ and Jacobsen's catalyst, a chromium(III)-cyclohexane salen complex,[71,72] resulted in no observed conversion, even when heated. Zinc chloride, with sub-stoichiometric quantities of pyridine added to moderate its acidity, after 5 days at 40°C was observed to achieve ~10% conversion to a 1:1 mixture of double bond migration adduct **3.55** and a new product similar to that observed in the Et$_2$AlCl experiments, however this material was unable to be separated from the starting material **1.69** or the double bond migration adduct **3.55**.

A number of products were extracted from the reaction mixtures, particularly when the reaction was quenched before all the starting material had been consumed, or when insufficient amounts of the Lewis acid were used. Two of these species have been tentatively characterised as arising from enol ether decomposition of the diene starting material and an *inter*-molecular Diels-Alder dimer adduct.

3.4.1.3   Mechanism of Double Bond Isomerisation

Consideration of the mechanisms that could account for the observed double bond migration led to an acid-catalysed proton-migration as the most probable reaction pathway as depicted in **Figure 3.20**.
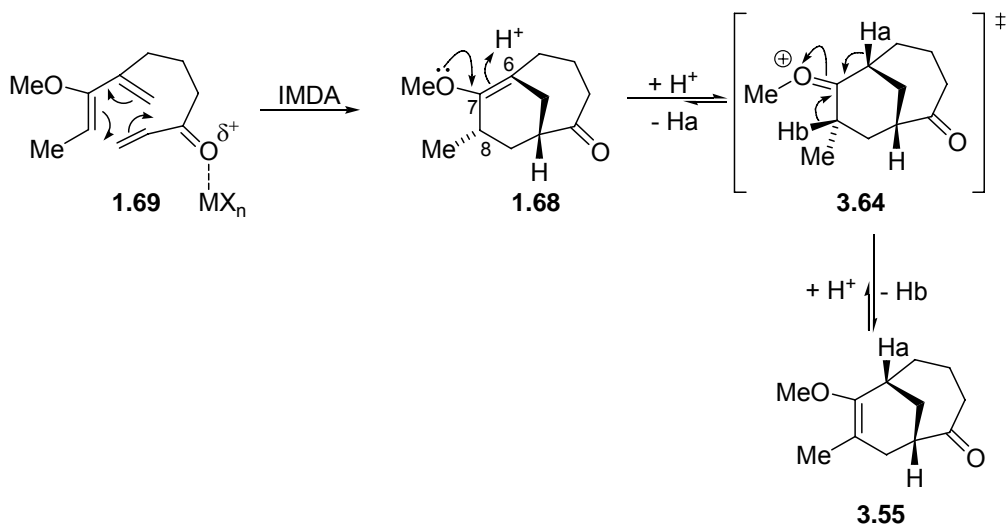
Figure 3.20   Proposed mechanism of $\Delta^{6,7} \rightarrow \Delta^{7,8}$ olefin isomerisation.

Double bond migrations are known to be catalysed by both protic and Lewis acids to form the most thermodynamically stable alkene.[73] Phillips proposed an acid-catalysed isomerisation of the bridgehead olefin adduct **3.63** to the non-bridgehead adduct **3.60** proceeding through the intermediacy of a tertiary C7 carbocation resulting from protonolysis of the torsionally strained bridgehead alkene.[66] The presence of a methyl enol ether substituent at C7 could be anticipated to stabilise an adjacent carbocation through delocalisation of the oxygen lone pair electrons to form a transient oxonium species, **3.64**. The loss of a proton would either regenerate the starting alkene (-Ha, **1.68**), or cause olefinic migration to occur (-Hb, **3.55**). Thermodynamically, the elimination of Hb would be expected to be more favourable as it forms a tetra-substituted olefin, and more importantly relieves the angular and torsional strain associated with the bridgehead double bond.

The dominant formation of the $\Delta^{7,8}$ isomerised IMDA adduct **3.55** under the conditions of Lewis acid catalysis (designed to ensure anhydrous aprotic conditions; Et$_2$AlCl) and anhydrous thermally initiated conditions (i.e. in the absence of a coordinating Lewis acid) implied that the observed migration was independent of the additive and possibly a function of the substrate. Adventitious protonation may have occurred *via* interaction with the silica glass of the reaction

vessel or intermolecularly following decomposition of the triene substrate. Subsequent efforts to eliminate these factors are detailed below (*vide infra*).

3.4.2   IMDA Cyclisation of Ethoxy-triene 1.80

Olefin migration under acidic conditions favours formation of the most thermodynamically stable adduct. Both the $\Delta^{6,7}$ adduct and the $\Delta^{7,8}$ adduct arising from the IMDA cyclisation of methoxy-triene **1.69** are tetra-substituted and could be anticipated to possess similar thermodynamic stability. Consequently, the product distribution will be dominated by the contributions from the relief of torsional strain associated with the bridgehead olefin.

The ethoxy-triene **1.80** upon cyclisation would generate the $\Delta^{6,7}$-olefinic bridgehead adduct **1.79**, which contains a tetra-substituted alkene. The $\Delta^{7,8}$ adduct **3.65** arising from olefinic migration would contain a tri-substituted alkene. If the energy of stabilisation associated with the tetra-substituted alkene was greater than the contribution derived from release of the bridgehead torsional strain, it might be possible to selectively isolate the desired $\Delta^{6,7}$ adduct **1.79** (**Figure 3.21**).
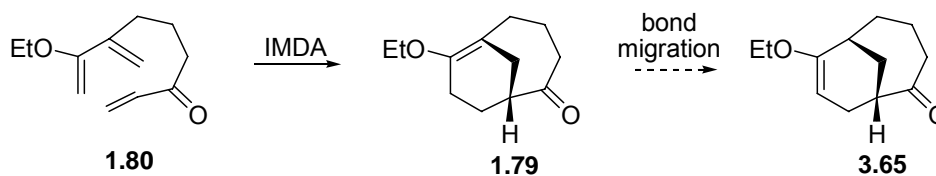
Figure 3.21   IMDA reaction of ethoxy-triene **1.80** and potential isomerisation.

The successful preparation of **1.79** would provide access to the florlide and florether natural products targets **1.41** and **1.43** as discussed in **Scheme 1.9**. A synthetic route that utilises **1.79** to intercept the nakafuran synthesis can also be readily devised (**Scheme 3.2**). Cyclopropanation followed by an acidic ring hydrolysis to establish the C6 bridgehead methyl and furan ring-annulation would deliver the intermediate **3.66**. Stereoselective mono-alkylation of **3.66** could reasonably be expected to occur adjacent to the C7 ketone to generate the *endo* disposition of the C11 methyl group observed in **1.65**.
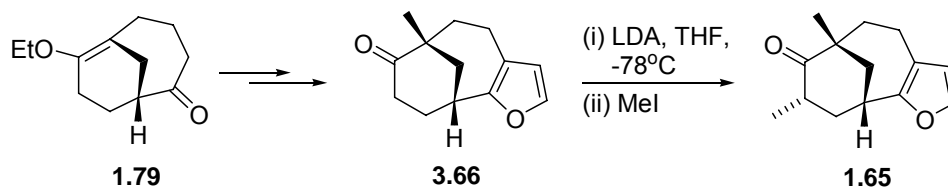
Scheme 3.2   Interception of the nakafuran route using florlide precursor **1.79**.

The ethoxy-triene **1.80** was subjected to thermal cyclisation conditions (50 mg, 0.01 M, cat. BHT, benzene, 160°C, 24 h) resulting in the clean conversion to the $\Delta^{7,8}$ adduct **3.65** as the sole observable product, which was isolated in 38% yield after column chromatography. The structural assignment was based on the presence of a vinylic sp^2 doublet at δ_H 4.67 ($J = 4.8$ Hz), assigned as Ha, resulting from olefinic bond migration (**Figure 3.22**).
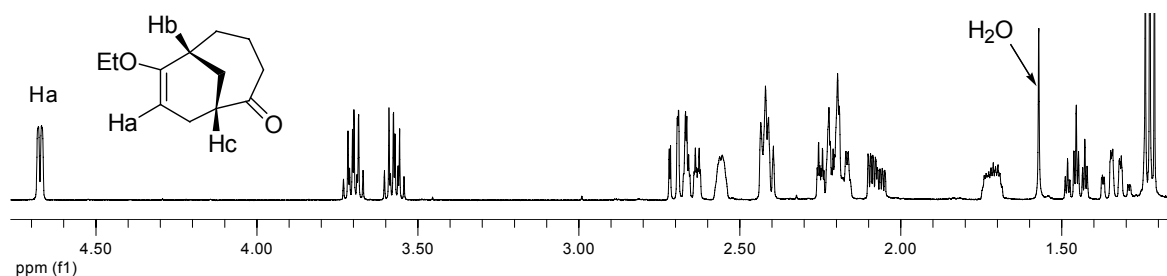
Figure 3.22   500 MHz ^{1}H NMR spectrum of the IMDA cyclisation adduct **3.65**.

Conducting the reaction under thermal conditions with the inclusion of 0.3 equivalents of Proton-sponge®, similarly resulted in the isolation of the isomerised material **3.65** as the sole product.

The use of the Lewis acids BF$_3$.Et$_2$O (1 equivalent, CH$_2$Cl$_2$, -78°C) and Et$_2$AlCl (1 equivalent, CH$_2$Cl$_2$, -78°C) resulted in complete decomposition of the starting material with no observed cycloaddition product.

The isolation of **3.65** as the sole product from the thermally initiated reactions and the complete decomposition of the triene starting material under Lewis acid conditions limited investigation of the cyclisation of **1.80**.

3.4.3   IMDA Cyclisation of Vinyl-triene 2.67

Preparation of the unsubstituted bridgehead bicyclic olefin **3.40** had previously been reported by Shea *et al.*, *via* an IMDA cyclisation of the triene **2.67** (**Figure 3.9**). Importantly this work included detailed methods of preparation,[59] and as such, replication of this protocol would serve to identify errors in the manipulation and methodology used in the attempted cyclisation of **1.69** and **1.80**.

The vinyl triene **2.67**, when subjected to the thermal cyclisation protocol utilised for methoxy-triene **1.69** and ethoxy-triene **1.80**, was observed to generate the bridgehead olefin **3.40** exclusively. No evidence of the $\Delta^{7,8}$-olefinic isomer **3.67** could be observed in the ^{1}H NMR spectrum of the crude reaction mixture (**Figure 3.23**).
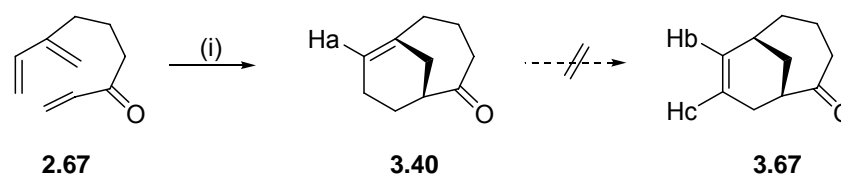
Figure 3.23   IMDA cyclisation of unsubstituted triene **2.67**.

Reagents and yields: (i) xylene, 30 mol % Proton-sponge®, 160°C, 16 h, 56%.

In further agreement with the work of Shea *et al.*, subjection of vinyl triene **2.67** to the Lewis acids $BF_3.Et_2O$ (1 equivalent, CH_2Cl_2, -78°C) and Et_2AlCl (1 equivalent, CH_2Cl_2, -78°C) resulted predominantly in decomposition, generating a large amount of polymeric material.

3.4.4   Intermolecular Diels-Alder Reaction of Methoxy-triene 1.69

A question of synthetic importance remained: whether the $\Delta^{6,7}$ enol ether functionality of the IMDA adduct **1.68** had a predisposition for olefinic migration to the $\Delta^{7,8}$ position in the absence of torsional strain imposed by the bicyclic ring system. Such a migration would indicate that a stabilisation energy associated with forming the $\Delta^{7,8}$ tetra-substituted double bond was also contributing to the observed olefinic migration for IMDA adduct **1.68**.

To investigate this possibility the intermolecular cyclisation of **1.70** was performed with the readily available dienophile, *N*-phenylmaleimide. The Diels-Alder reaction proceeded to

completion under remarkably mild conditions. Upon stirring a solution of **1.70** and the dienophile together at room temperature in toluene, a clean cyclisation occurred to furnish a single product **3.68** (**Figure 3.24**).
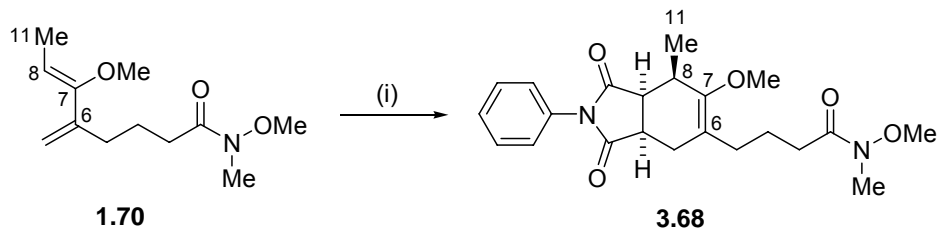
Figure 3.24   Intramolecular Diels-Alder cyclisation of **1.70**.

Reagents and yields: (i) **1.70** (1 equiv), *N*-phenylmaleimide (3 equiv), toluene, rt, 40 h, 46%.

^{1}H NMR spectroscopy performed upon the isolated adduct revealed a number of characteristic peaks including a doublet at δ_H 1.22 (*J* = 7.2 Hz, 3H), a non-first order quintet at δ_H 2.96 (1H) and two overlapping multiplets at δ_H 3.20-3.24 (2H). These signals were assigned respectively to the C11 methyl group, the C8 proton and the two maleimide-derived protons α to the imide carbonyls. The shift and the coupling constant of the C11 methyl group δ_H 1.22 (*J* = 7.2 Hz) is similar to that attributed to the $\Delta^{6,7}$-olefin adduct **1.68**, δ_H 1.19 (*J* = 6.8 Hz), observed as a minor component in IMDA cyclisation of **1.69**; and contrasts with that observed for the $\Delta^{7,8}$-olefin isomer [δ_H 1.68, s]. No evidence could be observed of an adduct resulting from the migration of the olefinic bond of **3.68** to the $\Delta^{7,8}$ position.

This intermolecular reaction indicated both that **1.70** was an effective diene, with cyclisation occurring readily at room temperature and that the $\Delta^{6,7} \rightarrow \Delta^{7,8}$ migration was not an inherent attribute of the cyclised cyclohexene adduct, but more probably a consequence of the increased torsional and geometric strain imposed by installing a bridgehead olefinic bond.

3.5   Revised Synthetic Plan

The inability to isolate the desired $\Delta^{6,7}$ bridgehead olefin adducts **1.68** and **1.79**, arising from the Diels-Alder cyclisation of the methoxy- and ethoxy-triene systems, represented a serious set-back to the proposed synthetic route. All experimental conditions investigated were unsuccessful. The apparent divergent reactivity of the C7 alkylether-substituted trienes **1.69** and **1.80** when compared to the unsubstituted triene **2.67** is noteworthy and is summarised in **Figure**

3.25. The alkylether-substituted trienes gave exclusively the $\Delta^{7,8}$ bicyclo[4.3.1]decene product presumably due to acid-catalysed olefin migration following the initial IMDA reaction. Conversely, the reaction of the unsubstituted vinyl derivative of **2.67** resulted in the isolation of the initially anticipated $\Delta^{6,7}$ bicyclo[4.3.1]decene adduct **3.40** in agreement with the literature precedence.
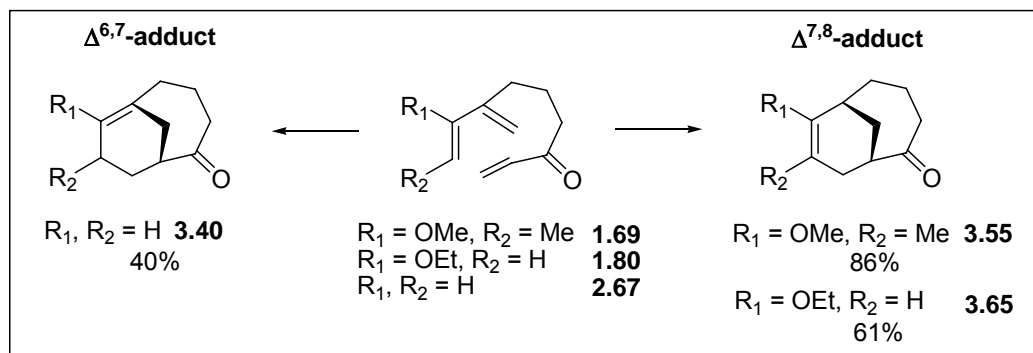
Figure 3.25   Results for the IMDA cyclisation of compounds **1.68**, **1.80** and **2.67**.

It was postulated that the presence of the enol ether group at the bridgehead olefin facilitated the observed $\Delta^{6,7} \rightarrow \Delta^{7,8}$ migration through the presence of a transient oxonium intermediate (see **Figure 3.20**). To address this issue, a scheme was devised that envisaged substitution of the heteroatom at C7 of **1.63** for a homomethyl ether to give the homomethyl triene **3.69**. It was anticipated that the diminished tautomeric ability of this substrate might retard or prevent the double bond isomerisation (**Scheme 3.3**).
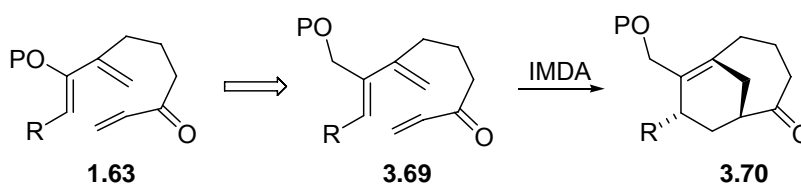
Scheme 3.3   Modification of **1.63** *via* one carbon homologation.

The successful application of this homologation approach is addressed in **Chapter Four**.

3.5.1   IMDA Cyclisation of Methoxy-triene 1.69: The Discovery of a Successful IMDA Cyclisation Route to $\Delta^{6,7}$-Olefinic Adducts

The use of an IMDA cyclisation to prepare 7-alkylether-$\Delta^{6,7}$ bridged bicyclic structures amenable to the synthesis of the nakafuran family of natural products had been unsuccessful due to a facile and uncontrollable $\Delta^{6,7} \rightarrow \Delta^{7,8}$ olefin migration. It was decided to conclude this synthetic work by focussing on the preparation of the 6-des-methyl nakafuran analogues from the readily accessible $\Delta^{7,8}$-olefin adduct **3.55**, (**Scheme 3.4**).
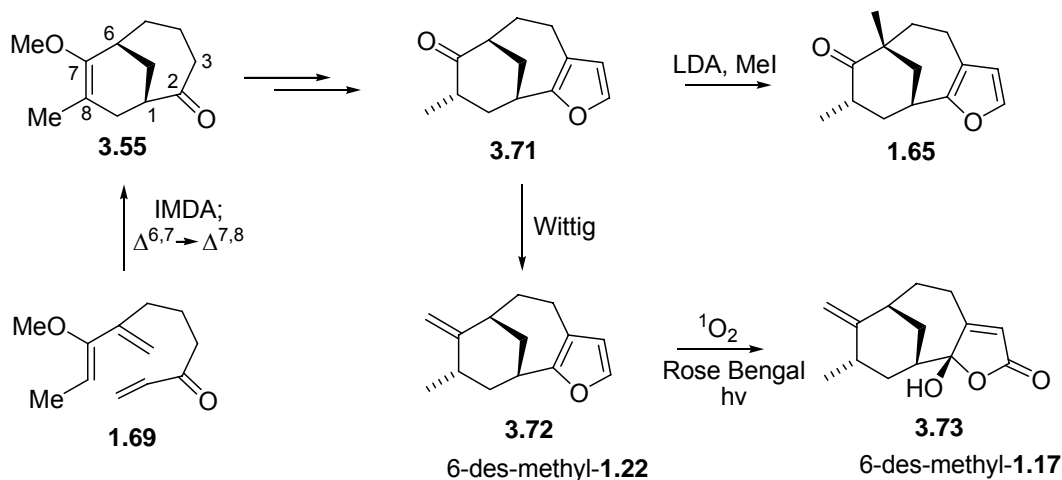
Scheme 3.4   Proposed route to nakafuran analogues *via* $\Delta^{7,8}$ bridgehead olefin **3.55**.

Annulation of a furan moiety to the C2-C3 position of **3.55** utilising the C2 ketone would generate the intermediate **3.71**. Wittig olefination of the pendant C7 ketone would yield the des-methyl nakafuran-9 species **3.72**. The 6-des-methyl butenolide **3.73** could be generated *via* oxidation of the furan ring with singlet oxidation under photolytic conditions.

This route would also allow examination of the possibility of regioselectively introducing the C6 bridgehead methyl group under alkylative conditions to generate **1.65**, an intermediate in the originally proposed route (**Scheme 1.8**).

However, almost as soon as the conclusion had been drawn that the preparation of 7-alkylether-$\Delta^{6,7}$ bicyclo[4.3.1]decenes was not feasible under IMDA protocols, evidence of the contrary arose.

Towards the synthetic goals depicted in **Scheme 3.4**, a large quantity of the methoxy-triene **1.69** was subjected to thermally initiated IMDA cycloaddition conditions. The triene material (2.22 grams dissolved in 50 mL of xylene) was added over 8 hours to a refluxing solution of 750 mL of freshly distilled xylene containing 0.3 equivalents of Proton-sponge®. ^{1}H NMR spectroscopy of aliquots removed from the bulk solution indicated that the starting material had been consumed after 40 hours. Evaporation of the excess solvent *via* low pressure distillation (60°C/24 mmHg; 25°C/0.01 mmHg) and flash column chromatography on basified silica was to yield, much to the chagrin of the author, 0.68 grams of $\Delta^{7,8}$ adduct **3.55** and 0.29 grams of a 2:3 mixture comprising of the $\Delta^{7,8}$ adduct **3.55** and the non-isomerised $\Delta^{6,7}$ adduct **1.68**!

The presumed identity and acid lability of **1.68** was confirmed by subjecting a small fraction of this mixture to a 0.01 M aqueous HCl wash (10 seconds), followed by organic extraction. The only material present in the ^{1}H NMR spectrum of the crude reaction mixture was the isomerised product **3.55**.

This mixture of $\Delta^{6,7}$ and $\Delta^{7,8}$-olefin isomers was not readily separated into its constituent parts. Conventional flash column chromatography on basified silica was unable to achieve sufficient separation. Analytical separation to two peaks could be observed using C18 reverse phase HPLC, with the isomerised product **3.55** and the desired adduct **1.68** displaying retention times of 19.5 and 21.2 minutes respectively on a 65% isocratic MeCN/H$_2$O gradient.

Transfer of the HPLC separation protocol to semi-preparative MPLC resulted in clean separation of the two adducts with retention times of 24.5-26.5 minutes and 29.5-31.5 minutes respectively, when 5 milligrams was eluted with 50% MeCN/H$_2$O using a flow rate of 10 mL min^{-1} on a C18-RP column. Evaporation of the elution solvent under rotary evaporation (24 mmHg) unfortunately resulted in complete isomerisation. Extraction of the aqueous solution containing the purified IMDA adduct **1.68** with Et$_2$O (containing trace NEt$_3$), followed by a careful work-up involving a distilled water wash, drying with Na$_2$SO$_4$ and evaporation, led to the successful isolation of the desired adduct **1.68**, although partial isomerisation was observed to have occurred (**1.68** 80 % : **3.55** 20 %).

The successful preparation and isolation of the $\Delta^{6,7}$ bridgehead cycloadduct **1.68**, albeit as a mixture of olefinic isomers, indicated that the compound **1.68** was indeed stable *and* isolable. Furthermore, this result suggested that conditions could indeed be found to minimise the acid

catalysed migration of the double bond. Experiments were performed to investigate the influence of the glassware surface and added base on the isomerisation reaction, as detailed in **Table 3.3**.

Table 3.3   Variation of the thermal IMDA experimental conditions.
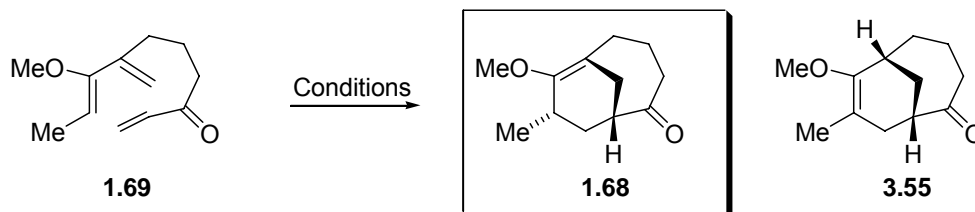
Entry	Conditions[a]	Products[b]
1	PS (0.3)	38:62
2	PS (1.0)	63:37
3	SG	3:97
4	SG, PS (1.0)	76:24
5	PS (1.0), Base washed glassware	5:95
6	SG, Hünig's base (1.5)	12:88
7	SG, 2,6-lutidine (1.5)	dec.
8	SG, Hünig's base[c]	86:14
9	SG, PS (1.25)	98:2

Notes: (a) reactions were conducted on 50 mg of triene in 25 mL of xylene, 160°C, 2d; PS = Proton-sponge® (equivalents); SG = silylated glassware. (b) Ratio of **1.68** : **3.55**, as determined by ^{1}H NMR integration. (c) 25 mL of Hünig's base was used as the solvent.

The first observation to be made from **Table 3.3**, *(entry 1)* is that 0.3 equivalents of Proton-sponge® is capable of preventing the olefinic isomerisation of **1.68** to **3.55**. These results differ from the thermal cyclisation reactions previously conducted (**Table 3.2**, *entry 1b*), in which **1.68** was not observable, in either aliquots from the crude reaction mixture or from isolated columned material. The source of these divergent outcomes from reactions conducted under 'identical' conditions was traced to the Proton-sponge®.

The Proton-sponge® used in the initial experiments had been a 'heritage' chemical of unknown age. It was a crystalline material, which was analytically pure as assessed by ^{1}H and ^{13}C NMR spectroscopy, but possessed a slight pink tinge which remained despite repeated recrystallisation from a basic aqueous solution (saturated K_2CO_3) and distillation under reduced pressure (Kugelrohr, 150°C/0.2 mmHg). New material received from Aldrich Chemical Company was a white crystalline powder. Subsequent experimentation revealed that the ability of this new

Proton-sponge® to retard olefin isomerism diminished over time, presumably due to aerial oxidation or acidification, despite being stored under an argon atmosphere. Consequently, in order to prevent $\Delta^{6,7} \rightarrow \Delta^{7,8}$ olefin migration it was found necessary to recrystallise and distill this new material immediately prior to use.

Increasing the amount of Proton-sponge® employed in the IMDA reaction to 1 equivalent produced a corresponding decrease in the observable isomerisation *(entry 1 vs. 2)*. Modification of the reaction vessel and reflux condenser's glass surface *via* the sequential base-washing and silyl capping of any free hydroxyl residues was also observed to have a beneficial effect. Even in the absence of Proton-sponge®, the desired adduct could be observed, admittedly in a very low yield *(entry 3)*. The inclusion of non-nucleophilic bases such as Hünig's base as an additive or preferentially as the solvent resulted in a dramatic improvement *(entries 6 and 8)*. The use of 2,6-lutidine, a bulky amine base, however was observed to give complete decomposition, presumably due to nucleophilic attack on the enone of the triene system *(entry 7)*. The best result was achieved when the reaction was run in silylated glassware in the presence of 1.25 equivalents of Proton-sponge®, which gratifyingly delivered the desired IMDA cyclisation adduct in an isomeric ratio of 98:2 (**1.68**:**3.55**). Isolation could be achieved by simple evaporation under low pressure (60°C/24 mmHg; 25°C/0.1 mmHg) and careful flash column chromatography on basified silica with the inclusion of 2% NEt₃ in the eluant. The spectrum of the isolated $\Delta^{6,7}$ bridgehead cycloadduct **1.68** is displayed in **Figure 3.26**, (*c.f.* **3.55**, **Figure 3.15)**.
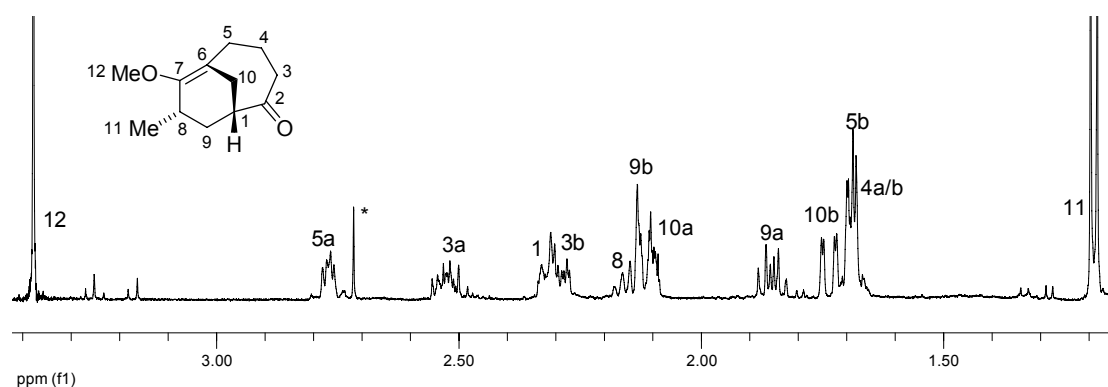

Figure 3.26   500 MHz ^{1}H NMR spectrum of IMDA adduct **1.68** recorded in C_6D_6 with hydrogen assignments derived from 2D correlation spectroscopy; * = residual Proton-sponge®.

The anticipated doublet, ascribed to the C11 methyl group, can clearly be seen at δ_H 1.19 ($J = 6.8$ Hz). Extensive 2D NMR spectroscopy (COSY, HSQC, CIGAR, NOE) in conjunction with a

crystal structure solved for a $\Delta^{6,7}$-cyclopropanated derivative confirmed the anticipated structure. Of particular interest is the deshielding effect experienced by the hydrogen H5a observed at δ_H 2.77 (dd, J = 3.9, 7.8 Hz). The δ-shift exhibited is considerably greater than H5b at δ 1.69 (upon the same carbon) and even the hydrogens H1, H3a and H3b adjacent to the C2 carbonyl. This observation would seem to indicate that H5a exists in a markedly different electronic environment. Subsequent theoretical modelling studies (**Section 3.7**) and the analysis of the ^{1}H NMR spectrum obtained from the homomethyl IMDA cyclised adducts (**Chapter 4**) seem to confirm this assessment.

The $\Delta^{6,7}$-olefinic adduct **1.68** was observed to be relatively stable to basic conditions, being recovered unchanged from alkylation reactions (*vide infra*), but rapidly isomerised to the $\Delta^{7,8}$-olefinic material upon exposure to trace acid. The residual acidity of CDCl$_3$ used as a solvent during NMR spectroscopy was observed to catalyse the isomerisation reaction, necessitating the use of d^6-benzene or CDCl$_3$ doped with 0.1% d^5-pyridine in order to prevent olefinic isomerisation.

3.5.2   IMDA Cyclisation of Ethoxy-triene 1.80

Application of the optimised protocols discovered for clean cyclisation of methoxy-triene **1.69** to the cyclisation of the ethoxy-triene derivative **1.80** was also successful in delivering the desired $\Delta^{6,7}$-bridgehead cycloadduct **1.79** (**Figure 3.27**).

1.80   **1.79**
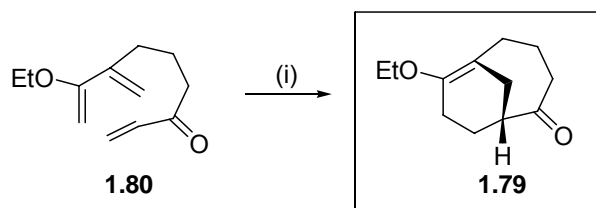
Figure 3.27   Optimised cyclisation of ethoxy-triene **1.80**

Reagents and yields: (a) Proton-sponge® (1.25 equiv), xylene, silylated glassware, reflux, 40 h, 35%**.**

3.6   Functional Group Modification of the $\Delta^{6,7}$ IMDA Bridgehead Adduct

With the hard-won $\Delta^{6,7}$-olefinic IMDA adduct **1.68** in hand, functionalisation of the carbocyclic core was investigated. Two reaction pathways were proposed as depicted in **Scheme 3.5**.
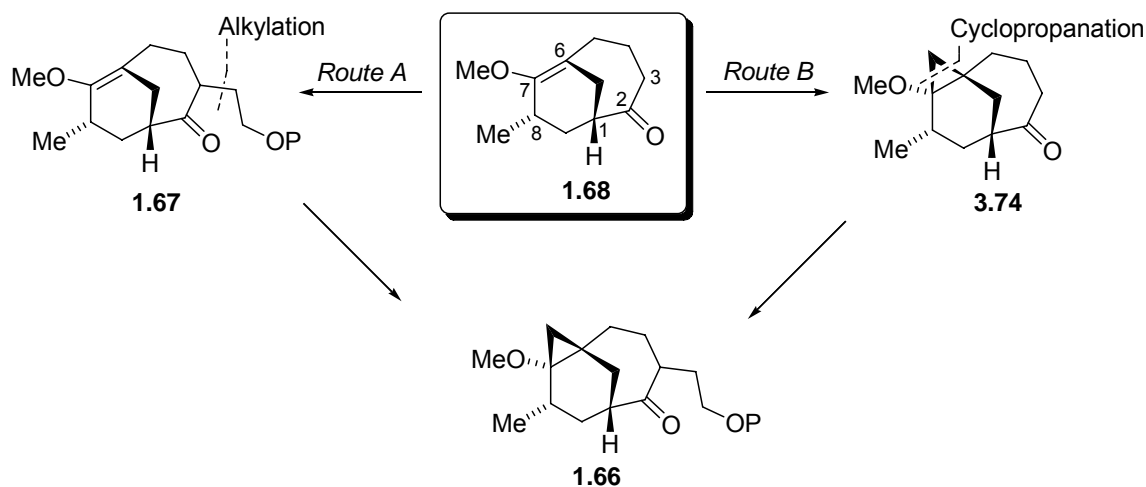
Scheme 3.5   Proposed route for the preparation of intermediate **1.66.**

Route A utilising regioselective C3 alkylation of **1.68** is based on the analogous reactions performed by Shea *et al.* which applied the conformational control afforded by the bicyclic skeleton to selectively alkylate the thermodynamic ring position. Subsequent cyclopropanation of the bridgehead olefin would yield **1.66**.

Alternatively, *Route B* depicts the initial cyclopropanation of **1.68** to secure the acid labile bridgehead olefin in position giving intermediate **3.74**. This would allow more vigorous conditions to be investigated for the regioselective alkylation.

3.6.1   Route A: Alkylation–Cyclopropanation

As demonstrated by Shea *et al.* in **Figure 3.11**, the rigid conformation of the bicyclo[5.3.1]undecenone carbocyclic core allows kinetic discrimination to be achieved between the C1 bridgehead hydrogen (Ha) and the two C3 hydrogens, Hb and Hc. Thermodynamic

equilibration of the enolate favours alkylation of the more thermodynamically stable C2-C3 enolate from the accessible *exo*-face.

To investigate the validity of Shea's bicyclo[5.3.1]undecenone studies to the alkylation of bicyclo[4.3.1]decenone, the initial alkylation studies were conducted on the $\Delta^{7,8}$ isomer **3.55**, due to the availability of this compound and the noted acid lability of the bridgehead isomer **1.68**.

The installation of the butenolide functionality, or a synthetic analogue, *via* either an aldol reaction of the ketone with glyxoylic acid, or alkylation of a metallo-enolate was uniformly unsuccessful. Representative examples are illustrated in the **Table 3.4**.

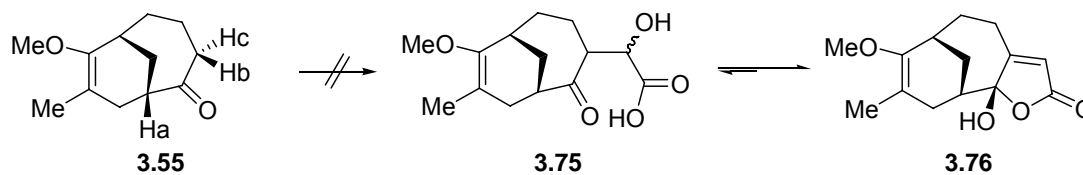**Table 3.4**   Summary of attempted C3-alkylation of $\Delta^{7,8}$-IMDA isomer **3.55**

Entry	Condition[a,b]	Result[c]
1	CHO-CO$_2$H, morpholine, EtOH, Δ	NR
2	CHO-CO$_2$H, Ac$_2$O, pyridine, Δ	NR
3	CHO-CO$_2$H, H$_3$PO$_4$, Benzene, Dean-Stark	Dec.
4	KHMDS, CHO-CO$_2$Me	NR
5	KHMDS, BrCH$_2$(OEt)$_2$	NR
6	KHMDS, ICH$_2$(OEt)$_2$	NR
7	LDA, CHO-CH$_2$OTHP	NR
8	LDA, ZnCl$_2$, CHO-CH$_2$OTHP	NR
9	KHMDS, allyl bromide, HMPA	CM
10	KHMDS, allyl iodide	CM
11	KHMDS, allyl bromide, equivalence studies	CM
12	KHMDS, methyl iodide	d
13	LDA, DMPU, methyl iodide	d
14	TBS-OTf, Hünig's base	d

Note: (a) Reactions were conducted on a 20 mg scale, with ~1 equiv of reagents. If unsuccessful at the stated literature temperature, the external temperature was raised by 40°C; if still no reaction had occurred, then 3 equiv of reagents were used. (b) The first equivalent of KHMDS was added over 1 h to allow equilibration of the initially formed enolate, additional base was then added more rapidly (~ 10 min). (c) The reaction mixtures were assessed by ^{1}H NMR spectroscopy and TLC of aliquots, with promising reactions subjected to column chromatography to isolate products. (d) see text for discussion.

No conditions could be found that would successfully and selectively alkylate the bridged carbocyclic core **3.55**.

The use of forcing conditions - such as elevated temperature, increasing the molar equivalents of the reagents and the incorporation of additives to the reaction mixture (HMPA, DMPU, LiI, $ZnCl_2$) - results in no reaction. ^1H NMR spectroscopy of aliquots taken from the reaction exhibited evidence of only the starting material or decomposition of the substrate. Many of these forcing conditions would not have been applicable to the correct $\Delta^{6,7}$ isomer **1.68**, due to the acidic nature of the reagents.

Some entries of note are the attempted alkylation of the potassium enolate of **3.55** with allyl bromide or allyl iodide *(entries 9-11)*. No reaction was observed to proceed until in excess of 2 equivalents of KHMDS were added. Quenching with excess allylating reagent resulted in the isolation of mono-, di- and tri-allylation products **3.77**. Alkylation was observed to occur preferentially at the C1 bridgehead site (for mono-alkylation), with subsequent alkylation occurring at the C3 non-bridgehead position. Restricting the quantity of quenching agent resulted in the same ratio of allylation and significantly more unreacted starting material (**Figure 3.28**).

Replication of the Shea quenching experiments under kinetic or thermodynamic conditions generated similar results *(entries 12-13)*. Methylation was observed to occur in all positions, irrespective of the experimental conditions applied. However, due to the use of equimolar equivalents of base: ketone only mono-alkylation was observed distributed between all three positions. The use of LDA was observed to give poor reactivity, returning predominantly starting material. The attempted extension of the non-specific alkylation with more functionalised substrates (1-bromo-2,2'-diethoxyethane or 1-iodo-2,2'-diethoxyethane), under a variety of conditions was unsuccessful in yielding any product *(entries 4-8)*.

The exception to this lack of reactivity was the reaction of **3.55** with TBS-OTf at low temperature. The only product isolated was the bridgehead TBS silyl enol ether **3.78**. This is in agreement with the alkylation studies that indicated that the C1 carbon was preferentially alkylated under kinetic control.
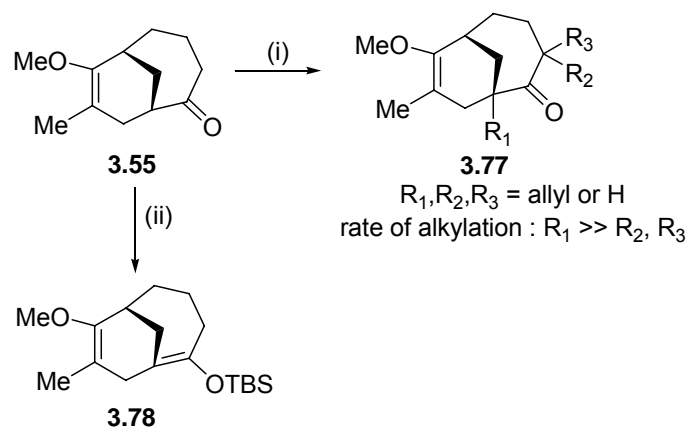
Figure 3.28   Attempted alkylation of **3.55**.

Reagents and yields: (i) KHMDS (2.2 equiv), -78°C → 0°C, THF; then at -78°C allyl bromide or methyl iodide; (ii) TBS-OTf, Hünig's base, CH$_2$Cl$_2$, -78°C, 87%.

The apparent lack of reactivity of the IMDA $\Delta^{7,8}$-isomer **3.55** led to investigation of the alkylation reactions of the desired $\Delta^{6,7}$-isomer **1.68**. Attempted alkylation of **1.68** using two equivalents of NaHMDS in THF at -78°C with HMPA as an additive was unsuccessful with a number of functionalised electrophiles (**Figure 3.29**). Only the starting material **1.68** could be isolated from these reactions, even upon reaction of the sodium enolate with aldehydes **3.79a-c** which had been observed to successfully undergo aldol additions on related substrates.[74]
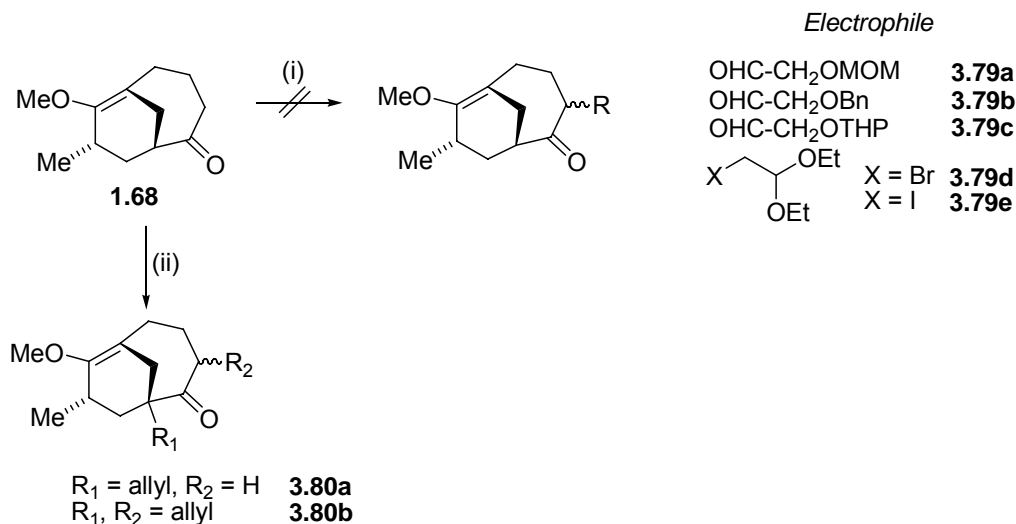
Figure 3.29   Alkylation studies of IMDA cycloadduct **1.68**.

Reagents and yields: (i) NaHMDS (2 equiv), HMPA (5 equiv), -78°C, 1 h; then electrophile (3 equiv), -78°C → rt; (ii) KHMDS (0.98 equiv), THF, -20°C → 0°C; then allyl bromide (1 equiv).

A lack of reactivity was also observed during attempted alkylation using **3.79d** and **3.79e** with HMPA or DMPU as an additive. Alkylation with the reactive electrophile allyl bromide using 0.98 equivalents of KHDMS was non-regioselective, resulting in the isolation of a mixture of the mono (**3.80a**) and di-alkylated (**3.80b**) products and starting material (**1.68**) following column chromatography.

The observed lack of reactivity for aldol addition and lack of regioselectivity in the case of allyl electrophiles prevented the use of this route to modify the central core. Furthermore, the introduction of only the highly reactive allyl species *via* alkylation did not advance the synthetic project, as reagents anticipated to react with the unactivated terminal alkene would also react with the activated and unstable bridgehead olefin.

### 3.6.2   Route B : Cyclopropanation – Alkylation

The use of the cyclopropanated adduct **3.74** allowed investigation of vigorous reagents and conditions to achieve the regioselective alkylation without the synthetically degradative process of $\Delta^{6,7} \rightarrow \Delta^{7,8}$ olefinic isomerisation occurring.

The traditional Simmons-Smith protocol (Zn-Cu couple, CH_2I_2, ethereal solvent)[75,76] was unsuccessful in effecting the cyclopropanation of the $\Delta^{7,8}$ IMDA adduct **3.55**. Modified protocols based on heterogeneous zinc catalysts were also unsuccessful, including the use of ultrasound and zinc activations.[77-79]

The Furukawa modification, which utilises diethylzinc to generate the cyclopropanation species bis(halomethyl)zinc (**3.81**) was successful, although excess reagent was required to achieve complete conversion (**Figure 3.30**).[80-82] Hydrolysis of the C7 methyl ether under acidic conditions was effective in revealing the intermediate cyclopropanol species (**3.82**) which proceeded *via* regioselective cyclopropane ring cleavage to deliver the *gem*-dimethyl diketone species **3.57**. Acid-catalysed aldol reaction of this intermediate generated the indenone product **3.58** as previously described.
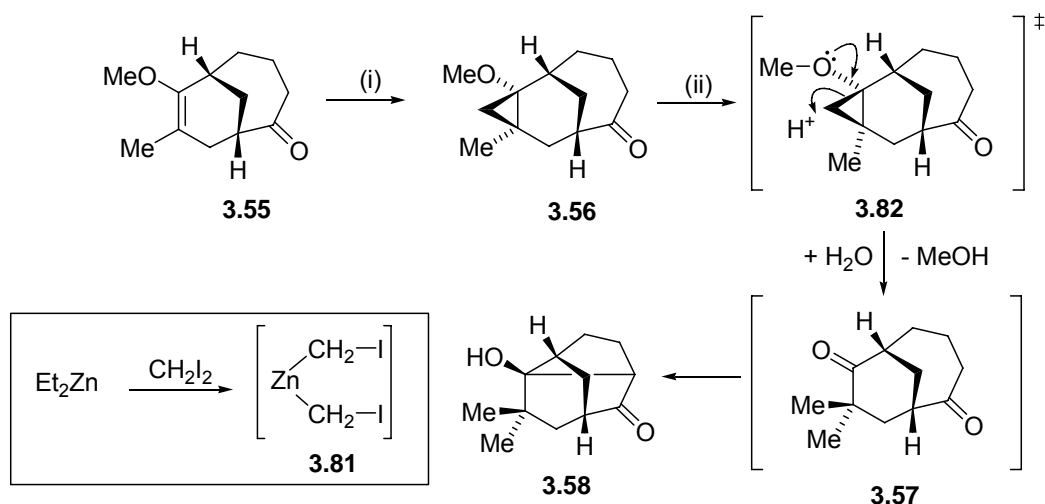
Figure 3.30   Cyclopropanation of **3.55**.

Reagents and yields: (i) ZnEt$_2$ (5 equiv), CH$_2$I$_2$ (10 equiv), DCE, 40°C, 16 h, 50%; (ii) conc. HCl (15%), EtOH, reflux, 12 h, quantitative.

Application of the Furukawa cyclopropanation protocol to the $\Delta^{6,7}$-adduct cleanly converted the olefinic functionality to the cyclopropane adduct **3.74**. No isomerism of the olefinic bond was observed under the reaction conditions, with starting isomeric ratios of **1.68**:**3.55** conserved in conversion to the cyclopropane adducts **3.74** and **3.56** respectively (**Figure 3.31**).

Figure 3.31   Cyclopropanation and hydrolysis of the bridged bicyclic olefins **1.68** and **3.55**.
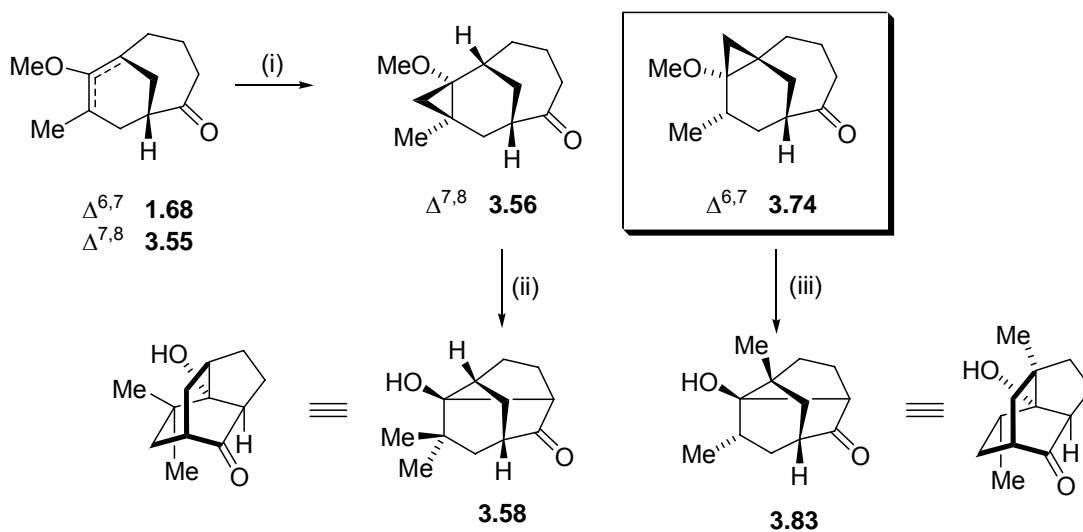
Regents and conditions: (i) ZnEt$_2$ (5 equiv), CH$_2$I$_2$ (10 equiv), DCE, 40°C, 16 h, 65%, (ii) conc. HCl (15%), EtOH (1:5), reflux, 12 h, quantitative; (iii) conc. HCl, EtOH (1:1), reflux, 12 h, 91%.

The two cyclopropane methyl ethers **3.56** and **3.74** showed differential hydrolysis selectivities. The $\Delta^{6,7}$-adduct **3.74** was stable to the conditions that effected the deprotection-ring cleavage of the $\Delta^{7,8}$-adduct **3.56**. Consequently, effective separation could be achieved *via* selective mild hydrolysis to generate a mixture of **3.58** and **3.74** which were readily separated by column chromatography. The use of more acidic conditions effected the hydrolysis of the $\Delta^{6,7}$-adduct to generate the desired dimethyl diketone, which underwent an intramolecular aldol reaction *in-situ* to deliver the indenone species **3.83**. This intermediate was fully characterised *via* 1D and 2D NMR spectroscopic techniques. Although generation of the novel indenone structures **3.58** and **3.83** was an unexpected result, following the acidic hydrolysis of the methoxy-cyclopropane structures, it was not believed that this represented a problem within the anticipated synthetic route. Hydrolysis of the $\Delta^{6,7}$-cyclopropane was envisaged to occur after installation of the C2-C3 furan moiety, which would prevent such an intramolecular reaction.

Confirmation of the structural assignment of **3.74** was achieved *via* single crystal X-ray diffraction of the $\Delta^{6,7}$-cyclopropanated adduct **3.84** derived from the sequential reduction and conversion of **3.74** into a 3,5-dinitrobenzoyl ester to facilitate crystallisation (**Figure 3.32**).
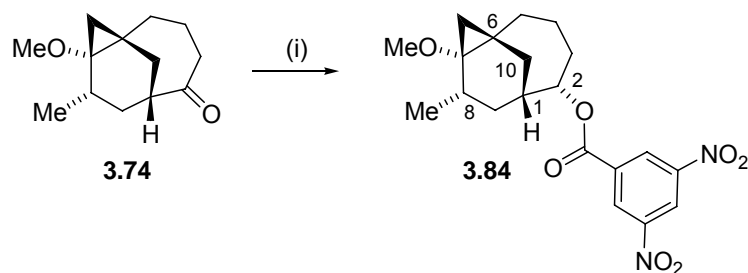
Figure 3.32   Preparation of the crystalline species **3.84** *via* reduction and esterification.

Reagents and yields: (i) *(a)* DIBAL-H, CH$_2$Cl$_2$, -78°C → rt, 90%, α:β (5:1); *(b)* 3,5-dinitrobenzoyl chloride, pyridine, CH$_2$Cl$_2$, 34%.

The structure, illustrated in **Figure 3.33a**, confirms a number of important assumptions in the synthetic route. As anticipated, the type II IMDA reaction had occurred in a *meta*-orientation with an *endo*-tether to yield the '*out*' hydrogen $\Delta^{6,7}$ bicyclo[4.3.1]decene. The orientation of the cyclopropane ring relative to the bridging C10 atom, and the orientation of the C2 alcohol indicate that both cyclopropanation and hydride delivery had occurred from the less hindered convex face of the bridgehead adduct (**Figure 3.33b**). The C8 methyl group occupies an equatorial position within a cyclohexane boat-conformation indicating conservation of the established diene stereochemistry during the Diels-Alder reaction.
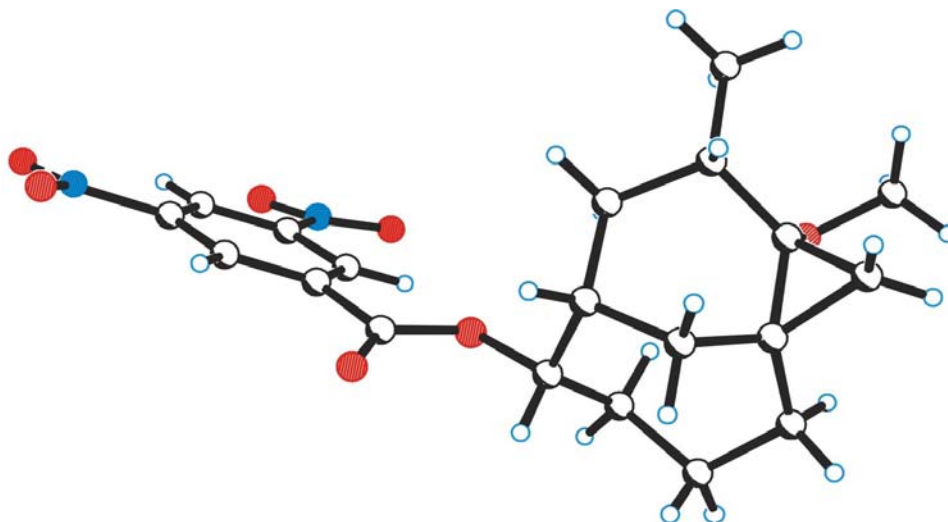
Figure 3.33a Crystallographic structure determined for cyclopropane adduct **3.84**, [P2$_1$/c, Z = 4, R = 3.6%], orientated to show the tricyclo[4.4.1.0^{1,3}]undecane core. The atom spheres are of an arbitrary radius.
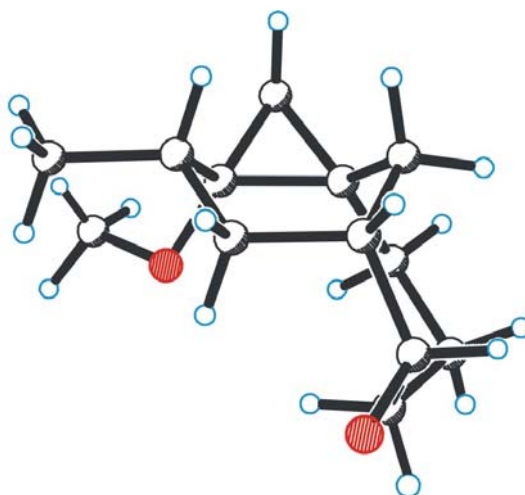
Figure 3.33b Horizontal view to show the exposed convex face within a cyclohexane boat structure, the relative orientation of the C2-alcohol, the C8-methyl group and the C6-C7 cyclopropane. The C2 aryl ester has been removed for clarity.

Efforts to obtain a crystal structure of the isomeric $\Delta^{7,8}$ cyclopropane species, derived from **3.56**, were unsuccessful in providing a suitable crystal, despite trying a number of crystallisation solvents and methods.

With the desired cyclopropane adduct **3.74** in hand, which had been demonstrated to regioselectively fragment to generate the desired C6 bridgehead methyl group, endeavours focused on the C3 regioselective alkylation.

However, efforts to alkylate the C3 position adjacent to the ketone, or engage it in a productive aldol reaction were unsuccessful. Synthetic methods attempted included alkylation of the potassium or sodium enolate with a number of electrophiles, the attempted use of C2 enamines, and aldol condensation with methyl glyoxylate. In all cases synthetically non-productive outcomes were obtained, including non-regioselective allyl alkylation and the return of starting material for the enamine and aldol condensation routes.

3.7   *Computational Model Studies*

In an effort to investigate the origins of the unexplained poor reactivity and lack of regioselectivity of the IMDA adducts **1.68, 3.55** and **3.74** towards alkylation, when compared with the research reported by Shea *et al.*, theoretical molecular modelling studies were conducted.

SPARTAN '04, (Wavefunction Inc.), was used to determine minimum conformational geometies *via* a Monte-Carlo search (MMFF94) for a number of alkylation substrates, which were subsequently optimised at a higher level of theory (HF 6-31G*) to allow calculation of the thermodynamic parameters and geometry.

Molecular mechanics force field (MMFF) models provide a good description of equilibrium geometries and conformations. The MMFF model describes molecules in terms of contributions arising from distortions to "ideal" bond distances (stretching), bond angles (bending) and torsional angles (torsional), together with contributions due to non-bonding van der Waals and Coulombic interactions. The derived value is commonly referred to as Strain energy, and although it does not reflect a thermodynamic parameter and cannot be used in thermodynamic calculations, it can give quantitative values of the differences in energy between related isomers and conformers.

Thermodynamic properties such as heat of formation and solvation, and electronic properties such as electron and orbital distributions (HOMO and LUMO), can be calculated using semi-empirical models such as AM1 and PM3, or higher level quantum-mechanical calculations performed with models such as Hartree-Fock and Density Functional theory. Theoretical modelling does not give correct *absolute* values as approximations inherent in the respective models give values constrained by the limitations and parameters imposed to make the model

solvable. However, the relative differences between calculated energies, when subjected to the same constraints, can give an indication of stability of different isomers and will more accurately represent *real* energy differences.

The substrates depicted in **Figure 3.34** and their C1,2 and C-2,3 enolates derived from deprotonation of either the Ha or Hb hydrogen respectively, were subjected to a MMFF Monte-Carlo conformational search. In all cases, a single geometry was located as a conformational minimum, as anticipated for these rigid bicyclic structures. The model systems were then optimised through semi-empirical methods (AM1 and then Hartree-Fock [6-31G*]), from which thermodynamic properties could be obtained. These structures allowed comparison of the relative strain energy between the bridgehead and non-bridgehead olefin isomers; determination of the kinetically most acidic proton, as determined by measurement of the carbonyl - α-proton dihedral angle; and prediction of the thermodynamic product as assessed by the relative energies of the C1 *vs*. C3 enolate. A number of unexpected results emerged from these calculations (**Table 3.5**).
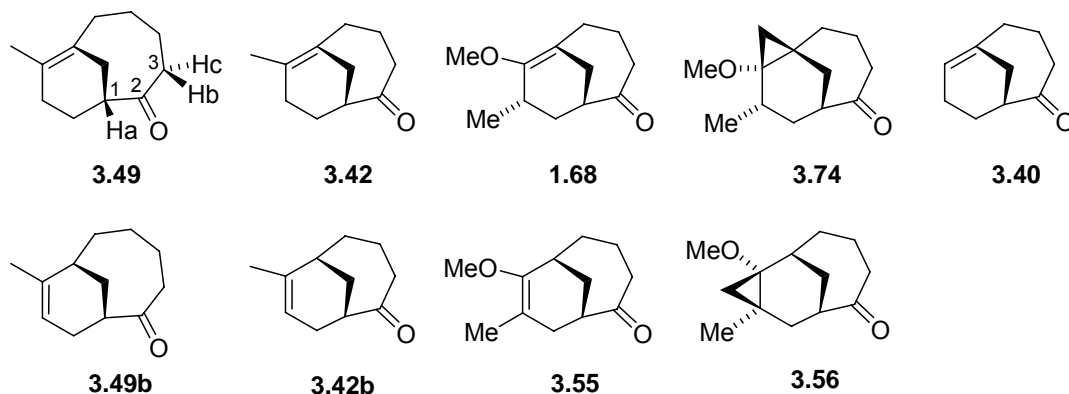

Figure 3.34   Bridged bicyclic molecular modelling substrates.

Table 3.5   Calculated theoretical parameters for compounds depicted in **Figure 3.34**

| Entry | Compound | Strain Energy[a] | Dihedral Angle[b,c] | | | ΔE C1 to C3[a] |
			Ha	Hb	Hc	
1	**3.49**	27.1	94 (4)	142 (52)	29 (61)	-5.8
2	**3.49b**	25.5	106 (16)	159 (69)	45 (45)	1.4
3	**3.42**	28.9	75 (15)	129 (39)	15 (75)	-8
4	**3.42b**	17.9	60 (30)	119 (29)	4 (86)	-16.9
5	**1.68**	33.8	15 (75)	3 (87)	117 (27)	-6.6
6	**3.55**	21.9	59 (31)	118 (28)	3 (87)	-11
7	**3.74**	28.3	48 (42)	110 (20)	5 (85)	-7.6
8	**3.56**	30.1	67 (23)	123 (33)	4 (86)	3.2
9	**3.40**	27.1	76 (14)	130 (40)	16 (74)	-8.4

Notes: (a) Energy measurements are in kcal mol^{-1} (b) Dihedral angles were measured along the Hn-C-C=O bond in degrees (c) The first value refers to the measured dihedral angle; the value in parentheses is displacement of the dihedral angle from perpendicular (90°) relative to the carbonyl σ bond.

The values obtained for the 9-methyl bicyclo[5.3.1]dodec-7-ene (**3.49** - *entry 1*) were in close agreement with those calculated by Shea *et al.* using MM2 determination of the lowest energy conformation.[61] Shea rationalised the experimentally observed kinetic deprotonation and alkylation at the bridgehead C1 carbon (**Figure 3.11**), by noting that deprotonation is stereoelectronically optimal with a 90° C-H dihedral angle relative to the carbonyl σ-plane. The "CH-π overlap effect" which results from the overlap of the CH σ-bond with the carbonyl π-orbitals contributes to the stabilisation of the enolate transition state and makes deprotonation of the C-H bond more facile. (**Figure 3.35**).[83-85]
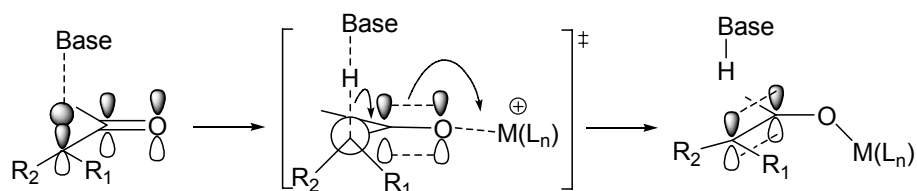
Figure 3.35   Illustration of the CH-π overlap effect.

As can be observed in **Table 3.5**, isomerisation of the bridgehead olefin to the non-bridgehead position within the cyclohexane ring, (**3.49** *vs.* **3.49b**), (**3.42** *vs.* **3.42b**) and (**1.68** *vs.* **3.55**) relieves the strain energy associated with the deformation of the alkene. In agreement with the hypotheses derived from Bredt's rule, the magnitude of this strain is larger in smaller bicyclic ring systems (**3.42**, **1.68** *vs.* **3.49**) where the expected olefin deformation is greatest.

Compounds **3.49**, **3.49b**, **3.42** and **3.40** *(entries 1-3,9)* have dihedral angles closest to 90° for the hydrogen Ha, favouring kinetic deprotonation at the C1 bridgehead carbon. The initially formed bridgehead enolate favours thermodynamic isomerisation to the C3 non-bridgehead enolate to release the unfavourable torsional strain for **3.49, 3.42** and **3.40**. Intriguingly, these calculations imply that the C1 enolate is more favourable for the non-bridgehead olefin **3.49b** than the C3 enolate. Investigation of the geometry of **3.49b** revealed considerable torsional twisting to accommodate the non-bridgehead enolate in the cyclooctane ring.

Isomerisation of the bridgehead olefin, which conformationally restricted the bridged bicyclic system, to the non-bridgehead position can be observed to degrade the ability to distinguish between the C1 and C3 hydrogen dihedral angles *(entries 1 vs. 2, 3 vs. 4, 5 vs. 6).* This could be anticipated to lead to diminished kinetic discrimination between the C1 and C3 enolates, however the thermodynamic enolate still favours C3 in most cases.

The noted exception to these observations and trends is **1.68** *(entry 5).* Despite containing a bridgehead olefinic bond, it exhibits poor dihedral discrimination between the C1 and C3 hydrogens; 15° and 3° respectively. Although the Hc hydrogen has a good dihedral orientation (118°) with respect to the carbonyl system, it is orientated to the concave face of the bicyclic ring where approach by a base could be anticipated to be sterically hindered (**Figure 3.36**). Consequently, it could be anticipated that deprotonation at the C3 atom would be kinetically slow, hindering the establishment of the thermodynamic C2-C3 enolate anion.
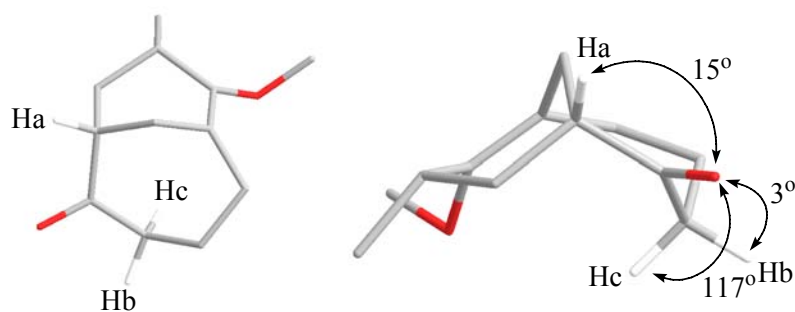
Figure 3.36   MM2 energy minimised conformation of **1.68** which illustrates the concave nature and sterically hindered access to the Hc hydrogen.

This theoretical prediction is in agreement with the experimental work performed on **1.68** in which the exclusive alkylation of the C3 position was not observed under conditions anticipated to preferentially select for the thermodynamic enolate.

Comparison of **1.68** with **3.42** revealed that the two models displayed different geometric conformational minima (**Figure 3.37**). To ensure that this conformational change was not due to the C8 methyl group, MMFF prediction of the energy minima for **3.85** was undertaken, in which the C8 methyl group is present and the C7 methyl-ether has been replaced with an isosteric ethyl group.

Although the conformationally restricted cyclohexene group of **1.68** mapped cleanly onto the cyclohexene group of **3.85**, it could readily be seen that the cycloheptane ring occupies a distorted chair structure in **1.68** (when viewed along the axis of H_b to H_f) (**Figure 3.37**-*A*), but an extended boat in **3.85** (**Figure 3.37**-*B).* The adoption of different conformational minima in the cycloheptane ring results in considerable differences in the observed dihedral angles.
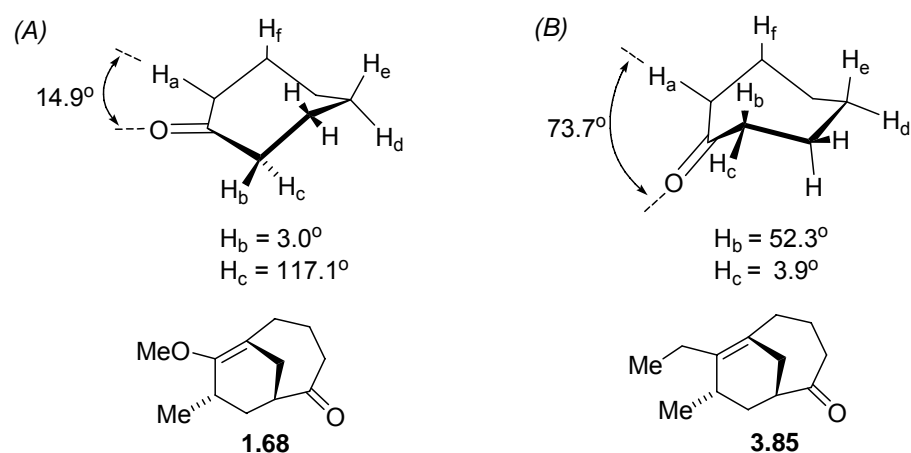
Figure 3.37   Calculated structure for **1.68** *(A)* and **3.85** *(B)* showing the geometrical conformation adopted by the cycloheptane ring.

Constraining **1.68** to occupy the cycloheptane conformation of **3.85**, resulted in an increase in the calculated strain energy of 8.5 kcal mol^{-1}, indicating that **Figure 3.37**-*A* was the conformational minimum geometry for **1.68**, rather than that of **Figure 3.37**-*B*. This unexpected result contrasts with **3.42b** and **3.55** which show very similar geometrical conformations, with the cycloheptane core occupying an extended boat structure (similar to **Figure 3.37**-*B*) and the cyclohexene groups possessing an essentially super-imposable bridged bicyclic core.

To investigate this phenomenon further, a number of model systems were briefly analysed using the MMFF model. The resulting minimised conformational models could be divided into three categories:

(A) geometrical conformations similar to that observed for **3.85**,

(B) distorted conformations such as that observed for **1.68**, and

(C) a hydrogen-bonded model where the concave nature of the bicyclo[4.3.1] ring system puts the R_1 hydrogen donor in close proximity (~2.1 Å) to the carbonyl oxygen.

Table 3.6   Conformational minima adopted by bicyclo[4.3.1]decenes with differing R_1 and R_2 substituents and the calculated Ha-carbonyl dihedral angles.
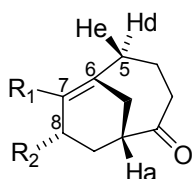
(A) Standard	Ha	*(B) Distorted*	Ha	*(C) H - Bonded*	Ha
R_1 = Me, R_2 = OMe	72	R_1 = OMe, R_2 = Me (**1.68**)	15	R_1 = Me, R_2 = OH	91
R_1 = Me, R_2 = H (**3.42**)	75	R_1 = OH, R_2 = Me	16	R_1 = H, R_2 = OH	90
R_1 = H, R_2 = Me	72	R_1 = H, R_2 = OMe	16		
R_1, R_2 = Me	73				
R_1 = Et, R_2 = Me	74				
R_1, R_2 = H (**3.40**)	76				
R_1 = OH, R_2 = H	74				

From inspection of **Table 3.6** it can be seen that *Model A* systems adopt an extended boat conformation similar to that depicted for **3.85** (**Figure 3.37-B**), which results in a dihedral Ha-carbonyl angle of 72-76°. Such systems would favour selective deprotonation at Ha relative to Hb or Hc. The *Model B* systems, by contrast, have a distorted chair structure (as depicted in **Figure 3.37-A**) with a dihedral angle of 15-16° which prevents efficient discrimination between Ha and Hb. The unfavourable orientation of Ha and Hb with respect to the carbonyl π-system may be expected to retard the rate of proton abstraction.

A distinct cause for the divergence of the conformational minima of *Group B* molecules relative to *Group A* is not readily apparent. Calculation of the orbital co-efficients of the *Group B* models displayed evidence of ionisation and hyperconjugation which extends the C6-C7 olefinic HOMO and LUMO surfaces onto the adjacent C5 carbon. The Hd hydrogen was observed to be planar with the olefinic $\Delta^{6,7}$ bond. This hyperconjugation was largely absent from the *Group A* and

Group C molecules, and may be responsible for the adoption of the unusual geometry observed within the cycloheptanone ring. Remarkably, this is in agreement with the ^{1}H NMR spectrum acquired for **1.68** (**Figure 3.26**) which indicated that one of the C5 hydrogen atoms exists in a unique electronic environment, resulting in a significant deshielding effect, [$\Delta\delta$ (5a-5b) = 1.08 ppm], possibly due to interaction with the adjacent $\Delta^{6,7}$-olefinic bond.

Whether these models, derived from theoretical calculations, accurately depict the actual molecular conformational geometry is unknown. However, the unexpected conformation discovered for **1.68** may explain much of the aberrant reactivity with respect to the lack of regioselectivity in the enolate formation and alkylation, when compared to molecule **3.49** utilised by Shea *et al.* when demonstrating regioselective alkylation (**Figure 3.11**).

3.8   Summary

The IMDA reaction of three triene systems was investigated under both thermal and Lewis acid catalysed conditions. The cyclisation was observed to proceed in good yield to generate bicyclo[4.3.1]decene carbocyclic skeletons but was complicated by a facile acid-catalysed $\Delta^{6,7} \rightarrow \Delta^{7,8}$ olefinic isomerisation for 7-alkoxy-trienes **1.69** and **1.80**. The same isomerisation process was found not to affect the vinyl triene system **2.67** which gave the $\Delta^{6,7}$-bicyclo[4.3.1]decene skeleton without evidence of the $\Delta^{7,8}$-isomer.

The use of greater than stoichiometric quantities of Proton-sponge® in silylated glassware was observed to retard the $\Delta^{6,7} \rightarrow \Delta^{7,8}$ isomerisation allowing the isolation of the $\Delta^{6,7}$-olefinic adducts in good yield. Efforts to appropriately functionalise these adducts however, were uniformly unsuccessful, in contrast to the work of Shea *et al.*

Molecular modelling conducted to explore the causes of this aberrant reactivity revealed an unexpected molecular conformation for the 7-alkoxy-IMDA adducts. This conformation was predicted to both diminish the kinetic discrimination between the bridgehead and ring protons and to retard the establishment of a thermodynamic enolate.

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Chapter Four

Diels-Alder Homomethyl Substrates

4.1 Homomethyl Homologation: Synthetic Plan

Investigations directed towards the synthesis of the bicyclo[4.3.1]decane core of the nakafuran and florlide natural products, *via* an IMDA reaction of triene precursors **1.69** and **1.80**, had shown the products to undergo a particularly facile $\Delta^{6,7} \rightarrow \Delta^{7,8}$ olefinic isomerisation. It is postulated that this very rapid, acid-catalysed isomerisation is assisted by the enol-ether functionality, presumably *via* a transient oxonium intermediate (**3.64**) (**Scheme 4.1 - *Route A***). The release of the strain associated with the bridgehead olefinic bond provides a thermodynamic driving force for this olefinic migration.

To address this issue a scheme was devised that saw the substitution of the C7 enol-ether (**1.69**) for a homomethyl ether (**3.69**). The diminished tautomeric ability of the C7 methylene group was anticipated to retard or prevent the double bond isomerisation (**Scheme 4.1 - *Route B***).
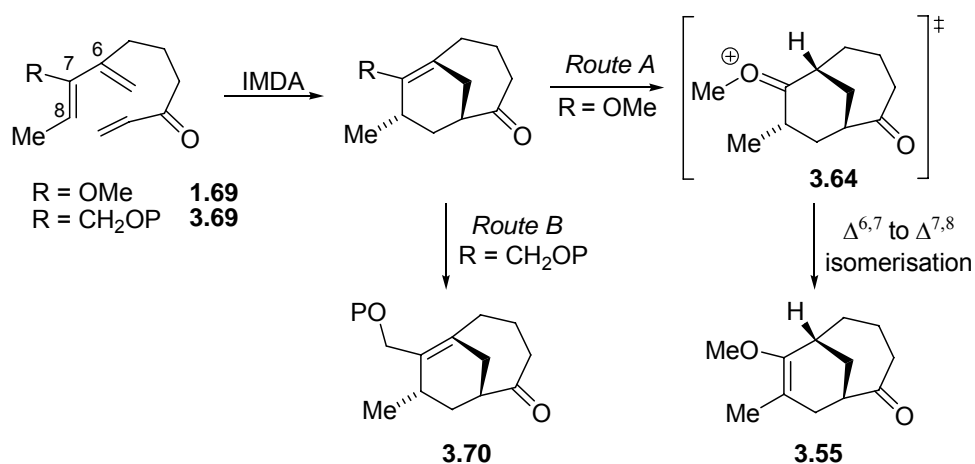

Scheme 4.1 Proposed IMDA cyclisation and subsequent olefinic isomerisation (*Route A*) and modified route incorporating a homomethyl extension (*Route B*).

4.1.1   Homomethyl Homologation: Retrosynthesis

The one carbon homologation of the C7 methyl ether necessitated both the development of a new synthetic route to the synthesis of the triene substrate **3.69** and a new method to install the quaternary C6 methyl group with sufficient functionality at the C7 carbon.

The synthetic route envisaged for the installation of the C6 bridgehead methyl group, *via* the simultaneous methyl ether deprotection and cyclopropanol fragmentation, as applied to adduct **3.74** under acidic conditions, was no longer accessible to the homologated substrate **4.1**. A synthetic plan was devised whereby radical scission of the allylic carbon-oxygen bond of **4.1** would furnish an intermediate cyclopropylcarbinyl radical **4.2**. Homoallyl-type rearrangement of this radical species would effect ring opening of the *exo*-cyclopropane bond to furnish the *exo*-methylene bridgehead methyl adduct **4.3**. Elaboration of this intermediate would intersect with the previously described synthetic route (**Scheme 4.2**).
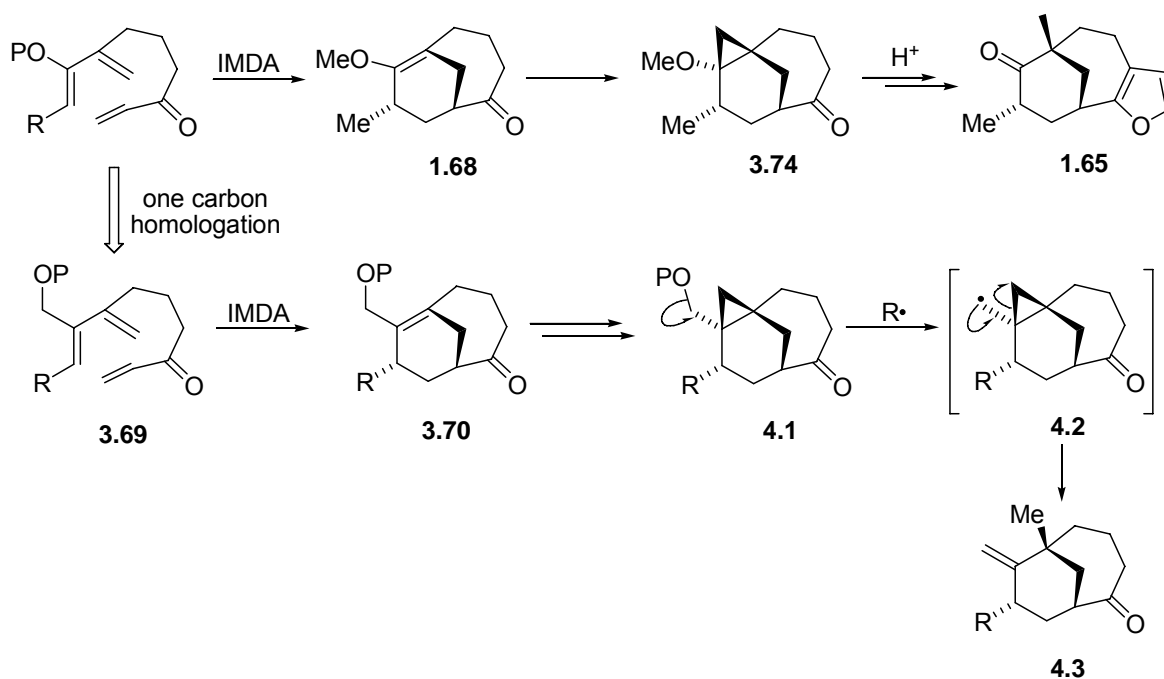
Scheme 4.2 Modified fragmentation route utilising a cyclopropylcarbinyl → homoallyl radical rearrangement.

Two retrosynthetic routes for the preparation of the triene system **3.69** were proposed and are depicted in **Scheme 4.3**.
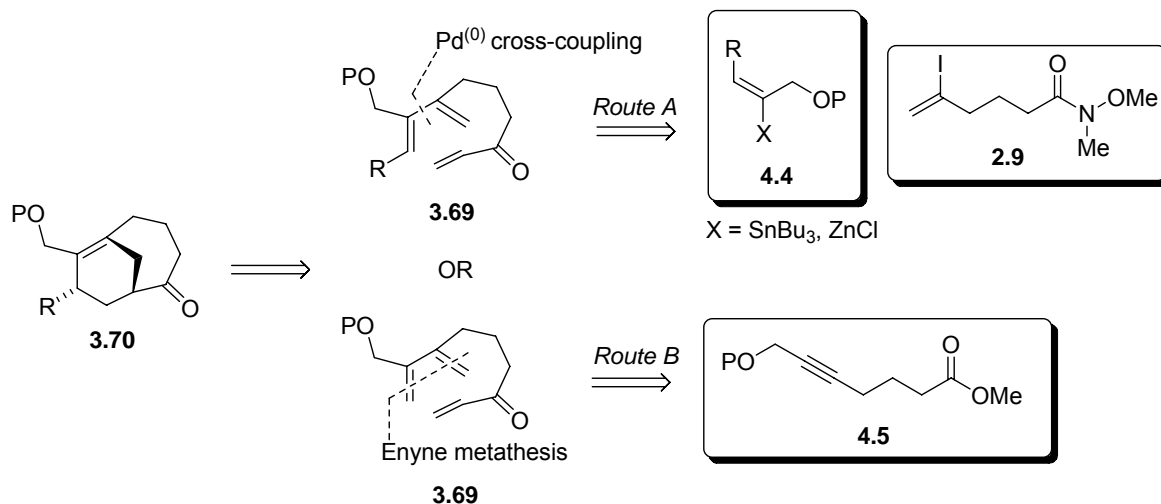
Scheme 4.3 Retrosynthetic routes to homomethyl triene **3.69**.

Route A utilises a palladium-catalysed cross-coupling reaction to form the required σ-bond between the sp^2 centres of vinyl iodide **2.9** and 2-functionalised but-2-en-1-ol **4.4**. This coupling methodology was successfully applied during synthetic endeavours conducted towards the triene systems **1.66**, **1.80** and **2.67** (**Chapter 2.8**).

Route B by contrast, features an intriguing alternative disconnection. By employing an enyne-metathesis reaction between an olefin and the alkyne substrate **4.5**, it is possible to install the two diene sp^2-centres from a single sp-precursor. This attractive route allows the rapid installation of the 1,3-diene substructure in a single step from an alkyne, the product of which can readily be advanced to the triene IMDA precursor **3.69**.

4.2   Route A: Palladium-Catalysed Cross-Coupling

The transition-metal catalysed coupling of the vinyl iodide **2.9** with a suitably substituted allylic alcohol **4.4** would result in the formation of the diene system **4.6** (**Scheme 4.4**). This adduct contains a methyl homologated C7 functional group when compared to the previously prepared enol-ether diene substrates generated *via* the coupling of **2.9** with **1.71**.
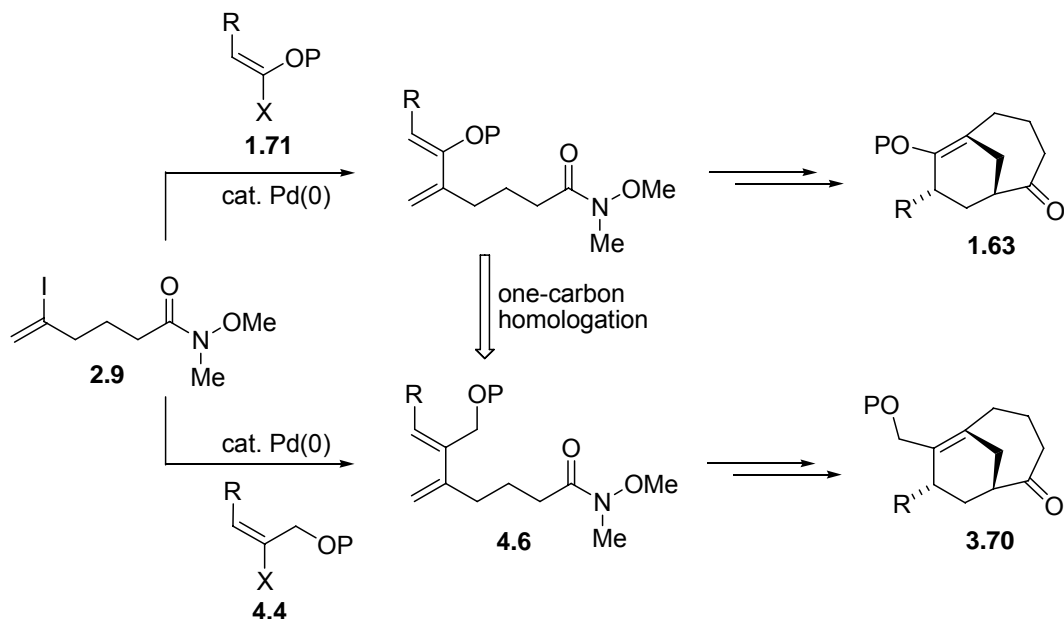
Scheme 4.4 Synthetic route to **3.70** *via* palladium-catalysed cross-coupling.

It was envisaged that the palladium-catalysed coupling could be achieved through the application of a Stille or Negishi coupling protocol. In the case of the Stille coupling this necessitates the preparation of the vinyl stannane species **4.4** (X = SnBu$_3$); whereas the Negishi coupling fragment would be accessed *via* the zinc-transmetallation of the vinyl iodo-adduct (**4.4**, X = I). Advancement through the previously described synthetic steps would generate the homomethyl IMDA adduct **3.70**.

4.2.1   Preparation of Coupling Fragments

Synthetic preparation of the vinyl iodide coupling partner **2.9** has previously been detailed in **Section 2.6.2.1**. The preparation of the homologated vinyl coupling partners **4.7**-**4.10** features

chemical transformations similar to those required to make the analogous vinyl ether coupling partners **1.71** and **1.82** (**Scheme 4.5**).
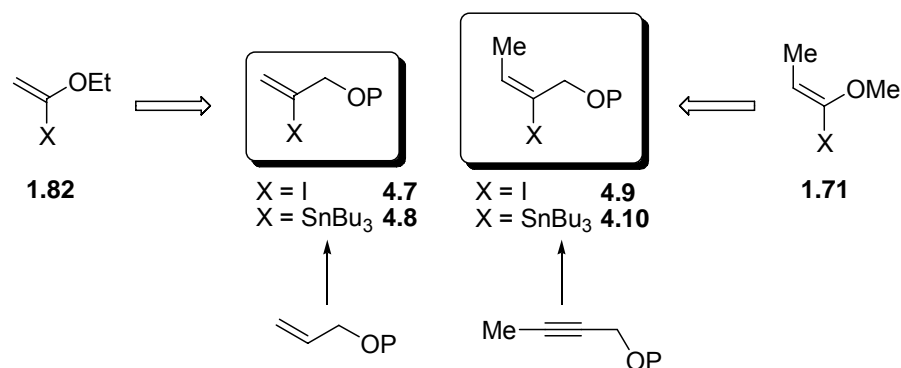
Scheme 4.5 Functionalised vinylic coupling targets for **4.7**-**4.10**.

4.2.1.1   Preparation of Iodo-Substituted Coupling Fragment 4.7

The differentially protected 2-iodoprop-2-en-1-ols **(4.7a-d)**, the homomethyl analogues of ethyl vinyl ether fragment **1.82**, were prepared utilising the hydrohalogenation methodology previously discussed. In contrast to the attempts to prepare isomerically pure α-iodohexenols such as **2.55**, which were hampered by double bond isomerisation, the exposure of propargyl alcohol to 2.4 equivalents of anhydrous HI, using the protocol of Ishii *et al.*,[1] resulted in the isolation of the single product **4.7a**, following column chromatography. The free alcohol was subsequently protected using standard synthetic protocols to yield the three differentially protected vinyl iodides **4.7b**, **4.7c** and **4.7d** in high yield (**Scheme 4.6**).
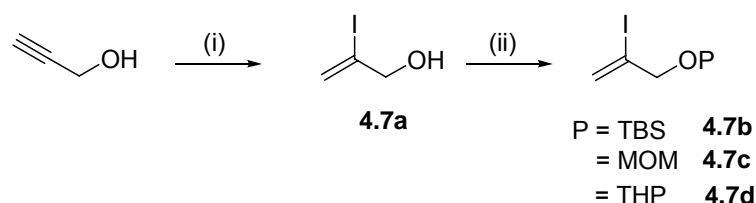
Scheme 4.6 Preparation of vinyl iodide coupling partners.

Reagents and yields: (i) NaI, TMSCl, H$_2$O, MeCN, 1 h, 51%; (ii) *(a)* TBSCl, imidazole, DMF, 98%, **4.7b**; or *(b)* DHP, *p*-TsOH, CH$_2$Cl$_2$, 74%, **4.7c**; or *(c)* MOM-Cl, DIPEA, CH$_2$Cl$_2$, 68%, **4.7d**.

4.2.1.2   Preparation of Stannane Coupling Fragment 4.8

The preparation of α-stannyl allylic alcohols from differentially protected propargyl ethers has previously been reported.[2-5] As illustrated in **Table 4.1**, radical hydrostannylation protocols primarily give the terminal stannylated alkenes as thermodynamic *E*/*Z* mixtures *(entry 1)*. Transition metal catalysts give clean *cis* addition, often with good to excellent regioselectivity at the α-position *(entries 2-6)*.[2-10] Recently, Muria and colleagues disclosed conditions that generate the *Z*-alkene adducts with high regio- and stereoselectivity *(entries 7-8)*.[11]

Table 4.1   Hydrostannylation of propargyl alcohol derivatives.

Entry	R	Conditions	Yield	α	*E*-β	*Z*-β	Reference
1	THP	AIBN	71	10	45	16	2
2	THP	RhCl(CO)(PPh$_3$)$_2$	72	94	6	-	3
3	THP	MoBr(allyl)(CO)$_2$(MeCN)$_2$	-	64	36	-	4
4	THP	PdCl$_2$(PPh$_3$)$_2$	68	67	33	-	4
5	THP	Mo(CO)$_3$(CN-*t*-Bu)$_3$	94	89	11	-	5
6	Ac	Mo(CO)$_3$(CN-*t*-Bu)$_3$	91	96	4	-	5
7	H	Bu$_2$Sn(OTf)H; *n*-BuLi	85	1	-	99	11
8	Me	Bu$_2$SnClH, AIBN; *n*-BuLi	95	9	-	86	12

Guibe *et al.* reported the application of a molybdenum catalyst MoBr(allyl)(CO)$_2$(MeCN)$_2$ to the hydrostannylation of a number of alkynes *(entry 3)*.[4] The molybdenum complex showed comparable reactivity and slightly higher selectivity in favour of the α-stannylated product than palladium-catalysed reactions, especially with hindered alkynes.

The laboratory of Kazmaier extended this research with the systematic modification of Mo$^{(0)}$ complexes.[2,5,9,10,13] The replacement of three carbon monoxide ligands on Mo(CO)$_6$, itself capable of moderate hydrostannylation ability, with isoelectric *tert*-butyl isonitrile ligands resulted in a significant increase in the yield and selectivity. The complex, Mo(CO)$_3$(CN-*t*-Bu)$_3$ (**4.11**), displayed favourable regioselectivity, adding to the alkyne bond such that the sterically more demanding molybdenum moiety is located at the least hindered position (**4.12**).[14] Reductive elimination gives the α-stannylated adduct **4.13** (**Figure 4.1**).
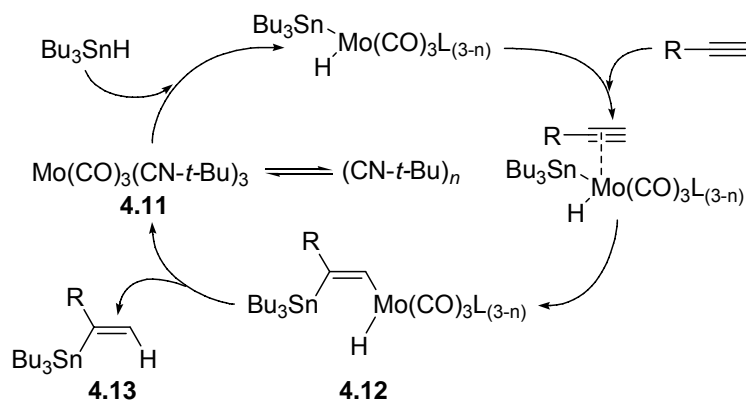
Figure 4.1 Proposed mechanism for the molybdenum-catalysed hydrostannylation of alkynes.

Application of the protocol of Kazmaier *et al.* to a number of differentially protected propargyl alkynes resulted in the generation of the vinyl stannanes **4.8a-4.8d** in good yield as displayed in **Table 4.2** *(entries 1-4)*. The observed hydrostannylations proceeded with excellent stereocontrol, due to the *syn*-addition of tributyltin hydride across the alkyne bond, although the regiocontrol was moderate (~6α : 1β).

Table 4.2   Hydrostannylation of propargyl alcohol substrates.

4.8a R = OH
4.8b R = OMOM
4.8c R = OTHP
4.8d R = OTBS
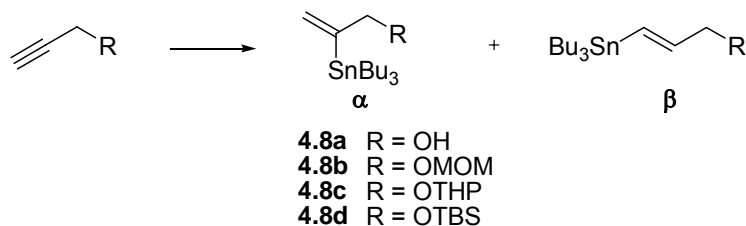
Entry	R	Conditions[a]	Conversion[b]	Yield[c]	Compound
1	OH	23°C	100 (85:15)	78%	**4.8a**
2	OMOM	23°C	100 (85:15)	81%	**4.8b**
3	OTHP	23°C	100 (90:10)	74%	**4.8c**
4	OTBS	23°C	100 (79:21)	60%	**4.8d**
5	2.54	23°C; 55°C	0	-	**2.7**

Note: (a) Reactions were conducted on 1 mmol scale, Mo(CO)$_3$(CN-*t*-Bu)$_3$ (2 mol %), Bu$_3$SnH (3 equiv), hydroquinone (10 mol %), THF, at room temperature for 16 h under Ar. (b) Conversion was determined by integration of the relevant ^{1}H NMR signal for the allylic CH$_2$; the value in parenthesis is the observed ratio of α:β vinyl stannane. (c) Yield refers to isolated chromatographically pure material.

Attempted hydrostannylation of the alkyne amide **2.54** did not proceed at ambient temperature. No reaction was observed after 16 hours at elevated temperature *(entry 5)*. Only a few instances

of the hydrostannylation of non-propargyl alkynes with the catalyst **4.11** have been reported in the literature and in these cases α-ketone or ester functionality has facilitated the reaction by activating the alkyne bond.[5,15]

4.2.2   Negishi Cross-Coupling

The advantages of the Negishi coupling in the preparation of the dienes **1.70**, **1.81** and **2.67**, relative to the Stille coupling protocols, prompted investigation of the palladium-catalysed coupling of the vinyl-zinc reagents **4.14**. However, all attempted couplings of the α-functionalised ethenyl alcohols **4.7b-4.7d** to the vinyl iodide **2.9** using the Negishi coupling methodology were unsuccessful (**Scheme 4.7**). The vinyl iodide **2.9** was recovered unchanged from the reaction mixtures. No evidence of products derived from the decomposition of the α-metallated intermediates could be detected, presumably due to their volatility upon aqueous work-up and extraction.

4.7b-d   **4.15**   **4.14**
R = MOM, THP, TBS
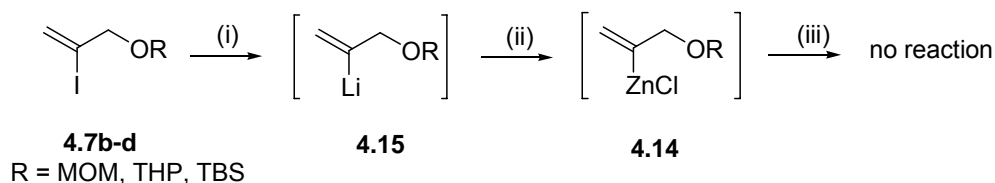
Scheme 4.7 Attempted Negishi coupling of the α-vinyl iodides **4.7b**–**4.7d**.

Reagents and conditions: (i) *n*-BuLi, ether, -90°C → -40°C; (ii) ZnCl₂; (iii) Pd(PPh₃)₄, **2.9**, THF, 25°C.

The failure of these reactions can probably be traced to the decomposition of the vinyl-lithium (**4.15**) or vinyl-zinc species (**4.14**) prior to participation in the palladium-catalysed cross-coupling reaction. It is postulated that decomposition occurs either *via* a rapid β-ether elimination to form an allene and an alkoxide (**Figure 4.2 –** *i*)[16] or that the organolithium or organo-zinc species participate in a π-allylic rearrangement resulting in the formation of a stabilised π-allyl or alkoxyl-chelated metallocycle species (see **Figure 2.12**).[17,18]
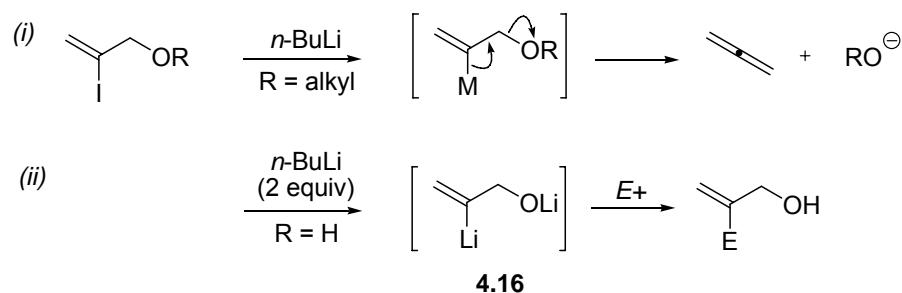
Figure 4.2 *(i)* Decomposition of hydroxyl-protected α-metallo allylic alcohols *via* allene formation and (*ii*) productive application of di-lithio derivatives.

Few instances have been reported in the literature of the successful application of α-metallo-derivatives of protected allylic alcohols. Corey *et al.* reported that *O*,2-dilithio-derivative of allylic alcohol (**4.16**) can be effectively applied as a nucleophilic alkylation reagent, in which the lithio-alkoxide anion prevents competing allene formation.[16]

Efforts to form the vinyl stannane species **4.8d** *via* a low temperature halogen-lithium transmetallation of **4.7b**, followed by quenching with tributyltin chloride, were similarly unsuccessful in yielding the desired product.

4.2.3   Stille Cross-Coupling

The Stille cross-coupling reactions of **4.8b** and **4.8d** with the vinyl iodide **2.9** were trialled under the previously optimised conditions, (**Scheme 4.8**). Poor conversions were observed in both cases, as assessed by analysis of the crude reaction mixtures *via* ^{1}H NMR spectroscopy. Reactions conducted at 60°C for 16 hours gave incomplete conversion (~5%), with both the vinyl stannane and iodide starting materials still in evidence. Increasing the external bath temperature to 85°C for 8 hours resulted in an increase in conversion to 37% for **4.17** and 12% for **4.18**. Also observed were vinylic signals attributed to double bond isomerisation or *cine* Stille coupling of the allylic component.[19-21] Extended reaction at this temperature resulted in complete consumption of the starting materials but was accompanied by decomposition of the coupled product.
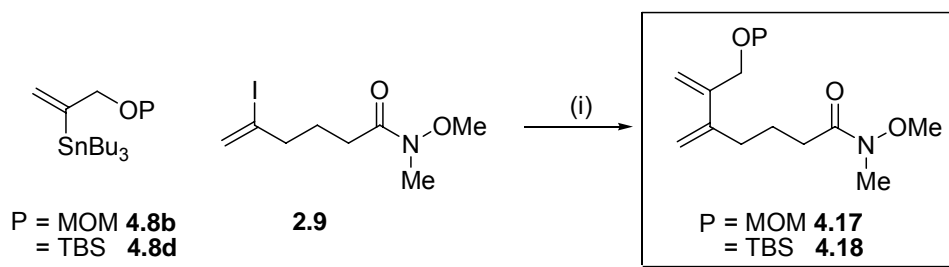
Scheme 4.8 Preparation of homomethyl ethylene derivatives **4.17** and **4.18** via Stille coupling. Reagents and yields: (i) **4.8b** or **4.8d** (1.2 equiv), **2.9** (1 equiv), $Pd_2(dba)_3$ (5 mol %), $AsPh_3$, (20 mol %), CuI (20 mol %), DMF, 85°C, 16 h; 37% **4.17**; 12% **4.18**, [as assessed by ^{1}H NMR spectroscopy].

It is plausible that conditions could be found that would optimise formation of the desired coupling product whilst minimising the undesirable decomposition and coupling pathways.[22,23] However, the success of an alternative synthetic route based on enyne metathesis, which delivered the diene system **4.6** in an isomerically pure fashion, meant that the Stille cross-coupling route was not further pursued.

4.2.4   Preparation of Coupling Fragment 4.10

In light of the failure to effect a successful Negishi coupling of vinyl iodide **2.9** with the organo-zinc derivatives of 2-iodopropenes **4.7b-4.7d**, only the Stille catalysed cross-coupling was investigated for the 2-functionalised butyn-1-ol derivatives.

Extensive studies have been carried out on the hydrostannylation of 1-alkynes (see **Table 4.1**), but the reactions of internal alkynes have received little attention.[24,25] It is known that the hydrostannylation of 2-butyn-1-ol (**4.19**) and its protected derivatives generate different regio- and stereochemical product distributions dependent upon the nature of the alcohol protecting group and the method of hydrostannylation (**Figure 4.3**).[26]
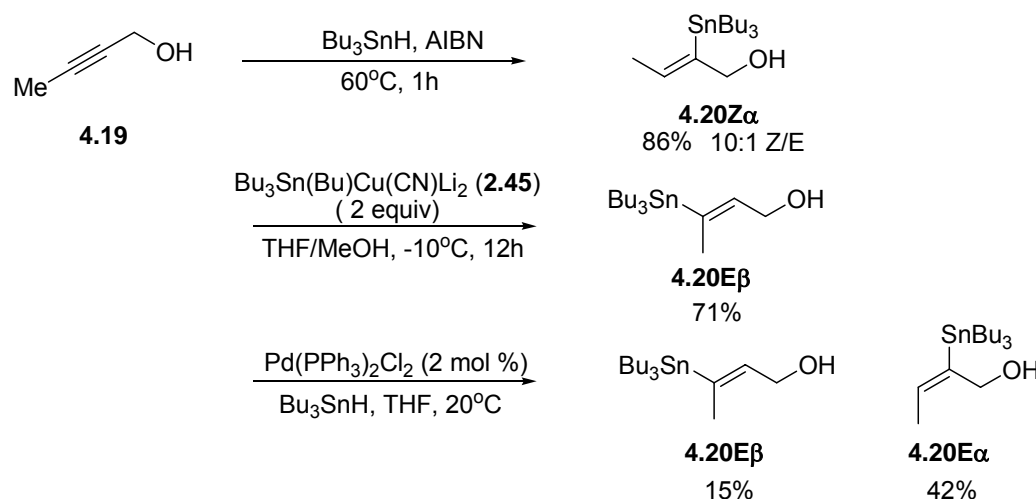
Figure 4.3   Hydrostannylation protocols for internal alkynes.

Radical hydrostannylation of **4.19** conducted under *pseudo*-kinetic conditions gives almost exclusively the regio-isomer with the stannylated moiety closest to the hydroxyl group (**4.20Zα**) due to the polarising influence of the alcohol on the alkyne bond. Stannylcupration of **4.19** performed using a proton-source such as methanol gives exclusively the regioisomer **4.20Eβ** in good yields. Transition metal-catalysed reactions, by contrast, give regioisomeric mixtures derived from the *syn*-addition of tributyltin hydride across the alkyne bond with distributions dependent on the steric effects of the alkyne substituents.[6]

Following the protocol of Betzer *et al.*[7] the protected 2-butyn-1-ol derivatives **4.21a** and **4.21b** were subjected to palladium-catalysed hydrostannylation to yield regioisomeric mixtures of vinylic stannanes (**Scheme 4.9**).
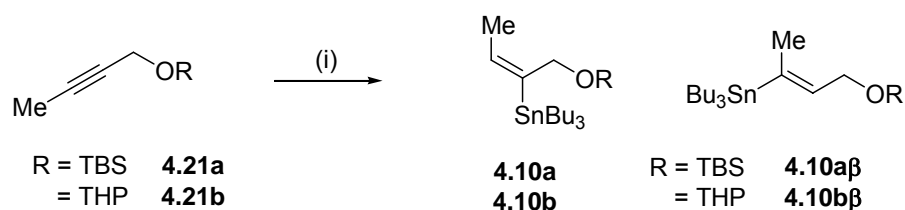
Scheme 4.9 Preparation of vinyl stannane coupling partners **4.10a** and **4.10b**.

Reagents and yields: (i) Pd(PPh$_3$)$_2$Cl$_2$ (2 mol %), Bu$_3$SnH, THF, 20°C; **4.10a** 36%, **4.10aβ** 21%; **4.10b** 29%, **4.10bβ** 14%.

Although TLC analysis and ^{1}H NMR spectroscopy of the crude reaction mixtures indicated complete consumption of the alkyne, only moderate yields of the separated isomers **4.10a** and **4.10b** were obtained following column chromatography despite the use of basified silica.

Attempted hydrostannylation of **4.21a** using the molybdenum catalyst **4.11**, a reagent in principle optimised for the hydrostannylation of terminal propargyl alcohols, was low yielding. Upon heating a solution of **4.21a** and Bu₃SnH at 55°C, in the presence of 2 mol % **4.11** and 10 mol % hydroquinone, marginal conversion was observed (~10%). The product distribution indicated the formation of a mixture of regioisomeric products favouring **4.10a** (3:2). Increased reaction temperature, the use of additional catalyst and tributyltin hydride resulted in only a marginal improvement in the yield (~30%). Presumably the steric bulk of the *tert*-butyl isonitrile molybdenum complex restricts facile addition to the alkyne bond in the presence of the terminal methyl group. Upon column chromatography the isolated yield of the desired α-stannylated species **4.10a** was observed to be 8.5%.

4.2.5   Stille Cross-Coupling

Subjection of vinyl stannane **4.10a** and vinyl iodide **2.9** to the previously optimised palladium-catalysed coupling conditions resulted in poor conversion and the formation of a 1:1 mixture of the *E/Z* diene adducts **4.22**, resulting from isomerisation of the terminal methyl group. Extensive decomposition of the vinyl stannane **4.10a** was inferred from the presence of unreacted starting material **2.9** in the ^{1}H NMR spectrum of aliquots taken from the crude reaction mixture (**Scheme 4.10**).
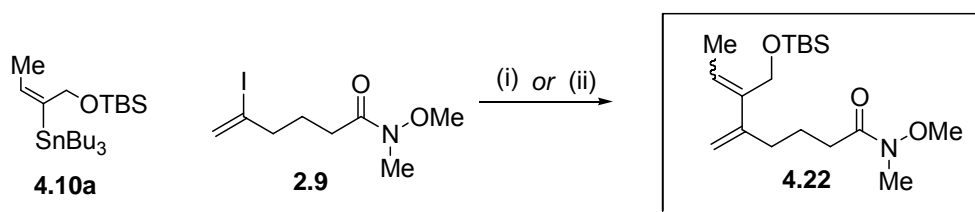
Scheme 4.10   Stille cross-coupling formation of the homomethyl diene system.

Reagents and yields: (i) **4.10a** (1.2 equiv), **2.9** (1 equiv), Pd₂(dba)₃ (5 mol %), AsPh₃ (20 mol %), CuI (20 mol %), DMF, 60°C, 16 h; (ii) **4.10a** (1.2 equiv), **2.9** (1 equiv), CuTC (1.3 equiv), NMP, 0°C → 23°C, 12 h, 24%.

During synthetic studies directed towards facilitating the Stille reaction, Liebeskind *et al.* reported the copper chelate complex, copper thiophene carboxylate (CuTC), was capable of catalysing the cross-coupling of organostannanes and organo-halides in the absence of added palladium or nickel co-catalysts. The reactions were high yielding and were performed under very mild conditions.[27-29] Synthetic work directed towards the preparation of the polysaturated sidechain of the florlide natural products (**1.75**) had revealed that the reagent CuTC was particularly effective in bringing about the reaction of substrates prone to isomerisation.

The reaction of vinyl stannane **4.10a** with the vinyl iodide **2.9** mediated by stoichiometric quantities of CuTC was successful in achieving the desired Stille coupling in the absence of any observed olefinic isomerisation. Column chromatography resulted in the isolation of the homomethyl diene system **4.22** in a somewhat disappointing 24% yield.

4.3 Summary of Palladium-Catalysed Cross-Coupling Routes

Whilst the desired propenyl and butenyl coupling fragments were readily prepared *via* hydrostannylation and hydroiodination methodology, the coupling of these intermediates with vinyl amide **2.9** was particularly challenging. No coupling adducts could be observed arising from the Negishi coupling protocol and poor rates of conversion, complicated with isomerisation, hampered application of the Stille coupling methodology.

The increased reactivity of allylic systems relative to vinyl systems is well known, with allylic systems often participating in π-allyl rearrangements and conjugate addition-displacement reactions.[30] Allylic stannane systems such as **4.8** and **4.10**, have seen only limited use in the synthetic literature and usually require the activation of the vinyl halide partner with an electron withdrawing group, or in the case of unactivated vinyl halides may require considerable optimisation of the coupling conditions to achieve acceptable yields.[23,31-35]

4.4   Route B: Enyne Metathesis

Olefin cross-metathesis, a process by which alkylidene groups on alkenes are exchanged, has recently emerged as an enormously powerful strategy for carbon-carbon bond formation.[36,37] Olefin metathesis reactions catalysed by discrete organometallic complexes of [W], [Ta], [Re] and [Ti] have been investigated since the 1960s but it has been the advent of well defined [Mo] and [Ru] catalysts, that show appreciable olefin reactivity and functional group compatibility, that has stimulated the interest of synthetic organic chemists.

In 1992 Grubbs and Fu published two seminal papers describing the application of ring-closing metathesis (RCM) to the synthesis of simple five, six and seven membered heterocyclic ring systems using Schrock's molybdenum catalyst (**4.23**).[38,39] This was followed in 1993 by the report of similar activity from a ruthenium-based metathesis catalyst (**4.24**).[40]

In the decade following these publications an enormous body of work has emerged applying the principles of olefin metathesis to natural product chemistry, chemical biology and material science.[36,37] Important variations of olefin cross-metathesis are depicted in **Figure 4.4** which include *(i)* ring-closing metathesis (RCM), *(ii)* ring-opening metathesis (ROM), *(iii)* acyclic diene metathesis polymerisation (ADMET), *(iv)* ring-opening polymerisation metathesis (ROMP) and *(v)* cross-metathesis (CM). The related extension of these reactions between an olefin and an alkyne are *(vi)* ring-closing enyne metathesis (RCEYM) and *(vii)* enyne cross-metathesis (EYCM). The synthetic complexity of metathesis adducts can also be enhanced by coupling two or more of these variations in tandem.
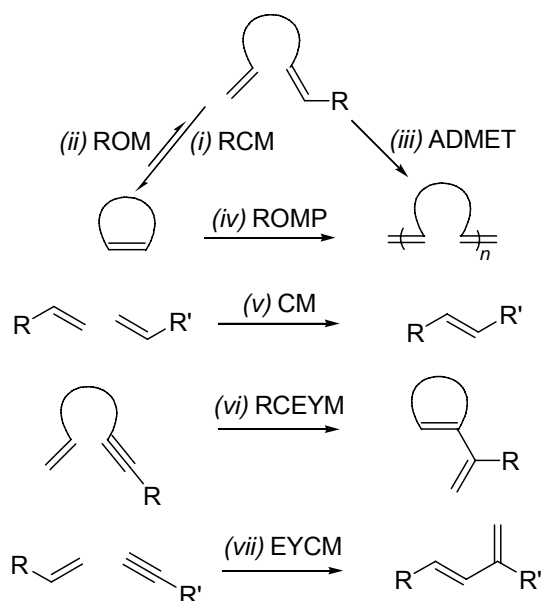
Figure 4.4   Types of olefin metathesis reactions.

The remarkable progress in the development of metathesis reactions can be directly correlated to improvements in the functional group compatibility and reactivity of the catalysts. There are two main types of catalysts in use today. The first group, known as the Schrock catalysts, consist of molybdenum complexes such as **4.23** and related catalysts, whereas the second group which comprises of ruthenium complexes such as **4.24-4.26** and related catalysts are known as the Grubbs catalysts (**Figure 4.5**).
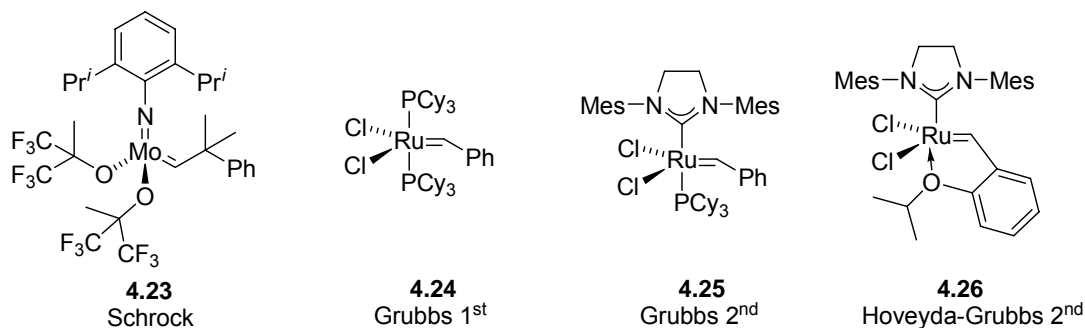
Figure 4.5   Commercially available metathesis catalysts.

In general, the Schrock catalysts display greater reactivity and less substrate inhibition than the ruthenium catalysts, but suffer the major disadvantages of incompatibility with a wide range of functionalities, non-trivial preparation and air and moisture sensitivity; necessitating the use of rigorous organometallic techniques.

In contrast, the Grubbs 1st generation catalyst **4.24**, whilst displaying diminished reactivity relative to **4.23**, is tolerant to a wide range of functional groups, is relatively insensitive to air,

moisture and other impurities and is readily accessible, either *via* synthesis or from commercial sources. A significant advancement was made with the displacement of one of the trialkyl phosphine ligands by an imidazolinylidene ligand to yield the 2nd generation Grubbs catalyst **4.25**, which displays increased rates of initiation and propagation, comparable to the Schrock catalysts.[41] Complete displacement of the phosphine ligands led to **4.26**, the robust Hoveyda-Grubbs 2nd generation catalyst, which is air stable and amenable to column chromatography and purification.[42] Numerous catalyst variants have also been investigated including the use of chiral ligands and solid supports.

The high olefin selectivity and reactivity of the catalysts **4.23**-**4.26** minimises the necessity for protecting group manipulations within the construction of complex chemical targets. The advantages offered by catalytic RCM can be evidenced by the application of this methodology to the successful total syntheses of complex natural products such as ciguatoxin CTX3C,[43,44] brevetoxin B,[45,46] cylindrocyclophanes,[47,48] prelaureatin,[49] manzamine,[50,51] epothilones and numerous others.[52]

4.4.1   Mechanism

The generally accepted mechanism for olefin metathesis was proposed by Chauvin and proceeds through a sequence of formal [2+2] cycloaddition-cycloreversion reactions *via* alkenyl metal carbene and metallacyclobutane intermediates, such as those depicted in **Figure 4.6**.[36] The catalytic cycle is reversible, with product formation driven by the entropic release of volatile ethene (RCM, CM).
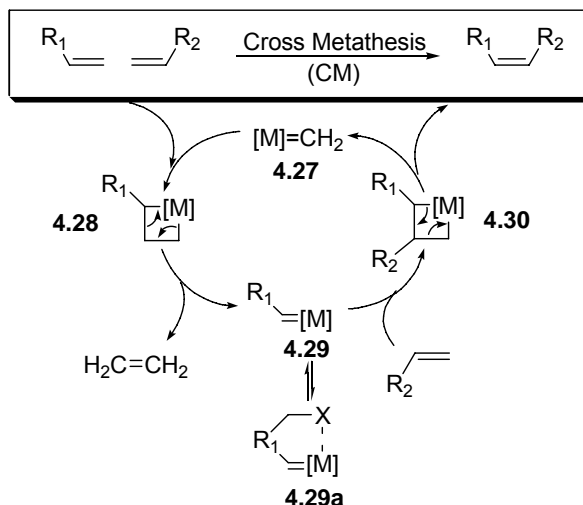

Figure 4.6   Proposed mechanism for carbene mediated cross-metathesis of alkenes.

Although a definitive mechanism is yet to be fully elucidated, experimental and theoretical calculations support this mechanistic interpretation (**Figure 4.6**).[53]

4.4.2   Ring Closing Enyne Metathesis and Enyne Cross-Metathesis

The bond reorganisation of an alkyne and an alkene to form a conjugated 1,3 diene can be divided into two categories (**Figure 4.7**).[54]

(A)   an oxidative cyclisation catalysed by low-valent transition metal salts[55] and;

(B)   cyclisation achieved *via* transition metal carbenes such as the Grubbs catalyst.
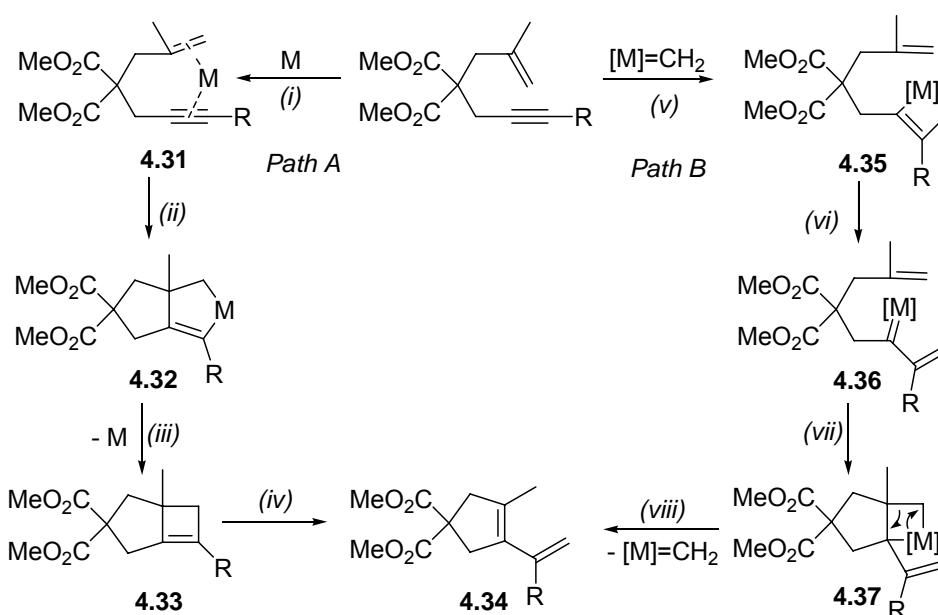
Figure 4.7   Metal-catalysed cationic (*Path A*) and carbene enyne metathesis (*Path B*).

The cyclisation process *(Path A)* catalysed by cationic [Pt] or [Pd] metal salts is often referred to as an enyne cycloisomerisation. The mechanism is postulated to proceed *via* the bidentate coordination of the enyne to the metal (*i*), followed by oxidative addition-cyclometalation to produce the metallacyclopentene **4.32** (*ii*). Reductive elimination produces a cyclobutene **4.33** (*iii*) which relieves strain by undergoing an electrocyclic ring opening to deliver the 1,3-diene structure **4.34** (*iv*).

The process utilising metal carbenes *(Path B)*, referred to as an enyne metathesis, is believed to proceed *via* a mechanism similar to that proposed for the alkene metathesis reaction depicted in **Figure 4.6**. The metal methylidene carbene reacts with the alkyne, undergoing a [2+2]-

cycloaddition to form the metallacyclobutene **4.35** (*v*). Upon ring opening (*vi*), the vinyl carbene complex **4.36** reacts intramolecularly with the tethered olefin to generate the metallocyclobutane **4.37** (*vii*). Subsequent cycloreversion provides the 1,3-diene system and regenerates the propagating carbene (*viii*).[54,56]

Intramolecular ring closing 1,*n*-enyne metathesis (RCEYM), which results in skeletal rearrangement to a 1,3-diene substituted cycloalkene (**Figure 4.7** - *Path B*), has been applied to a number of natural products including, notably, longithorone A[57] and (-)-stemoamide[58] (**Figure 4.8**).
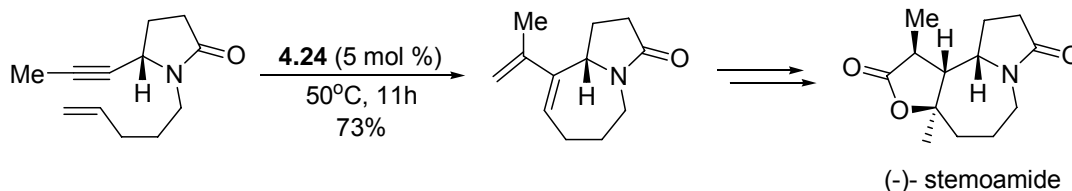
Figure 4.8   The application of RCEYM by Mori *et al.* in the total synthesis of (-)- stemoamide.

The related intermolecular enyne cross-metathesis (EYCM) has not been extensively investigated for, despite the remarkable promise that EYCM reactions offer, additional complications exist when compared to the unimolecular reaction which hinder the synthetic application.[59] Slower bimolecular reaction rates allow competition from undesired diene and alkyne metathesis pathways, adducts display limited *E*/*Z* stereochemical control and geometric diene isomers are commonly generated for non-terminal alkynes.

4.4.3   Ethylene Enyne Cross-Metathesis

A noted exception to the unresolved issues of intermolecular alkene-alkyne cross metathesis is the application of ethylene reported by Mori *et al.* Ethylene gas employed at atmospheric pressure in the presence of a catalytic amount of **4.24** was reported to effect the EYCM reaction of a number of substrates featuring both terminal and internal alkynes to generate 1,3-substituted butadienes (**4.38**) (**Figure 4.9**).[60]
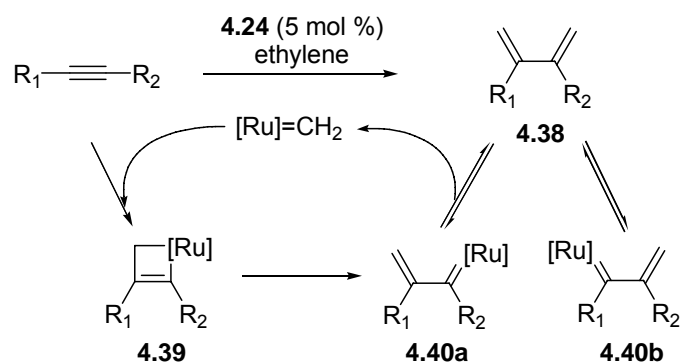
Figure 4.9 EYCM metathesis utilising ethylene.

The use of ethylene eliminates the problems associated with multiple cross-metathesis reactions. All modes of the regiochemistry and stereochemistry of addition of the symmetrical alkene to the alkyne bond are degenerate, leading to a single product.

Mori *et al.* demonstrated that ethylene EYCM presented an attractive route to 1,3-dienes, such as **4.41**, which could be productively utilised in subsequent Diels-Alder reactions (**Figure 4.10**).[59] The isolated yield of the 1,3-diene **4.41** was low in this instance, presumably due to undesirable competitive metathesis reactions involving cleavage or intramolecular CM cyclisation of the α,β unsaturated ester.
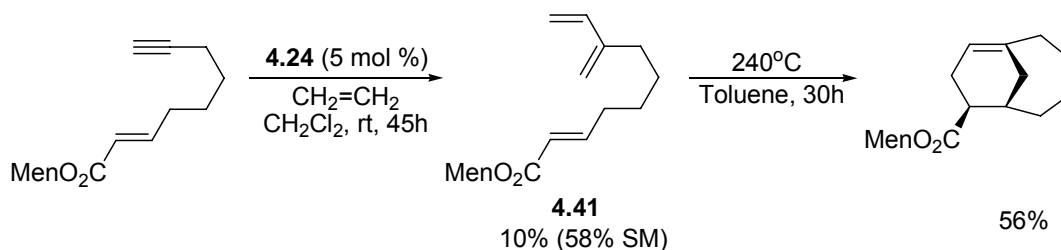
Figure 4.10 Bicyclo[4.3.1]decene adducts prepared *via* EYCM-IMDA methodology.

Diver *et al.* investigated the use of elevated ethylene pressures (up to 60 psi) in conjunction with the use of Grubbs second generation catalyst (**4.25**). Substantial improvements were obtained when compared to the use of Grubbs first generation catalyst (**4.24**) with atmospheric pressures of ethylene. Tolerance was observed to a wide range of functionality at the propargyl position providing access to a variety of 2-substituted butadienes. The improved yields were attributed to the enhanced turnover rate of the catalyst **4.25**, a higher effective molar concentration of ethylene which minimized unfavorable heteroatom chelation (**Figure 4.6** - **4.29a**) and the ability

to drive the reaction to completion *via* mass action. Additionally, the greater thermal stability of **4.25** allows the use of elevated temperature, without significant catalyst decomposition.[61,62] The use of an ethylene atmosphere was also discovered to be valuable in RCEYM and EYCM reactions where the ethylene was *not* incorporated into the cyclic product.[63,64] It is postulated that ethylene maintains a high concentration of the active ruthenium methylidene catalyst [Ru=CH$_2$] by reducing the number of unproductive catalyst resting states.

As illustrated in **Figure 4.10**, the application of an ethylene EYCM reaction represents a highly succinct and efficient route to the preparation of the disubstituted 1,3-dienes. If such a reaction could be conducted on a substrate that lacked competing olefinic functionality, rapid entry to diene systems such as **3.69** could be achieved, whilst minimising undesirable CM reactions.

4.5   *Preparation of Diels-Alder Homomethyl Substrates*

4.5.1   Preparation of Trienes Directed Towards Florlide Precursors

Applying the principles discussed in **Section 4.4.3**, a suitable retron for the diene functionality of **3.69** is an alkyne motif, such as that of the structure **4.5**.
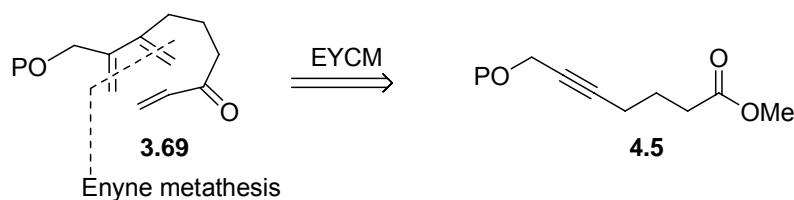
Scheme 4.11   1,3-Diene to alkyne retrosynthesis using the EYCM transform.

Methyl 7-hydroxyhept-5-ynoate (**4.42**) is an important intermediate in the synthesis of the α-side chain of prostaglandins.[65-67] The preparation of methyl 7-hydroxyhept-5-ynoate protected as either the MOM- (**4.43**) or TBS-ether (**4.44**) commenced from commercially available propargyl alcohol using the method of Corey and Sachdev as detailed in **Scheme 4.12**.[65]
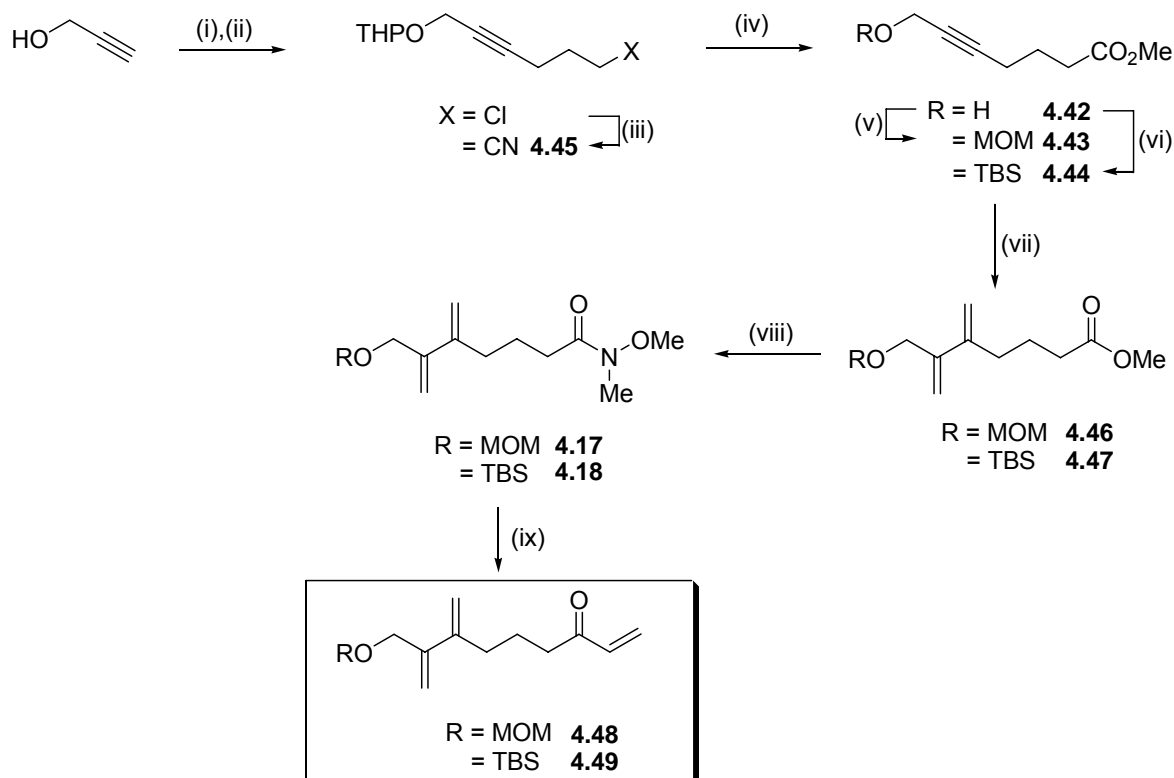
Scheme 4.12 Preparation of the homomethyl triene **4.48** and **4.49**.

Reagents and yields: (i) DHP (1.05 equiv), CH$_2$Cl$_2$, CSA, rt, 98%; (ii) *n*-BuLi (1.1 equiv), THF, Br-(CH$_2$)$_3$-Cl (1.5 equiv), 0°C → reflux, 82%; (iii) NaCN (1.1 equiv), DMSO, 75°C, 84%; (iv) *(a)* 10% aqueous NaOH, EtOH, reflux; *(b)* K$_2$CO$_3$, MeI, DMF; *(c)* PPTS, MeOH, 85% (three steps); (v) MOMCl, DIPEA, CH$_2$Cl$_2$, 100%; (vi) TBSCl, imidazole, DMF, 100%; (vii) see **Table 4.3**; (viii) Me$_2$Al-N(OMe)Me, CH$_2$Cl$_2$, reflux, 12 h, **4.16**, 73%; **4.17**, 75%; (ix) vinyl-MgBr (2 equiv), THF, 12 h, **4.48**, 94%; **4.49**, 98%.

The lithium-alkynide of THP-protected propargyl alcohol was alkylated with 1-bromo-3-chloro-propane and the resultant chloride reacted with sodium cyanide in DMSO to give the alkynyl nitrile **4.45**. Hydrolysis of the nitrile proceeded readily under basic conditions to yield the carboxylic acid, which was esterified with methyl iodide to yield the THP protected methyl 7-hydroxyhept-5-ynoate. Hydrolysis of the THP protecting group proceeded cleanly in aqueous methanol with catalytic PPTS to deliver the desired methyl 7-hydroxyhept-5-ynoate **4.42**. Protection under standard conditions gave the MOM or TBS ether adducts **4.43** and **4.44**. The simultaneous nitrile hydrolysis-esterification and THP hydrolysis could be performed in a solution of concentrated H$_2$SO$_4$ and methanol to generate **4.42** in similar yields to the three step basic procedure but required in excess of 5 equivalents of H$_2$SO$_4$ with reflux for 4 days.

The conversion of the internal alkyne moiety to the desired 1,3-diene system was readily accomplished by exposure of the alkyne to an ethylene atmosphere in the presence of Grubbs

catalyst **4.25**. The conversion could be monitored by ^{1}H NMR spectroscopy of sample aliquots by observing the disappearance of the propargyl singlet resonance, coupled with the appearance of the newly emergent vinylic protons. The optimisation of this reaction is detailed in **Table 4.3**.

Table 4.3   EYCM of alkyne substrates under an ethylene atmosphere.

R = MOM **4.43**
 = TBS   **4.44**

R = MOM **4.46**
 = TBS   **4.47**
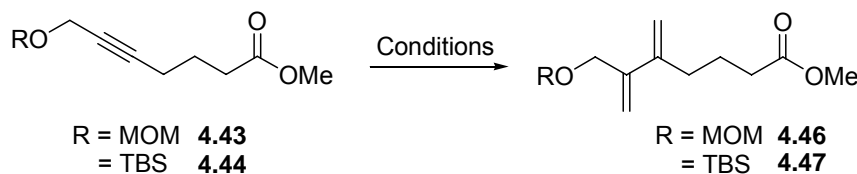
Entry	R	Condition[a]	Yield[b]
1	H (**4.42**)	Toluene, 1 atm, **4.25** (5 mol %), 80°C	0[c]
2	MOM (**4.43**)	Toluene, 1 atm, **4.25** (4 mol %), 55°C → 80°C	86%
3	MOM (**4.43**)	Toluene, 1 atm, **4.25** (2 mol %), 80°C	96%
4	TBS (**4.44**)	Toluene, 1 atm, **4.25** (10 mol %), 80°C	87%
5	TBS (**4.44**)	DCE, 5.4 atm, **4.25** (2 mol %), 55°C	92%

Note: (a) Reactions were conducted at 0.1 M in standard glassware with an ethylene filled balloon (pressure ~1 atm); or in a Parr benchtop Micro-reactor with internal pressure and temperature control (pressure >1 atm). Prior to reaction solutions were degassed and sparged with ethylene three times. Reactions were quenched *via* the addition of ethyl vinyl ether (10 equiv). (b) Refers to chromatographically pure isolated material. (c) No reaction after 24 hours.

The initial EYCM reactions were conducted on the alkyne **4.43** in toluene, using an ethylene atmosphere supplied by an attached balloon (~1 atmosphere) *(entry 2)*. No reaction was observed at ambient temperature. Heating to 55°C with 2 mol % **4.25** effected a clean conversion from the starting alkyne to the desired 1,3-diene system (**4.46**) over a period of 24 hours in approximately 20% yield. Increasing the temperature to 80°C improved the conversion (~60 %), with two subsequent additions of 1 mol % catalyst over 24 hours achieving the complete consumption of the alkyne starting material. The diene system was readily isolated following evaporation of the solvent and purification of the crude mixture *via* silica column chromatography to yield **4.46** as a colourless oil in high yield. Under optimised conditions, the complete conversion of **4.43** to **4.46** could be accomplished with 2 mol % **4.25** at 80°C in 6 hours, allowing the isolation of **4.46** in 96% yield, *(entry 3)*. The reaction of **4.44** under identical conditions gave lower rates of conversion (~10% with 2 mol % **4.25** at 55°C) and necessitated increased catalyst loading and prolonged reaction times to effect complete consumption (10 mol % **4.25** over 3 days; 5 mol % initially, with two subsequent additions of 2.5 mol % after 24 hour periods) *(entry 4)*. The

desired 1,3-diene system **4.47** was isolated in high yield despite the prolonged reaction time. The unprotected alkyne did not undergo conversion, despite prolonged exposure to the metathesis catalyst *(entry 1)*.

The reactivity profile of the internal alkyne substrates **4.42**-**4.44** to enyne metathesis can be rationalised by comparison with the work of Mori *et al.* The kinetics of catalyst binding and turn-over are known to be strongly influenced by the steric environment and chelating properties of groups present in the reaction substrate. The MOM-protected alkyne **4.43** displays similar catalyst loading requirements and time to effect complete conversion as those reported by Mori[59] and Diver[61] when using catalyst **4.25** on internal alkyne substrates. The absence of EYCM reaction with the free alcohol **4.42** can be interpreted as due to the formation of a stable chelate intermediate between the propargyl alcohol and the ruthenium catalyst deactivating the catalytic cycle (**Figure 4.6** - **4.29a**). The increased steric bulk associated with the TBS protecting group of **4.44** is presumably responsible for the diminished reactivity at the adjacent alkyne, necessitating prolonged reaction times and increased catalyst loading to effect the complete conversion.

It was also noted that the rate of conversion was enhanced when a high surface-area to solvent ratio was employed. For example, a reaction utilising 15 mL of solvent proceeded more readily when stirred rapidly in a 100 mL reaction vessel, than in a 25 mL vessel, implying that the gaseous-exchange and diffusion of ethylene into the heated solvent might be a limiting factor. Indeed, the application of elevated ethylene pressures using a Parr high-pressure apparatus resulted in significant improvements to both the rate of reaction and isolated yield. Complete conversion of the alkyne **4.44** to the 1,3-diene **4.47** could be achieved in 92% yield, with 2 mol % **4.25** at 55°C, using an internal ethylene pressure of 80-85 psi in 36 hours *(entry 5)*. The increased ethylene pressure and decreased temperature reflected favourably upon catalyst stability, enabling complete conversion to be achieved with the addition of a single charge of catalyst at the commencement of the reaction.

With the desired 1,3-diene systems **4.46** and **4.47** in hand, the conversion of the terminal methyl ester to a Weinreb's amide was investigated.
Hydrolysis of the methyl ester under basic conditions caused concomitant decomposition of the diene functionality. Initial attempts to prepare the Weinreb's amide derivative **4.17** *via* the reaction of methyl ester **4.46** with dimethylaluminium-*N,O*-dimethylhydroxylamine, prepared according to literature procedure at ambient temperature[68] or 0°C,[69,70] resulted in the isolation of

the desired amide (**4.17**), in conjunction with a significant number of impurities attributed to coupling of decomposed amine-alkylaluminate species. In order to eliminate side-product formation it was found necessary to prepare the amino-aluminate complex at -30°C, *via* the slow addition of trimethylaluminium to a pre-cooled slurry of the amine hydrochloride salt in dichloromethane, followed by warming to ambient temperature. The ester substrate was then added and the solution brought to reflux for 12 hours affording the desired amide materials **4.17** and **4.18** in high yield.

Addition of vinyl magnesium bromide to the diene systems **4.17** and **4.18** effected a selective mono-nucleophilic addition to the Weinreb's amide functionality generating the IMDA homomethyl triene precursors **4.48** and **4.49** in high yield. The colourless oils, **4.48** and **4.49**, were observed to be stable but to decompose upon prolonged standing at ambient temperature

4.5.2   Preparation of Trienes Directed Towards the Nakafuran Precursors

Examples of enyne metathesis reported to date have primarily focused on the intramolecular ring closing metathesis (RCEYM) and the intermolecular enyne cross-metathesis (EYCM) of terminal alkynes.[36,56,71] In the first instance, the intramolecular nature of the RCEYM reaction controls the relative orientation of the alkene and alkyne functional groups achieving high regio- and stereocontrol in the bond reorganisation. The internal tether between the reactants results in a higher relative molecular concentration, whilst minimising the entropy requirements relative to the analogous bimolecular reaction. The intermolecular reaction (EYCM) by contrast suffers issues arising from both the bimolecular nature of the reaction and the formation of terminal alkene isomeric *E*/*Z* mixtures.[72,73] The few reported examples of intermolecular EYCM of internal 1,2-dialkyl substituted alkynes have been restricted to symmetrical alkyne substrates or have utilised ethylene as an alkene. In both instances symmetry eliminates the formation or detection of geometrical isomers. Silyloxy- and borylated terminal alkynes, by contrast, have been observed to exhibit strong directing effects, delivering high regioselectivity.[74,75]

The enyne metathesis of **4.5** utilising the symmetrical alkene ethylene results in the formation of the 1,3-diene **3.69** (R_1 = H), which can be advanced synthetically to form the core structure **3.70** (R_1 = H). Functional modification of this bicyclic structure would lead to the florlide natural product family (**Scheme 4.13**).
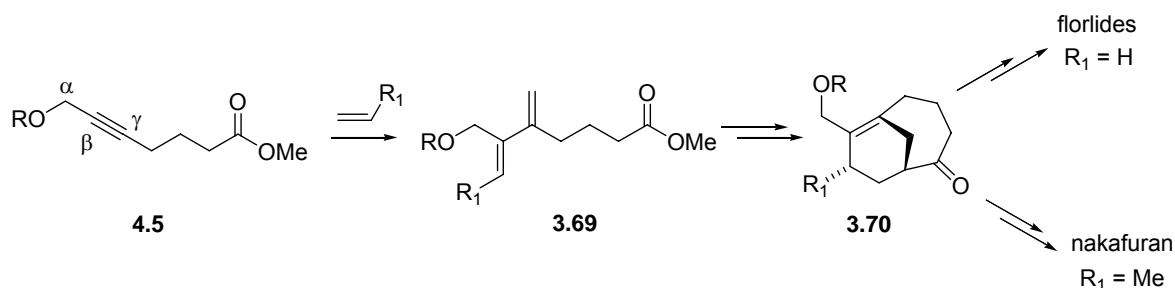
Scheme 4.13 EYCM to generate precursors suitable to the synthesis of florlide and nakafuran natural products.

Access to the nakafuran family requires the controlled stereochemical and regiochemical introduction of propene (R_1 = Me) to the unsymmetrical alkyne **4.5** during an EYCM reaction. A number of difficulties were anticipated in such a reaction that would severely hinder the synthetic application (**Figure 4.11**).

The initial [2+2] addition of the active ruthenium carbene **4.50** to the non-symmetric alkyne **4.51** to form the ruthenacyclobutene **4.52** could be expected to be controlled by the dominant steric and electronic interactions of the alkene and alkyne substituents. For example, heteroatom coordination by a propargyl substituent (MOM, Ac) may favour formation of a chelate structure (**4.53**) which places the metal carbene complex adjacent to the chelating substituent, whereas non-chelating substituents may favour remote placement of the metal carbene to minimise steric interactions. The small steric size of the propene methyl group was predicted to provide little, if any, steric control on the metathesis cycle. In addition to regiochemical aspects, the relative orientation of the methyl group within the ruthenacyclobutene **4.52** will give rise to E/Z mixtures.

Formation of di-substituted adducts may also arise due to the relative orientation of the propene unit upon formation of the ruthenacyclobutanes **4.54** and **4.55**. Cycloreversion of **4.54** generates the mono-addition adducts **4.56** and **4.57** and the metal carbene **4.50**, whereas **4.55** generates the di-substituted adduct **4.58**. Subsequent CM of the adducts **4.56**-**4.58** may result in stereochemical and regiochemical scrambling. Nevertheless, it was decided to attempt such a reaction as it would allow rapid access to the desired diene system **4.22**, which was only accessible in low yields *via* the Stille coupling previously investigated (**Section 4.2.5**).
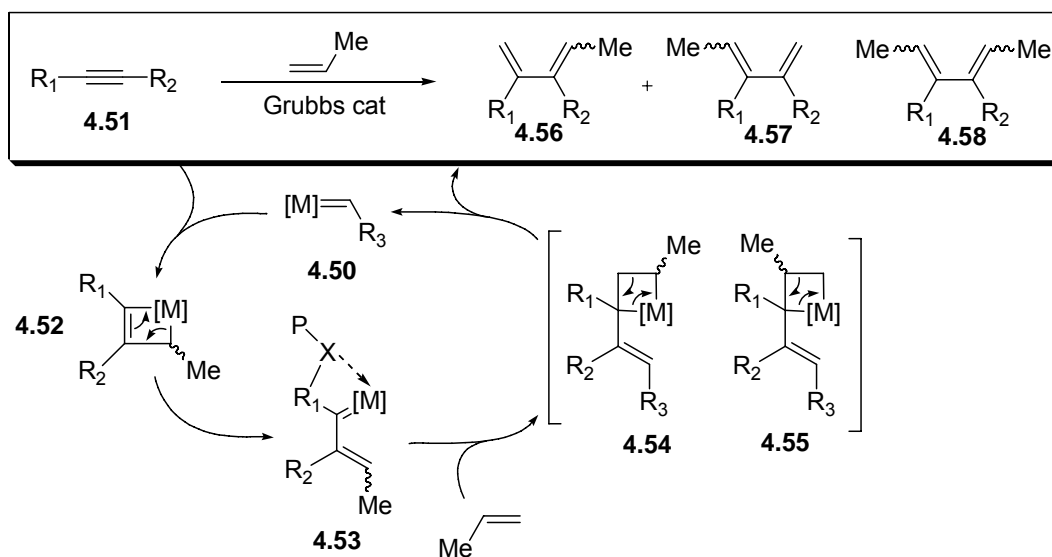
Figure 4.11 Regio- and stereochemical adducts from the EYCM between an unsymmetric alkyne **4.51** and propene.

In practice, the exposure of **4.44** to Grubbs catalyst **4.25** under an atmosphere of propene resulted in the isolation of an inseparable mixture of four isomeric diene products (**Scheme 4.14**). A slight preference was observed for placement of the methyl group in the desired allylic β-position (R_1 and R_2). Presumably this is due to minimisation of the steric strain arising from interaction between the TBS protecting group and the bulky ruthenium metal centre.
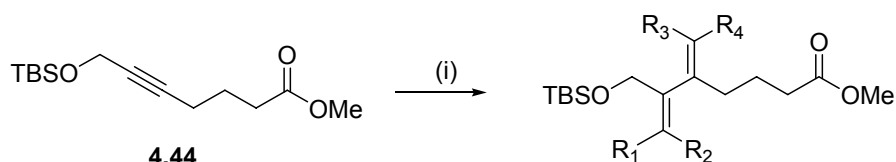
Scheme 4.14   EYCM of **4.44** with propene.

Reagents and yields: (i) **4.25** (4 mol %), toluene, 85°C, propene (1 atm), 48 h, 80%. Methyl position ratios: 26(R_1): 41(R_2): 16(R_3): 16(R_4); determined *via* ^{1}H NMR integration.

The poor regio- and stereocontrol observed in this reaction, accompanied by the inability to separate the isomers *via* silica flash column chromatography, meant that this synthetic route was not pursued further.

4.5.3   Attempted Enyne Metathesis Utilising Temporary Silicon Tethers

An expedient solution to the lack of regiocontrol in intermolecular EYCM reactions was reported by Yao, who utilised the temporary silicon connection methodology devised by Stork[76-78] to prepare a series of highly functionalised dienes through RCEYM (**Figure 4.12**).[79,80] Treatment of the tethered enyne **4.59**, prepared from the propargyl alcohol **4.60** and allylchlorodimethylsilane, with Grubbs catalyst **4.24** gave the cyclic product **4.61** in high yield. Oxidative cleavage of the silyl-tether using the protocol of Tamao[81] gives access to the dihydroxylated diene adduct **4.62**. Alternatively, the silyl-tethered 1,3-diene adduct **4.61** was demonstrated to be a competent substrate for the Diels-Alder reaction yielding a single diastereoisomer (**4.63**) upon reaction with maleimide under thermal conditions.
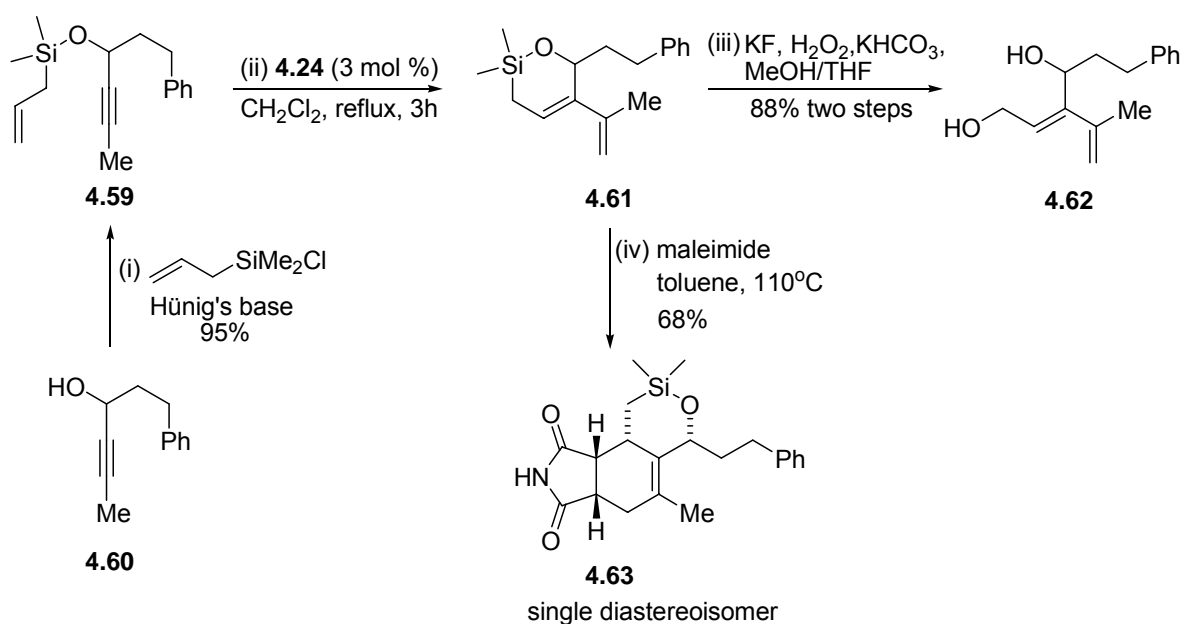
Figure 4.12 EYCM utilising a silyl tethered allyl group to establish regio- and stereocontrol.

Utilising this concept, a modified RCEYM route incorporating a temporary silicon connection to promote formation of the desired β-regiochemistry and stereochemistry in the diene system is depicted in **Scheme 4.15**. Advancement of metathesis adduct **4.65** to a Diels-Alder triene precursor may readily be envisaged. A Type II IMDA cycloaddition of this substrate would generate the tricyclic bridgehead alkene and establish the desired stereochemistry at the C8 position.[82] Cleaving the silyl tether *via* reductive desilylation would liberate the desired bicyclic structure **4.67**.[79]
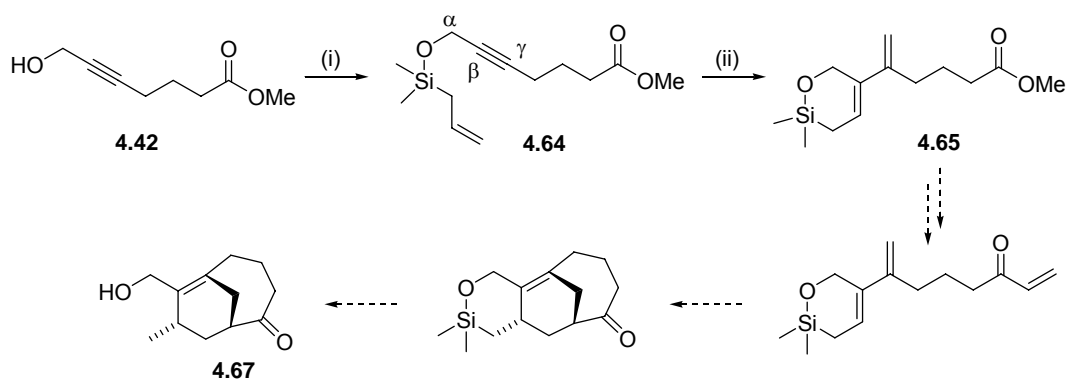
Scheme 4.15 EYCM-temporary silicon tether route enabling the stereoselective installation of the C8 methyl.

Reagents and yields: i) allyl-SiMe$_2$Cl, DMAP, NEt$_3$, 94%; (ii) **4.25** (2 mol %), DCM, 40°C, 4 h, 93%.

The route depicted in **Scheme 4.15** was briefly investigated *via* the conversion of the alkyne **4.42** to the allyl silyl derivative **4.64** in high yield upon reaction with allylchlorodimethylsilane and NEt$_3$. Exposure of the enyne **4.64** to Grubbs catalyst **4.25** (2 mol %) effected clean RCEYM to give the desired siloxane adduct **4.65** in high yield.

In agreement with literature precedent,[79,83,84] the formation of the seven-membered ring adduct **4.66**, arising *via* an *endo* mode of ring closure of the metallo-carbene intermediate **4.68** was not observed (**Figure 4.13**).
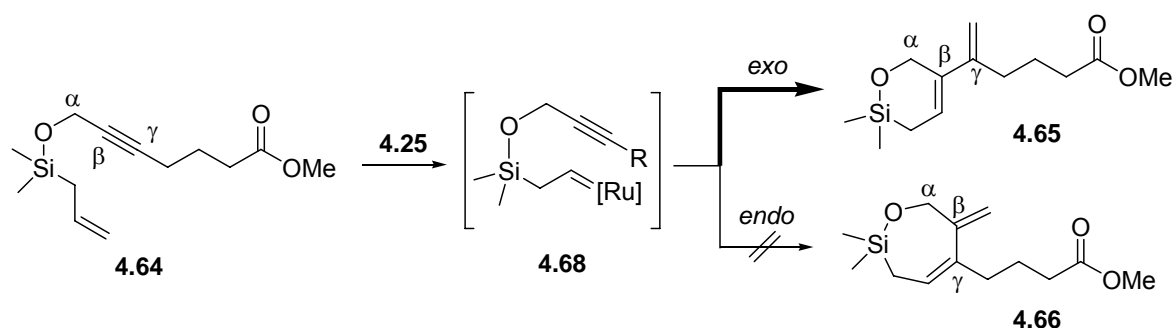
Figure 4.13   Preferential formation of **4.65** due to unfavourable torsional constraints and steric interactions associated with the formation of the *endo* transition state.

Due to time constraints and the results described in **Section 4.8** (*vide infra*) the advancement of this adduct (**4.65**) and the formation of the subsequent intermediates depicted in **Scheme 4.15** was not investigated further, but clearly this strategy could lead to the facile preparation of **4.67**.

4.6   *Diels-Alder Cyclisation of Homomethyl Trienes*

With the differentially protected triene precursors **4.48** and **4.49** in hand, the opportunity presented itself to investigate whether the C7-methyl extension was successful in retarding the $\Delta^{6,7} \rightarrow \Delta^{7,8}$ olefinic migration previously observed for the 7-alkoxy triene substrates. The homomethyl triene substrates **4.48** and **4.49** were subjected to thermal and Lewis acid catalysed cyclisation conditions. Representative results are detailed in **Table 4.4**.

Table 4.4   IMDA reactions of **4.48** and **4.49**.

R = MOM   **4.48**
R = TBS   **4.49**

4.69
4.71

4.70
4.72
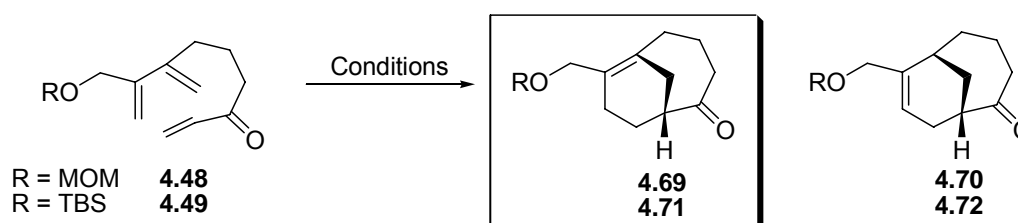
Entry	Conditions[a]	Yield[b,c]
1 – **4.48**	Benzene (0.015 M), PS (0.3), 130°C, sealed tube, 36 h	45% (**4.69**)
2 – **4.48**	Benzene (0.04 M), PS (0.3), 160°C, sealed tube, 16 h	51% (**4.69**)
3 – **4.48**	BF$_3$.Et$_2$O (1 equiv), -78°C, 30 min, NaHCO$_3$ quench	C.M.
4 – **4.48**	BF$_3$.Et$_2$O (2 equiv), -78°C, 30 min, NaHCO$_3$ quench	C.M.
5 – **4.48**	Et$_2$AlCl (1 equiv), CH$_2$Cl$_2$, 0°C, NaHCO$_3$ quench	NR
6 – **4.48**	Et$_2$AlCl (2 equiv), CH$_2$Cl$_2$, 0°C, NaHCO$_3$ quench	C.M.
7 – **4.49**	Benzene (0.01 M), PS (0.25 M), sealed tube 160°C, 36 h	75% (**4.71**)
8 – **4.49**	Xylene (0.005 M), PS (0.25), 160°C, 40 h	78%[d] (**4.71**)
9 – **4.49**	DCE, ZnCl$_2$.OEt$_2$ (1 equiv), pyridine (10%), rt	Dec.

Note: (a) Reactions monitored *via* ^{1}H NMR spectroscopy. Reactions in benzene at > 80°C were conducted in Carius pressure tubes; reactions in xylene were conducted under an inert Ar atmosphere, using a standard reflux setup. PS = Proton-Sponge® (equivalents). (b) Isolated chromatographically pure material. (c) S.M. = starting material, C.M. = complex mixture, N.R. = No reaction. (d) Two step yield from **4.18.**

The thermally initiated IMDA reaction of **4.48** in the presence of 0.3 equivalents of Proton-sponge® resulted in clean conversion to a single product *(entry 1)*. ^{1}H NMR spectroscopy of the isolated adduct **(Figure 4.14-*B*)** indicated a number of promising aspects when compared to the starting triene material **(Figure 4.14-*A*)**. Elevation of the temperature from 130°C to 160°C decreased the time required for complete consumption of the stating materials from 36 to 16 hours *(entry 2)*.
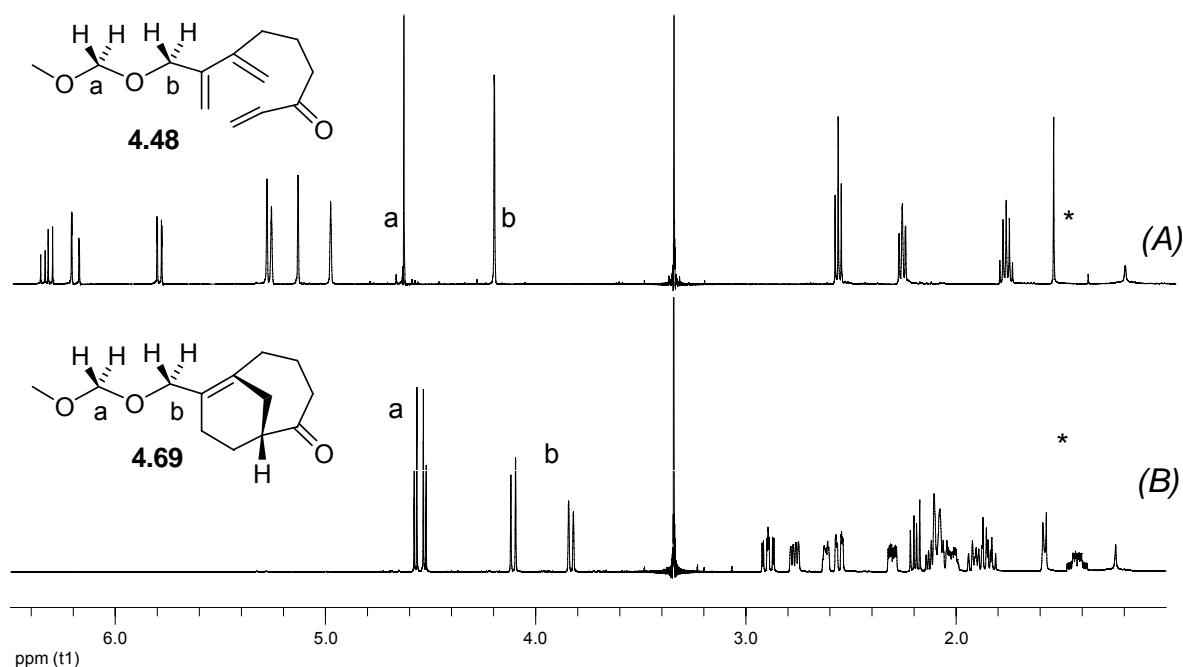
Figure 4.14 500 MHz ^{1}H NMR spectra of triene **4.48** *(A)* and IMDA adduct **4.69** *(B)*; (* = residual water in CDCl$_3$ NMR solvent).

The proton signals from δ_H 5.00-6.37, correlating to the vinylic 1,3-diene and the enone system, and the clearly resolved quintet at δ_H 1.80 and triplets at δ_H 2.30 and δ_H 2.60, arising from the three carbon tether, had disappeared. They had been replaced by a number of heavily coupled, but resolvable, aliphatic signals from δ_H 1.38-2.93. Additionally, the allylic CH$_2$ and methoxy-methyl signals, previously present as singlets at δ_H 4.22 and δ_H 4.65 in the triene material **4.48** *(spectrum A)* had been split into two pairs of doublets centred at δ_H 3.97 and δ_H 4.55 respectively *(spectrum B)*. This evidence pointed towards the successful cyclisation of **4.48** to generate the IMDA adduct **4.69**. The increased ^{1}H NMR spectral complexity and the resolution of individual diastereotopic hydrogen, upon forming a bicyclo[4.3.1]decane ring system, had previously been observed in the analogous cyclisation of **1.69** to form the methoxy-IMDA derivatives **1.68** and **3.55**.

Importantly, the spectrum lacked a vinylic proton signal that would arise following a $\Delta^{6,7} \rightarrow \Delta^{7,8}$ isomerisation to the non-bridgehead adduct **4.70**. The proposed assignment was subsequently confirmed by subjecting **4.69** to a full range of one and two-dimensional NMR spectroscopic experiments.

The cycloaddition reactions of **4.48** conducted in the presence of the Lewis acid catalysts BF$_3$.Et$_2$O or Et$_2$AlCl were dominated by complex decomposition products and exhibited

evidence of $\Delta^{6,7} \rightarrow \Delta^{7,8}$ olefinic isomerisation. The use of two equivalents of $BF_3.Et_2O$ resulted in the predominant decomposition of the triene starting material, with trace evidence of only the $\Delta^{7,8}$ cycloadduct **4.70** in the crude reaction mixture. The application of one equivalent of Et_2AlCl was ineffective in catalysing the IMDA reaction at 0°C, whereas two equivalents resulted in the generation of both the $\Delta^{6,7}$ and $\Delta^{7,8}$ cycloadducts in trace quantities dominated by decomposition products. Consequently, investigation of the IMDA reaction of the homomethyl analogues were restricted to thermally initiated conditions. This is in agreement with the work of Shea *et al.* where vinyl substituted diene system displayed noted sensitivity to Lewis acid catalysts, resulting in diminished yields relative to the thermally initiated conditions.[85]

Subjection of the TBS protected triene **4.49** to thermal cyclisation conditions was also successful in bringing about the desired IMDA reaction in good yield *(entry 7)*. No material arising from bridgehead olefinic migration was observed. The IMDA cyclisation could be successfully scaled-up from ~100 mg (employing benzene in a Carius resealable pressure tube) to 5 g (0.015 mol) utilising refluxing xylene at atmosphere pressure without a loss in isolated yield *(entry 8)*. The slow addition of the triene **4.49** over 8 hours, using a syringe pump, into a dilute (0.005 M) solution of refluxing xylene was found to eliminate a minor impurity (~2-5%) arising from intermolecular dimerisation.

The cyclisation of **4.49** under the mild Lewis acid conditions described by Fukuyama for the preparation of the phomoidride core[86] was very slow, with competing reactions such as enone decomposition and dimerisation dominating the reaction products *(entry 9)*.

The successful thermally initiated IMDA cyclisation of the homomethyl trienes **4.48** and **4.49**, without observable double bond isomerisation is significant. It supports the hypothesis that the C7 ether functionality was a significant factor contributing to the $\Delta^{6,7} \rightarrow \Delta^{7,8}$ olefinic isomerisation previously observed for **1.69** and **1.80**. The improved stability of the $\Delta^{6,7}$ IMDA adducts **4.69** and **4.71** is further illustrated by the fact that these reactions were conducted chronologically before the importance of the purity and requirement for greater than stoichiometric quantities of Proton-sponge® was fully appreciated. The reactions were performed with only 0.25 or 0.3 equivalent of the 'old' Proton-sponge®; conditions which had been demonstrated as ineffective in retarding the double bond isomerisation in the C7 alkylethers **1.68** and **1.79**. Furthermore, an aqueous acidic wash (0.05 M HCl) facilitated the removal of

residual Proton-sponge® from the crude reaction mixture without initiating the double bond migration previously observed.

4.7   *Cyclopropanation Studies*

As discussed in **Scheme 4.2**, the use of a C7-homomethyl adduct requires modification of the fragmentation route employed to generate the desired C6 quaternary methyl group and the C7 *exo*-methylene group. Specifically, it was envisaged that installation of the bridgehead cyclopropane **4.74** would be guided by the allyl alcohol functionality of **4.73**. Subsequent radical fragmentation of the cyclopropane moiety, initiated at the homomethyl functional group, would simultaneously establish the C6-methyl group and the C7 double bond to deliver **4.76** (**Scheme 4.16**).

4.73   **4.74**   **4.75**   **4.76**
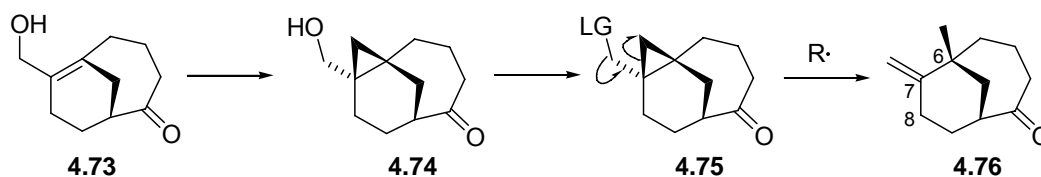
Scheme 4.16   Allyl directed cyclopropanation and subsequent ring fragmentation.

4.7.1   **Cyclopropanation of Methoxy-Methyl Adduct 4.69**

Removal of the MOM protecting group from the IMDA adduct **4.69** prior to cyclopropanation proved problematic. Common literature methods employing acidic reagents, such as catalytic concentrated HCl in MeOH; *p*-TsOH in *t*-BuOH or CBr$_4$ in *i*-PrOH[87] did not effect cleavage at ambient temperature. Increasing the reaction temperature or the proportion of acidic reagent resulted in slow consumption of the MOM adduct **4.69**, but generated considerable decomposition including double bond isomerisation, as assessed by the appearance of vinylic signals attributable to a C8 vinyl proton. The use of alkyl-thiols in conjunction with magnesium bromide was reported by Lee and co-workers to effect the cleavage of MOM and MEM ethers under mild non-acidic conditions.[88] The reported conditions of 2.5 equivalents of ethanethiol and 3 equivalents of MgBr$_2$ in diethyl ether at room temperature were unsuccessful in achieving the

desired hydrolysis. The use of excess reagent (15 equivalents) resulted in MOM ether cleavage with the generation of unidentified decomposition products.
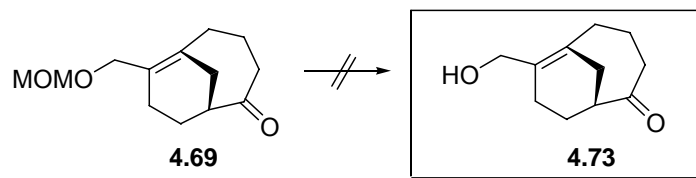

Figure 4.15 Attempted deprotection of the MOM ether **4.69**.

Due to the difficulties described in the preceding deprotection step, cyclopropanation studies were performed on the MOM protected IMDA adduct **4.69**. Furukawa's reagent, bis(iodomethyl)zinc (**3.81**), generated *in-situ* from diethylzinc and diiodomethane, was used under an atmosphere of oxygen to cyclopropanate the bridgehead olefin.[89-91] Although no reaction was observed with 2 equivalents of this cyclopropanation reagent, the use of 3 equivalents resulted in consumption of the starting material and led to the isolation of two products in high yield in a 1:1 ratio. The isolated adducts were identified as the desired bridgehead cyclopropane adduct **4.77** and a product arising from bridgehead cyclopropanation and *exo*-methylene replacement of the C2 ketone **4.78** (**Scheme 4.17**). Reducing the amount of cyclopropanating reagent resulted only in diminished rates of conversion, whilst delivering **4.77** and **4.78** in a similar ratio (~1:1), indicating that cyclopropanation and *exo*-methylene formation were on a competitive time scale.
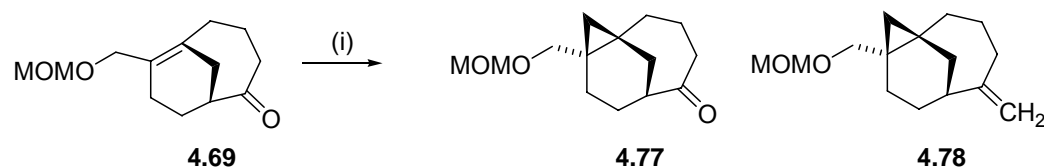
Scheme 4.17 Cyclopropanation of **4.69** using the Furukawa reagent.
Reagents and yields: (i) Et$_2$Zn (3 equiv), CH$_2$I$_2$ (6 equiv), toluene, O$_2$, 40°C, **4.77** 42%, **4.78** 49%.

Prior observation of *exo*-methylene formation mediated by Furukawa's reagent is, to the author's knowledge, unknown. Related *gem*-dimetallic species have been reported as effective methylenation reagents of enolisable ketones, including the Takai olefination, Oshima-Lombardo reaction and Nysted reagent (**Figure 4.16**).[92] To achieve high synthetic yields the *gem*-dimetallic methylene reagent is usually further activated by the addition of a Lewis acid, commonly TiCl$_4$, which increases the nucleophilicity of the methylene carbon favouring attack and *exo*-methylene formation at carbonyl centres.[93] In contrast, the Furukawa reagent, postulated to be the

bis(iodomethyl)zinc species **3.81**, is anticipated to display electrophilic properties, favouring cyclopropanation of olefinic bonds.
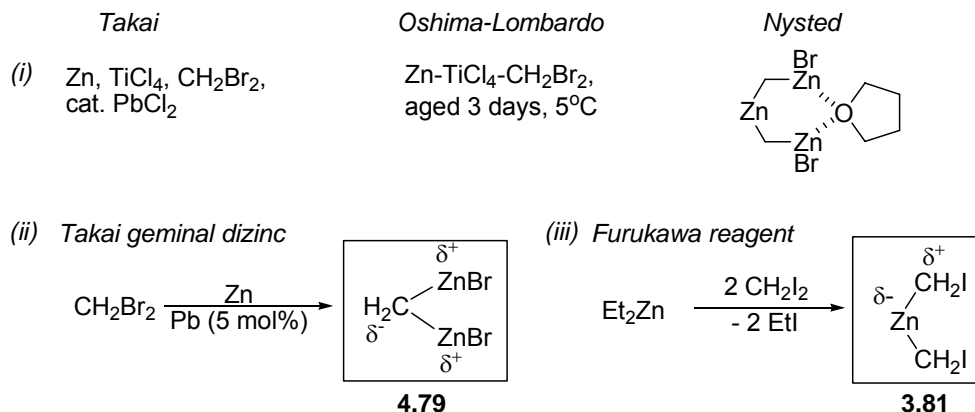
Takai   *Oshima-Lombardo*   *Nysted*

(i) Zn, TiCl$_4$, CH$_2$Br$_2$,   Zn-TiCl$_4$-CH$_2$Br$_2$,
  cat. PbCl$_2$ aged 3 days, 5°C

(ii) Takai geminal dizinc   *(iii) Furukawa reagent*

$$CH_2Br_2 \xrightarrow[\text{Pb (5 mol\%)}]{\text{Zn}}$$

4.79   **3.81**

Figure 4.16 *(i)* Carbonyl olefination reagents and comparison of the active methylene centre in the *(ii)* Takai methylenation reagent and *(iii)* Furukawa cyclopropanating reagent.

Fried *et al.* reported an example of *exo*-methylene formation during the attempted Simmons-Smith cyclopropanation of the β-hydroxy-estren-3-one **4.80**.[94,95] Methylenation of the C3 carbonyl to form **4.81** was observed when **4.80** was refluxed in ether with a large excess of zinc-copper couple and diiodomethane. The proposed mechanism for this transformation featured chelation of the bis(iodozinc)methylene reagent **4.82** to the 11β-hydroxyl group, temporarily tethering the methylene reagent within bonding distance of the C3 carbonyl (**4.83**), from where nucleophilic attack and oxide elimination generated the *exo*-methylene group. In contrast, the reagent I-Zn-CH$_2$I (**4.84**), prepared with one equivalent of Zn in excess CH$_2$I$_2$, afforded the angular methylation product **4.85**, *via* a postulated $\Delta^{3,5(10)}$-dienol (**4.86**) formed by Lewis acids present in solution (**Figure 4.17**).

Matsubara *et al.* subsequently demonstrated both the generality of this reaction and the importance of the intramolecular heteroatom coordination in achieving *exo*-methylene formation.[96-98]
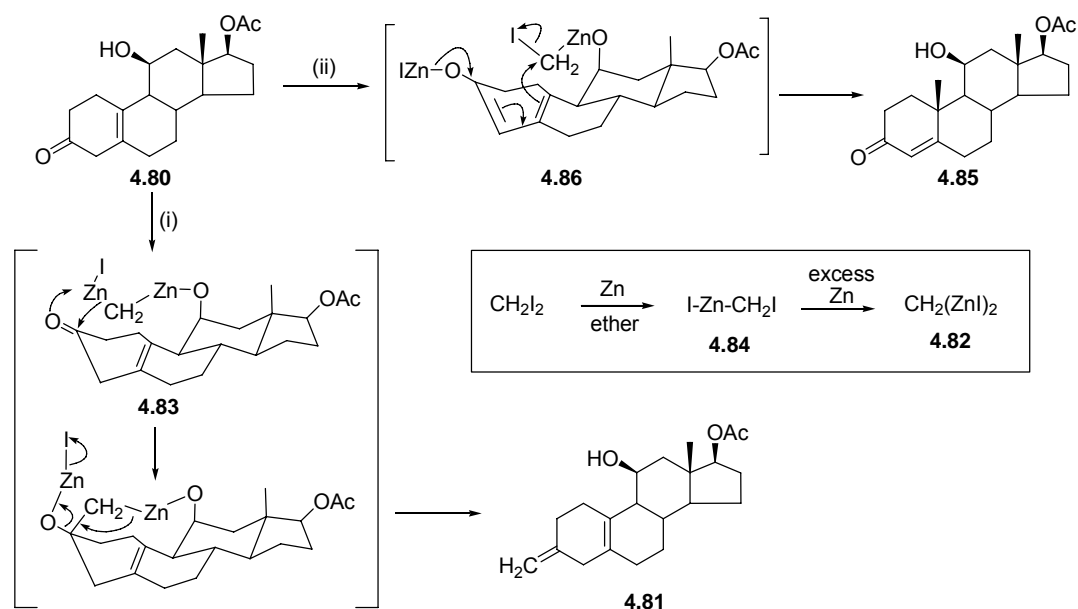
Figure 4.17 Observation of *exo*-methylene formation on β-hydroxy-steroids by Fried *et al.*
Reagents and conditions: (i) Zn-Cu couple, CH_2I_2, ether, reflux, 4 h, then addition of **4.80**; (ii) Zn-Cu couple, ether, addition of **4.80** in CH_2I_2 over 1 h at reflux.

Inspection of the geometry of the cyclopropanated adduct **4.77** reveals that the allylic alcohol methoxy-methyl protecting group displays considerable flexibility in orientation, having the potential to exist in close proximity to the concave face of the C2 carbonyl. Chelation of the dialkylzinc to the ether oxygens forms an intermediate (**4.87**) in which the tethered zinc methylene reagent may be assisted to undergo a nucleophilic attack at the C2 carbonyl. Subsequent oxide elimination yields the *exo*-methylene group observed in **4.78** (**Figure 4.18**).

Figure 4.18 MOM coordination of the zinc methylenating reagent and directed *exo*-methylene formation from the concave face.

Although the reaction was conducted using the Furukawa cyclopropanating reagent **3.81**, it is plausible that the active olefination species could be either the methoxy-methyl ether coordinated to a dialkyl zinc (**3.81**)or a geminal dizinc species (**4.82**) generated *via* a Schlenk equilibrium.
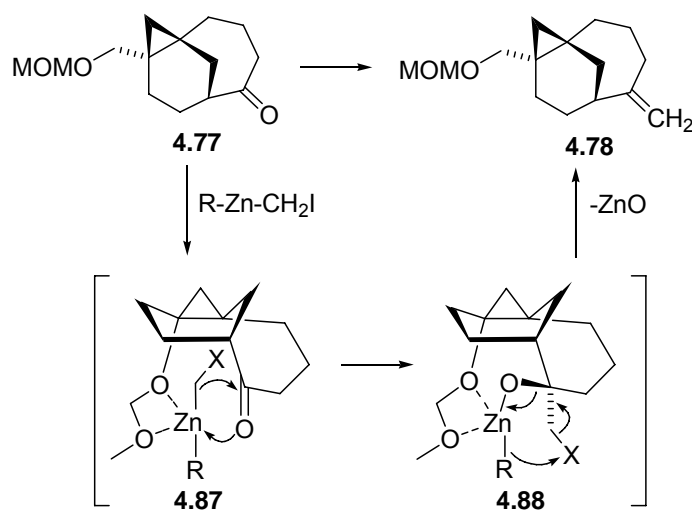
The role of the allylic MOM group in promoting the methylenation of the C2 ketone is supported by a number of observations. No C2 olefination products were observed with the free alcohol or TBS protected alcohol, indicating the potential importance of chelation of the organozinc species *(vide infra)*. Additionally, no product arising from the exclusive methylenation of the C2 ketone in the absence of C6-C7 olefin cyclopropanation was observed, perhaps indicating that the spatial orientation of the chelated-zinc reagent relative to the carbonyl group (**4.87**) was only obtained upon conversion of C7 from an sp^2 to an sp^3 centre *via* cyclopropanation.

The moderate yields of **4.77** coupled with the difficulty in removing the MOM protecting group from either the $\Delta^{6,7}$-olefinic adduct **4.69** or the cyclopropanated adduct **4.77** lead to investigation of the TBS analogue.

4.7.2   Cyclopropanation of TBS-Protected IMDA Adduct 4.71

Concern about the potential for $\Delta^{6,7} \rightarrow \Delta^{7,8}$ olefinic isomerisation observed when attempting to remove the MOM protecting group, saw cyclopropanation attempts focus on the TBS protected species **4.71**.

Furukawa conditions were not successful in introducing the cyclopropane functionality to **4.71** even with excess reagent and prolonged heating. Low conversion was observed, accompanied by significant decomposition as determined by the appearance of new allylic CH_2 peaks in the ^{1}H NMR spectrum. A number of modifications reported to accelerate the cyclopropanation reaction were also ineffective.[99,100]

Modified Simmons-Smith conditions, comprising the slow addition of diiodomethane to a sonicated solution of the olefin **4.71** and activated metallic zinc (admixed with 2% cuprous chloride) in ether resulted in a slow reaction to give complete conversion in 12 hours, as assessed by ^{1}H NMR analysis (**Scheme 4.18**).[101] Disappointingly however, the isolated yield was only 37%, which dropped precipitously on scale-up to 12%.
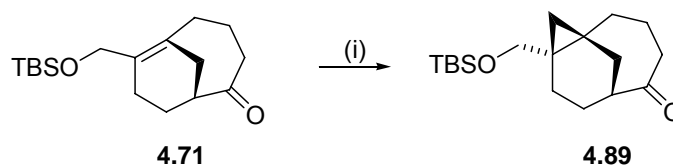
Scheme 4.18 Cyclopropanation of **4.71** under modified Simmons-Smith conditions.

Reagents and yields: (i) Zn (20 equiv), CuCl (2 mol %), ether, sonication, 35°C; addition of CH_2I_2 (10 equiv over 8 h), 37%.

Presumably steric hindrance by the TBS protecting group is responsible for the poor reactivity and slow rate of cyclopropanation of the allylic double bond; with adsorption of the adduct **4.89** onto the excess zinc reagent responsible for the low isolated yields. Removal of the TBS protecting group was expected to eliminate the steric obstruction and provide an allylic alcohol to act as a directing group.

4.7.3   Allylic Alcohol Directed Cyclopropanation

The use of allylic alcohols to achieve stereoselective and asymmetric cyclopropanation has been extensively investigated.[89,102,103] It is postulated that prior coordination of the zinc reagent to the allylic hydroxyl group facilitates stereoselective facial addition of the methylene reagent to the neighbouring alkene *via* a concerted [2+1] mechanism (**4.90**). This interaction promotes both the rate of reaction and controls the stereochemistry of the product to deliver predominantly *syn* orientated adducts (**Figure 4.19**). Protection of the allylic alcohol diminishes the directing ability and for sufficiently bulky substituents (TBS) results in reversal of the stereochemistry due to steric effects.
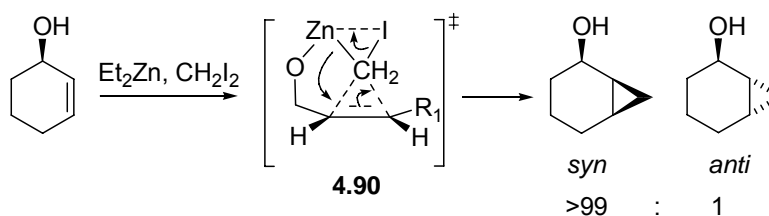

Figure 4.19 Stereoselectivity of cyclopropanation due to allylic alcohol directing effects.

The deprotection of **4.71** to reveal the free hydroxyl $\Delta^{6,7}$-olefin adduct **4.73** was readily achieved with TBAF in THF. No double bond migration was observed. However attempted cyclopropanation of **4.73**, using a number of synthetic protocols including modified Simmons-

Smith protocols (Zn/CuCl/CH_2I_2 under reflux or sonication; Zn-Ag couple),[99] Furukawa conditions ($ZnEt_2$/CH_2I_2)[90] and modified zinc carbenoids ($ZnEt_2$/CH_2I_2/TFA;[100] $ZnEt_2$/CH_2I_2/2,4,6-trichlorophenol[104]) were ineffective in achieving useful synthetic yields.

After extensive investigation success was achieved using the modification reported by Charette *et al.*, involving the pre-chelation of diethylzinc to dimethoxyethane (*c.f.* **4.87**) with subsequent CH_2I_2 addition generating the complex $Zn(CH_2I)_2$.DME (**4.91**) (**Scheme 4.19**-*A*).[105,106] This reagent resulted in clean cyclopropanation of **4.73** in 4 hours at room temperature to yield the desired cyclopropanated adduct **4.92** in 73% yield, accompanied by the methyl ether (**4.93**), which was produced in 13% yield and must arise from methylation of the allylic alcohol (**Scheme 4.19**-*B*).
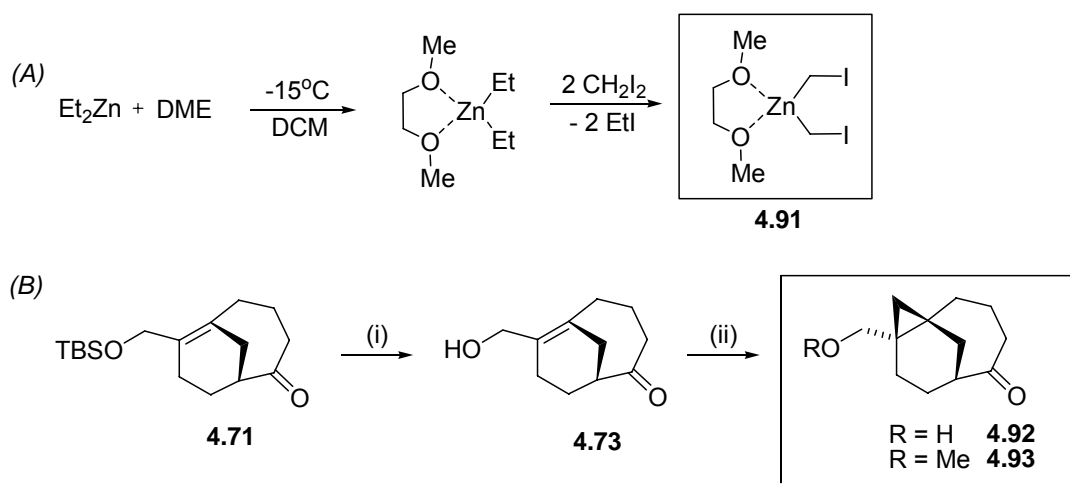
Scheme 4.19 *(A)* Preparation of DME.$Zn(CH_2I)_2$ complex **4.91**; *(B)* Deprotection and cyclopropanation to generated **4.92**.

Regents and Yields: (i) TBAF, THF, 0°C → rt, 80%; (ii) 2 equiv $Zn(CH_2I)_2$.DME, CH_2Cl_2, -15°C → rt, 4 h, 73% **4.92**; 13% **4.93**.

4.8   *Cyclopropylcarbinyl Radical Ring Fragmentations*

As detailed in **Scheme 4.2**, the fragmentation of the newly installed $\Delta^{6,7}$ cyclopropane ring *via* a cyclopropylcarbinyl radical required the functionalisation of the C7 homomethyl alcohol. The approach pursued involved generating a primary radical *via* the deoxygenative-fragmentation of

an *S*-methyl dithiocarbonate (xanthate ester) under free radical conditions as devised by Barton and McCombie.[107-109]

Fragmentation of cyclopropylcarbinyl radical systems *via* a homoallyl-type rearrangement is known to be a facile process, with the release of bond strain providing a thermodynamic driving force for the rearrangement.[110] The kinetics of prototypical systems have been studied by many research groups[111,112] and synthetic applications have been found in ring expansion, ring opening and annulation reactions.[113]
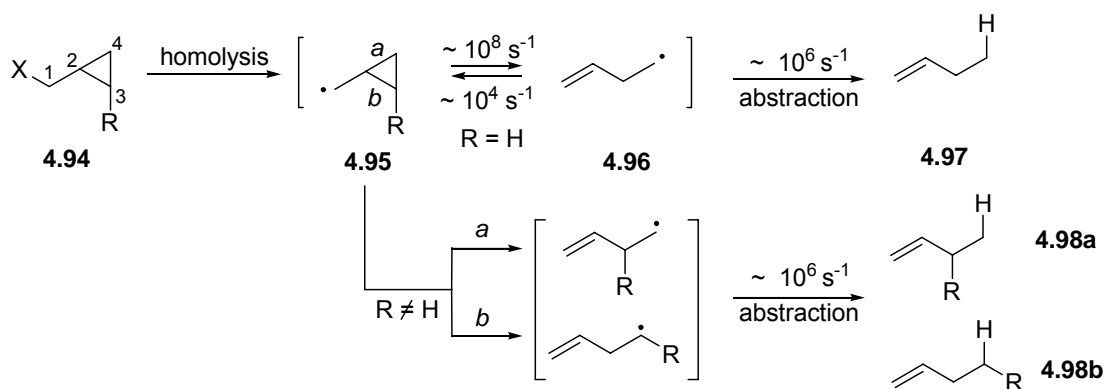
Figure 4.20 Radical fragmentation of prototypical homomethyl-cyclopropanes. Kinetic rates for reactions conducted at 25°C.

The radical fragmentation pathway for a prototypical homomethyl-cyclopropane **4.94** (R = H) is depicted in **Figure 4.20**. Initiation of fragmentation begins with the homolytic generation of a radical at the C1 position (**4.95**) which can undergo fragmentation of either bond *a* (C2-C4) or bond *b* (C2-C3) generating a homoallyl radical **4.96**, which is reduced to **4.97** *via* hydrogen abstraction.

Substitution of the cyclopropane skeleton (R ≠ H) renders the bond cleavage non-equivalent, generating the regioisomeric products **4.98a** and **4.98b**. The nature of the substituents can have a large effect on the absolute and relative rates of cleavage of either the *a* or *b* bond and consequently on the preferred regiochemistry of opening.

With respect to **4.92**, two potential non-equivalent fragmentation routes exist for the primary cyclopropylcarbinyl radical **4.100**, generated *via* radical deoxygenation of the xanthate ester **4.99**. *Path A* features C7-C13 cyclopropane bond homolysis, *exo* to the cyclohexane ring, to generate a primary radical centred at C13 (**4.101**). Radical hydrogen abstraction delivers the

desired C6 bridgehead methyl group **4.102** observed in the target structure **1.22** and **1.73**. *Path B*, in contrast, fragments the internal C6-C7 bond to form a C6-centred tertiary radical (**4.103**), which gives the seven-membered ring expanded product **4.104** upon reduction (**Scheme 4.20**).
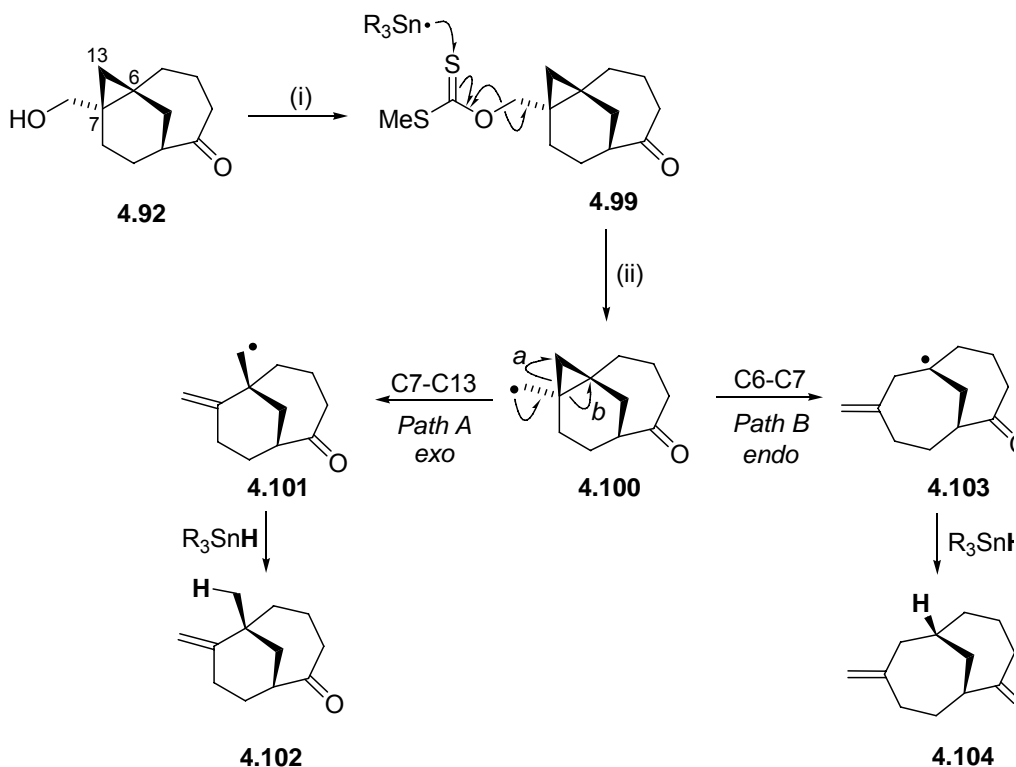
Scheme 4.20   Radical fragmentation pathways for xanthate ester **4.99**.

Reagents and yields: (i) NaH; CS$_2$; MeI, 74%; (ii) R$_3$SnH, initiator.

The preferential generation of **4.102** or **4.104** will depend upon the relative bond fragmentation rates of the cyclopropylcarbinyl radical **4.100** and the stability of the generated radicals and reduced adducts.

4.8.1   Xanthate Functionalised Cyclopropane Ring Fragmentation

The xanthate functional group was introduced to the allylic position of **4.92** in good yield *via* sequential reaction with sodium hydride, dimethyl sulfide and quenching with methyl iodide, to generate the *S*-methyl dithiocarbonate **4.99** as a yellow oil (**Scheme 4.20**).

Radical deoxygenation conducted under thermally initiated fragmentation conditions (Bu$_3$SnH, AIBN, benzene, reflux, 2 h) resulted in the conversion of the xanthate material into two products, both of which displayed an exocyclic methylene group, in a ratio of 5:1.

Initial attempts to determine the structure of the isolated species *via* 1D and 2D NMR correlation spectroscopy were hampered by the co-elution of stannane residues and volatility of the compounds. Inclusion of a reduction step prior to work-up generated the C2 secondary alcohol which was of diminished volatility and allowed separation of two major products from the co-eluting stannane residues. Based on the established work of Shea *et al.*, who demonstrated that reduction of related bicyclic ketones affords predominantly the stereoisomer whereby reduction takes place from the beta-face,[85] it was initially presumed that these reduced adducts were **4.105** and **4.106** (**Scheme 4.21**).
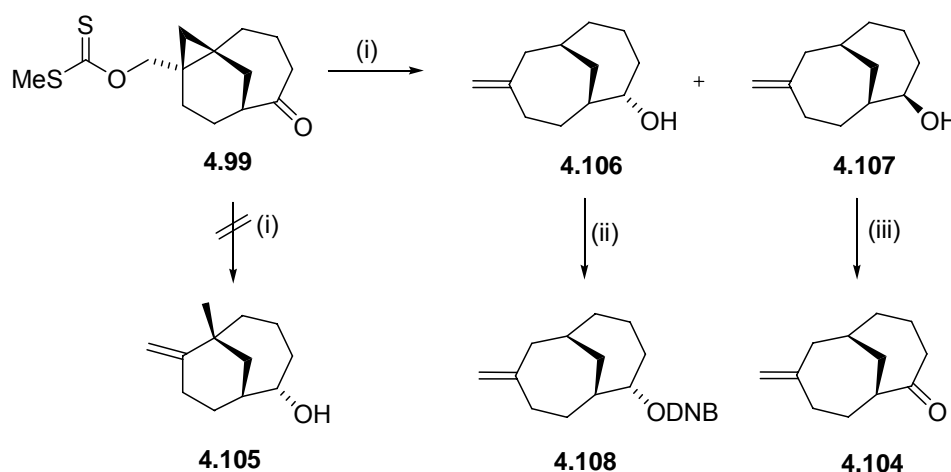
Scheme 4.21   Xanthate radical fragmentation under thermal conditions.

Reagents and yields: (i) *(a)* Bu$_3$SnH, AIBN, 80°C, 2 h; *(b)* DIBAL-H, toluene, -78°C, 1 h, **4.106** 63%, **4.107** 13%; (ii) 3,5-dinitrobenzoyl-Cl, DMAP, NEt$_3$, 54%, (iii) PDC (2 equiv), CH$_2$Cl$_2$, quantitative.

Structural assignment of the two alcohol products *via* 2D NMR spectroscopic techniques was unsuccessful due to considerable overlap of the diastereotopic proton signals in the ^{1}H NMR spectra. Previously distinct ^{1}H NMR resonances due to the conformational rigidity of the cyclopropyl-bicyclic ring system, or as a result of proximity to the carbonyl functionality, were lost upon radical fragmentation and reduction. However, a crystal structure was successfully obtained of the major product, following condensation of **4.106** with 3,5-dinitrobenzoyl chloride. This allowed unambiguous assignment of **4.108** as the seven-membered ring expanded product (**Figure 4.21**).
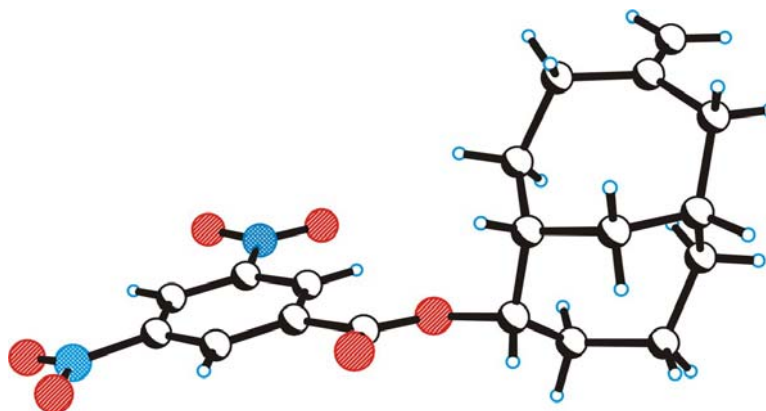
Figure 4.21a   Crystallographic structure determined for the fragmentation adduct **4.108** [P-1, Z = 2, R = 3.4%].
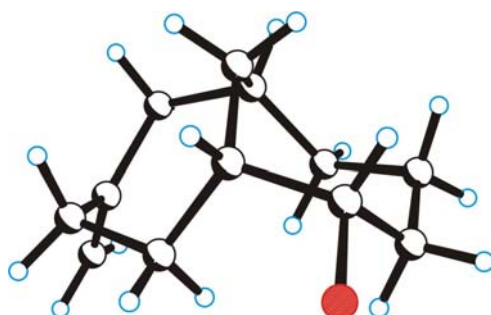
Figure 4.21b   The bicyclo[4.4.1]undecanone carbocyclic core, illustrating reduction of the C2 ketone from the less sterically hindered convex face. The crystallisation group (DNB) has been removed for clarity.

Efforts to obtain a suitable single crystal of the minor product for use in X-ray crystal analysis were unsuccessful, with the DNB-adduct instead obtained as an oil under a number of crystallisation procedures. Oxidation of the minor alcohol product with PDC in CH_2Cl_2 generated the ring expanded adduct (**4.104**) in quantitative yield. This demonstrated that the reduction had resulted in the isolation of the two diastereomeric alcohols, **4.106** and **4.107**, both of which contained the bicyclo[4.4.1]undecanone core, rather than the desired bicyclo[4.3.1]decanone core. The presumed exocyclic ring cleavage adducts **4.102** and **4.105** could not be isolated in sufficient purity to allow comprehensive spectroscopic analysis.

Disappointingly, with the crystal structure of the major adduct in hand, it was apparent that the radical fragmentation had proceeded predominantly with scission of the C6-C7 *endo* bond (**4.103**) rather than the desired C7-C13 *exo* bond (**4.101**). This unexpected setback necessitated the further investigation of this fragmentation in an effort to enhance the formation of the desired bridgehead methyl adduct **4.102**.

4.8.2   Prior Literature Fragmentation Studies

Although cyclopropyl ring opening is well understood for simple substituted monocyclic systems such as **4.94**, incorporation into a bicyclo[*n*.1.0] framework introduces factors of increased conformational rigidity, ring strain and different rates of ring opening and reclosure.[114-116] The literature on radical cyclopropane ring cleavage reveals a preference for exocyclic opening upon kinetic (*n* = 3-6) and thermodynamic grounds (*n* = 4-6) which contrasts with the cationic preference for endocyclic ring opening.[116,117] However, most of these studies have been based upon systems in which the generated radical is located within the carbocyclic ring system.

4.8.2.1   Synthetic Examination of Cyclopropylcarbinyl Fragmentation

(i) Kurth

The preferential formation of the ring-expanded product **4.104**, *via* an endocyclic radical fragmentation, can be put in context by consideration of the research conducted by Kurth *et al.*, who had reported that variable distributions of six- and seven-membered ring systems were generated upon fragmentation of 1-bicyclo[4.1.0]heptanylmethyl radicals (**4.109**) (**Figure 4.22**).[118]

4.110a R = H
4.110b R = -O(CH$_2$)$_2$O-

4.109   **4.111**   **4.112**

4.113   **4.114**
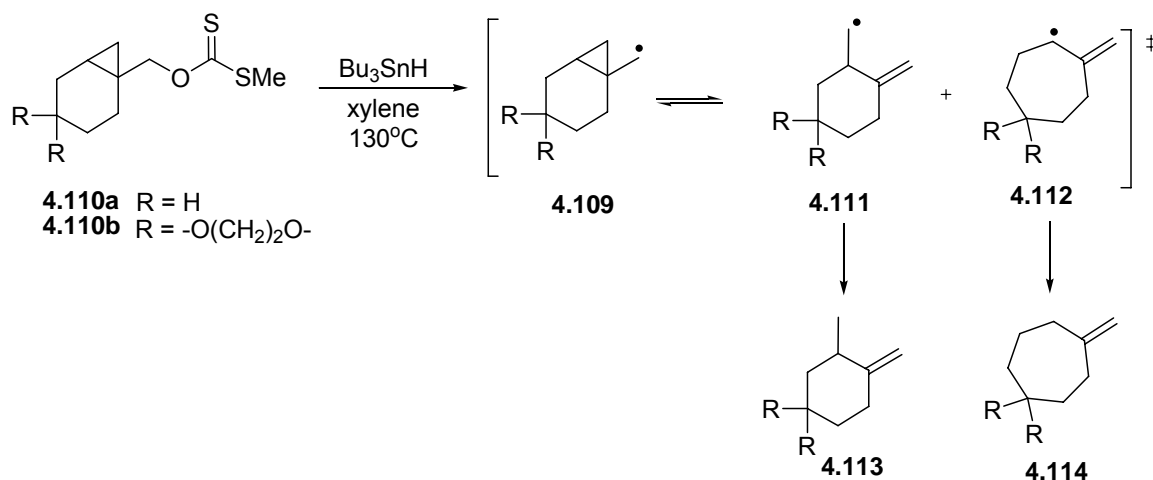
Figure 4.22 Fragmentation of cyclopropylcarbinyl xanthates fused to a cyclohexane core.

Fragmentation of cyclopropane species **4.110a** at 150°C, with [0.4 M] Bu$_3$SnH as a reducing agent, resulted in a 1:1 ratio of adducts **4.113** and **4.114**. Preferential kinetic formation of the ring expanded secondary radical **4.112** was observed by increasing the concentration of Bu$_3$SnH, from [0.4 M] to ≥ [0.8 M] which resulted in the near exclusive formation of **4.114** (>95:5).

Interestingly, the preferred fragmentation pathway for the cyclopropylcarbinyl radical **4.109** could be influenced by substituents and geometrical constraints imposed on the cyclohexane ring. 1,3-Dioxolane **4.110b** formed a mixture of **4.113** and **4.114** (57:43) at high reducing agent concentrations, (Bu₃SnH = [0.43 M]), but displayed a preference for **4.113** (68:32) at low hydride concentrations, (Bu₃SnH = [0.05 M]).

Kurth *et al.* subsequently examined the cyclopropylcarbinyl radical system **4.116** to determine both the rate constants for the cyclopropylcarbinyl rearrangement and conducted theoretical calculations on the preferred transition state and intermediate radical structure.[119]

Kinetic analysis was conducted upon the fragmentation of **4.116**, derived from the photolytic cleavage of *N*-hydroxypyridine-2-(*1H*)-thione homomethyl cyclopropyl ester **4.117** in the presence of either tributyltin hydride or thiophenol as a reducing agent over a range of temperatures (-75°C to +59°C) (**Figure 4.23**).[120] At all temperatures, the 3-methylenecycloheptyl radical **4.119** was formed 3.2-3.8 times faster than the non-expanded 2-methylenecyclohexyl-1-methyl **4.118**. A slight equilibration of the primary **4.118** and secondary radical **4.119** was observed by restricting the reducing agent concentration.
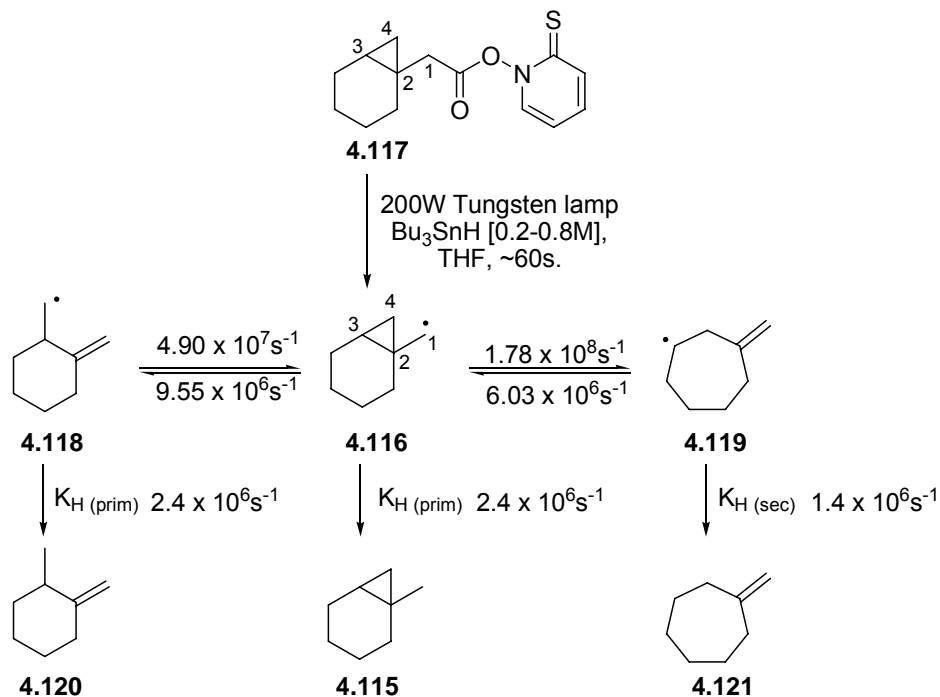
Figure 4.23 Endo- and exocyclic cyclopropylcarbinyl radical fragmentation.

(*ii*) *Motherwell and Clive*

It is perhaps pertinent at this point to contrast the work of Kurth *et al,*. which focused on the fragmentation of 1-bicyclo[4.1.0]heptanylmethyl radicals (**4.116**), with that of Motherwell *et al.*[114,116,121] and Clive *et al.*[117] who have investigated the fragmentation of 6-bicyclo[4.1.0]-heptanyl radicals (**4.122**). In the first instance, the incipient radical is *exo* to the bicyclic ring system (**4.116**) whereas in the second, the radical centre is embedded within the bicyclo[*n*.1.0] system (**4.122**) (**Figure 4.24**).
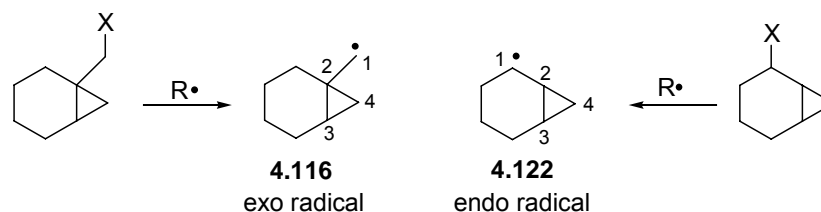
Figure 4.24 1-Bicyclo[4.1.0]heptanylmethyl radical **4.116** and 2-bicyclo[4.1.0]heptanyl radical **4.122**.

In cases such as **4.123**, an example of the radical system **4.122**, restricted rotation of the C1-C2 bond due to conformational rigidity and ring strain causes a strong stereoelectronic preference for exocyclic ring opening generating the product **4.124** exclusively (**Figure 4.25**).[117,122]
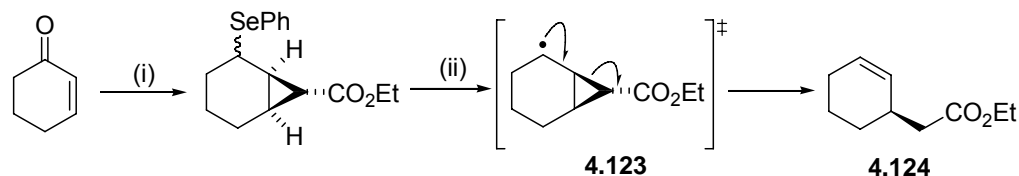
Figure 4.25 Exocyclic fragmentation of ring centred radical.

Reagents and yields: (i) *(a)* Me$_2$S=CHCO$_2$Et, 73%; *(b)* NaBH$_4$, CeCl$_3$.7H$_2$O, MeOH, 85%; *(c)* Bu$_3$P, PhSeCN, 80%; *(ii)* Bu$_3$SnH, AIBN, benzene, 92%.

This obviously contrasts with the radical structure **4.116** in which rotation of the C1 radical-bearing centre allows overlap of the SOMO with either the C2-C3 or C2-C4 β-cyclopropyl bonds; allowing access to both homoallylic **4.118** and **4.119** radical fragmentation routes.

(iii) Prunet

Prunet and colleagues made use of a cyclopropylcarbinyl rearrangement during synthetic studies directed towards the C15-C25 spiroketal subunit of bafilomycin A$_1$.[123] Barton-McCombie radical deoxygenation of **4.125** proceeded readily to furnish the exocyclic vinyl derivative **4.126** with no

detectable trace of the corresponding ring expanded product. Due to a facile endocyclic double bond migration, the crude material was submitted to a hydroboration-oxidation protocol to generate spirocyclic alcohol **4.127** as a single diastereoisomer in high yield (**Figure 4.26**). In this instance the tetrahydropyran ring oxygen may play a significant role in determining the dominant stereoelectronic effect in radical fragmentation.
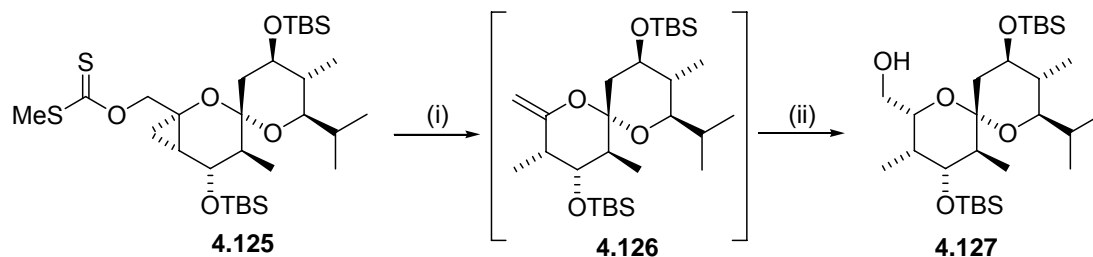
Figure 4.26 Cyclopropylcarbinyl cleavage to stereoselectively establish an *exo*-methyl group.

Reagents and yields: (i) Bu₃SnH, AIBN, toluene, reflux; (ii) BH₃.THF; H₂O₂, NaOH; 85% two steps.

4.8.2.2   Theoretical Examination of Cyclopropylcarbinyl Fragmentation

The opening of conformationally unrestricted cyclopropylcarbinyl systems (**4.94**) has been investigated in the context of radical clocks in mechanistic studies[124] and in preparative chemistry.[113]

A qualitative interpretation of the preferred regiochemistry of opening is provided by frontier molecular orbital theory. The SOMO p-orbitals of the cyclopropylcarbinyl radical, through rotation of the C1-C2 bond, preferentially interact with the vicinal cyclopropyl LUMO σ-bond which achieves the best overlap and allows the greatest stabilising radical delocalisation into the cyclopropane ring.[125] The nature of the substitution pattern, in conjunction with steric effects, allows stereoelectronic differentiation between the two cyclopropyl bonds resulting in a preferential regioselective cleavage.[126-128]

However, *a priori* prediction of product distributions arising from conformationally restricted cyclopropylcarbinyl systems is not a trivial matter. The number of influencing variables, such as *(i)* primary, secondary or tertiary radical character, *(ii)* substituent stabilisation, *(iii)* relief of strain derived from eclipsing interactions and *(iv)* the preferred orientation and overlap of the radical SOMO with the β-cyclopropyl *exo* or *endo* bond, often mean that no specific factor can be isolated as the dominant effect.

Theoretical examination of the radical system **4.116** by Kurth *et al.* using PMP4/6-31G*//HF/6-31G* level of theory to correlate stereoelectronic variables with the observed rearrangement of cyclopropylcarbinyl radical **4.116** to **4.118** and **4.119** were essentially inconclusive.[119] Although the origins of the regioselectivity remained obscure, the results derived from these calculations suggested formation of **4.121** was favoured both thermodynamically by ~1-2 kcal mol^{-1} and kinetically by ~3.0 kcal mol^{-1} for all levels of theory. It was postulated that the formation of **4.119** was favoured primarily due to the reduction of eclipsing interactions in the transition state between the cyclopropyl substituents and due to thermodynamic stabilisation associated with the formation of a secondary radical centre from the primary incipient radical.

The Kurth studies emphasised the importance of accurate conformational analysis when endeavouring to predict the product distributions arising from conformationally restricted cyclopropylcarbinyl radicals. As such the radical fragmentation of **4.99** bears significant structural differences.

Firstly, although the radical fragmentation of **4.99** generates a 1-bicyclo[4.1.0]-heptanylmethyl radical (**4.116**), the fusion of this moiety within a second bicyclic ring could be expected to significantly influence the conformation of the incipient radical, the relative alignment of the SOMO orbital and the stability of the reduced product (*c.f.* **4.110a** vs. **4.110b**).

Secondly, whereas the radical intermediate derived from an endocyclic cleavage in the Kurth studies (**4.119**) is of secondary nature, the product of an endocyclic cleavage of **4.100** is a tertiary radical. The stabilisation of the radical **4.103** (derived from an *endo* primary → tertiary rearrangement) could be anticipated to provide a significant thermodynamic advantage compared to the primary → primary radical transition associated with exocyclic fragmentation to yield **4.101**.

4.8.3   Theoretical Investigation of the Cyclopropyl Fragmentation of 4.99

The preference of **4.99** for *endo* or *exo* bond cleavage, leading to cycloheptyl ring expansion or C6 bridgehead methyl formation respectively, was further investigated both theoretically and synthetically.

Preliminary semi-empirical and HF/6-31G* theoretical calculations were conducted with Spartan software to investigate the orientation of the C12 methyl radical relative to the cyclopropane ring

and to determine the extent of hyperconjugation of the radical centre into the cyclopropane ring system (**Table 4.5**).

Table 4.5   Selected electron spin-density overlap values for **4.100**.
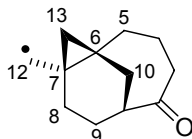
Position	C12	C7	C6	C8	C13	C5	C9	C10
Spin Density	1.0732	-0.1401	0.0988	0.0133	0.0711	-0.0064	0.0037	0.0060

As can be observed, partial spin hyperconjugation has occurred from the incipient C12 methyl radical into the adjacent quaternary C7 centre, with subsequent delocalisation occurring predominantly into the cyclopropane structure (C6, C13) as opposed to the cyclohexane ring (C8). The attenuation of spin character is then rapid (C5, C9, C10 *vs* C8, C13, C6). In agreement with the modelling studies of Kurth, greater spin delocalisation can be observed at C6, favouring formation of the tertiary radical and the ring-expanded seven-membered adduct, than into the C13 bond which would favour the desired six membered ring. Inspection of the energy minimised conformation of **4.100** shows a partial twisting of the C12 SOMO towards the C6-C7 bond (9.6°), indicating the potential for preferential overlap.

However, a caveat should be noted, that the relative orbital-alignment of the SOMO will be more important for a transition state that is more 'reactant-like', whereas radical stability and conformational strain will contribute more significantly if the transition state is more 'product-like' when determining the product distributions of rearrangement.[129]

4.8.4   Synthetic Investigation of Cyclopropyl Fragmentation of 4.99

The Preferential fragmentation of **4.99** to generate the seven-membered ring adduct **4.104** was an unexpected difficulty arising from adopting a homomethyl cyclopropane strategy. It was hoped that modification of the reaction conditions, reagents or substrates might sufficiently shift the ratio to favour generation of the six-membered ring **4.102** in a synthetically useful fashion. Efforts directed towards this approach are displayed in **Table 4.6**.

Table 4.6   Radical fragmentation conditions.
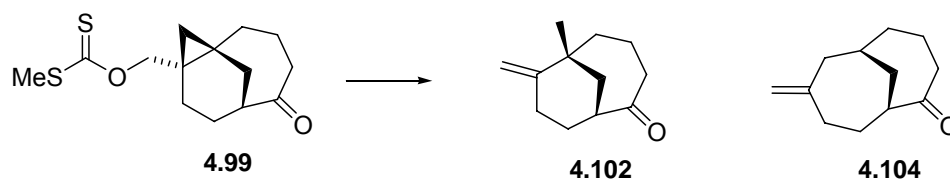
Entry	Substrate	Reagent	Conditions[a,]	Ratio (4.102:4.104)	k_H[c]
1	4.99	n-Bu$_3$SnH (3)	AIBN, benzene	1 : 4	7.4×10^5
2	4.99	Ph$_3$SnH (3)	AIBN, benzene	0 : 1	3.1×10^6
3	4.99	Me$_3$SnH (6)	AIBN, benzene	0 : 1	2.9×10^5
4	4.99	Et$_3$SiH (3)	AIBN, benzene	n.r.	5.2×10^3
5	4.99	Et$_3$SiH (solvent)	Benzoyl peroxide	0 : 1	
6	4. 99	Et$_3$SiH (solvent)	Benzoyl peroxide, dodecanethiol	1:4	
7	4. 99	n-Bu$_3$SnH (3)	BEt$_3$, toluene[b]	1 : 4	
8	4. 99	n-Bu$_3$SnH (3)	BEt$_3$, MeOH[b]	n.r	
9	4. 99	n-Bu$_3$SnH (3)	BEt$_3$, THF [b]	0 : 1	
10	4. 99	n-Bu$_3$SnH (3)	BEt$_3$, hexane[b]	0 : 1	
11	4.134α	n-Bu$_3$SnH (3)	AIBN, benzene	0 : 1	
12	4.134β	n-Bu$_3$SnH (3)	AIBN, benzene	0 : 1	

Note: (a) Reactions performed by combining the xanthate (1 equiv), hydride (3 equiv) and radical initiator (0.1 equiv) in the stated solvent at room temperature and heating to reflux. Monitored *via* TLC. (b) Conducted at -78°C with addition of (0.1 equiv) of BEt$_3$ and then portionwise addition of dry air over 1 h whilst allowing to warm to room temperature. (c) Literature values for the rate of hydrogen abstraction from the hydrogen source by the *t*-Bu radical in cyclohexane at 25°C.[130]

a) Hydrogen Donor Source *(Entries 1-6)*

To promote reduction of the primary radical **4.101**, in preference to the sterically hindered tertiary radical **4.103**, the use of sterically demanding hydride reagents was investigated.[131] Barton-McCombie radical deoxygenation conducted under thermal conditions utilising triphenyltin hydride, tri-*n*-butyltin hydride, trimethyltin hydride or triethylsilane gave differing results.

Radical fragmentation conducted with tributyltin hydride as a reducing agent resulted in a 1:4 mixture of the adduct **4.102** to **4.104** *(entry 1)*, whereas the use of both sterically demanding *(entry 2)* and a non-demanding hydrogen sources *(entry 3)* resulted in the exclusive formation of the seven-membered ring. Two factors may account for this observed bimodal reactivity. The

rate of radical hydrogen abstraction from the trialkyltin hydrides increases by a factor of ten along the series $Me_3SnH < n\text{-}Bu_3SnH < Ph_3SnH$ (see the values of k_H in **Table 4.6**), whilst the steric bulk also increases over this range.[130] Calculations by Kurth and colleagues, based on kinetic data, have indicated that the rate constants for the homoallyl $\rightarrow$ cyclopropylcarbinyl radical rearrangements (**4.118** and **4.119** to **4.116**) are in the order of 6×10^6 to $9.6 \times 10^6 \text{ s}^{-1}$. As such, it is possible that thermolysis in the presence of Ph_3SnH results in a rapid trapping of the kinetic product **4.104** without equilibration of the radical intermediates **4.101** and **4.103**. In contrast, the small steric bulk of Me_3SnH allows close approach of the hydride to the tertiary radical centre of **4**.**103**, resulting in rapid reduction and ring expansion. $n\text{-}Bu_3SnH$, which is of moderate steric hindrance and has a rate of radical hydrogen abstraction of a similar order to the rearrangement processes, allows equilibration of the radical intermediates **4.101** and **4.103** resulting in the isolation of a mixture of reduced products.

To investigate whether equilibration of the primary radical (**4.101**) and the tertiary radical (**4.103**) was occurring under the reaction conditions, triethylsilane, which has a rate constant of hydrogen abstraction several orders of magnitude slower than the cyclopropylcarbinyl radical rearrangement, was utilised. Triethylsilane has previously been reported to effect the radical deoxygenation of xanthate esters under forcing conditions[132-135] or with the inclusion of alkyl thiols to effect polarity reversal catalysis.[136]

Under the standard conditions used for the stannane reductions (3 equivalents of triethylsilane, AIBN, benzene, reflux) no reaction was observed *(entry 4)*. When triethylsilane was used as the solvent, with stoichiometric quantities of benzoyl peroxide as the initiator, complete consumption of the starting material occurred to generate the seven-membered ring exclusively. Two other products were identified – the free alcohol resulting from reduction of the xanthate functionality and a product arising from radical trapping of the triethylsilyl xanthate addition intermediate *(entry 5)*. The inclusion of a catalytic amount of dodecanethiol, to effect polarity reversal catalysis, resulted in a mixture of adducts in the ratio 4:1 favouring the ring expanded adduct. A significant amount of unidentified adducts were also formed during this thermolysis.

b) Temperature and Solvent *(Entries 7-10)*

Clive and Daigneault reported that thermal deoxygenation of the xanthate and phenylseleno-decalin derivatives **4.128** and **4.129**, which lack an electron withdrawing group on the cyclopropane skeleton, were best conducted at moderate to low temperatures (-20 °C to 25°C) to suppress the significant amount of ring expansion observed when the reaction was performed in

refluxing benzene. However, even under optimised conditions a minor amount (~5%) of the ring-expanded product **4.131** was observed. Ring expansion was proposed to proceed *via* formation of the more thermodynamically stable tertiary radical under equilibrating conditions (**Figure 4.27**).[117]

X = OC(S)SMe **4.128**   **4.130**   **4.131**
  = SePh   **4.129**
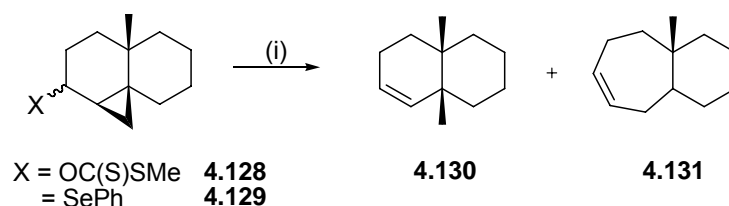
Figure 4.27 Temperature dependent fragmentation.

Reagents and yields: (i) *(a)* Bu₃SnH, AIBN, benzene, 80°C, mixture of **4.130**:**4.131**; *(b)* Bu₃SnH, sunlamp, -5°C, **4.130** 84%; **4.131,** 7%; c) Bu₃SnH, BEt₃, -5°C, **4.130**, 85%; **4.131**, 4%.

Although radical intermediates are generally considered to be insensitive to the solvent medium and polarity, instances have been observed where solvent effects have a significant influence on the product distribution and selectivity.[137] Solvent and temperature studies were conducted simultaneously using the BEt₃/O₂ radical initiation system which allows low-temperature radical initiation.[138]

The reactions were conducted at -78°C in the stated solvent (**Table 4.6**) and allowed to warm to room temperature whilst being monitored *via* TLC. Radical fragmentation of **4.99** was not observed to occur until the reaction temperature approached 0°C. Examples in the literature indicate that the radical fragmentation of primary xanthates, *via* the Barton-McCombie method, is temperature sensitive due to the requirement for the formation of a highly enthalpic primary radical species **4.132** from a reversible stannane addition adduct **4.133** (**Figure 4.28**).

4.133   **4.132**

Figure 4.28 Xanthate radical fragmentation.

In all cases the observed radical fragmentation results were inferior to those provided by the thermal system of *entry 1*. The reaction performed in toluene gave the same isomeric ratio as *entry 1* as well as generating a number of decomposition products *(entry 7)*. The use of THF was

observed to exclusively generate **4.104** with considerable amounts of decomposition. No reaction was observed in MeOH.

3) Substrate (Entries 11-12)

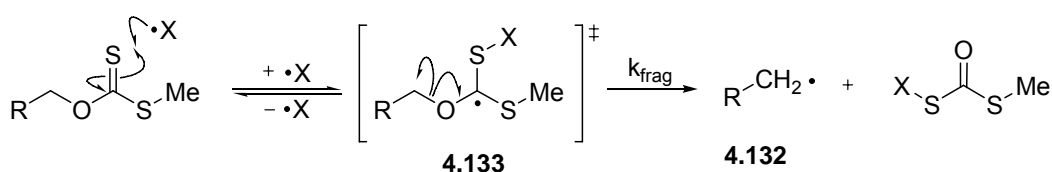As discussed previously, elements of torsional strain, orbital alignment and stereoelectronic effects may influence the preferred fragmentation route taken by an incipient radical. It was plausible that modification of the bicyclic core to reduce the ring strain could result in the adoption of a conformer that could favourably influence these factors and increase the isomeric ratio in favour of **4.102**.

Reduction of the C2 ketone group, in the presence of the C12 xanthate, was selectively achieved using sodium borohydride in aqueous ethanol to yield a 2:1 mixture of the diastereoisomeric C2 alcohols **4.134α** and **4.134β**, which could be separated by careful column chromatography (**Scheme 4.22**).
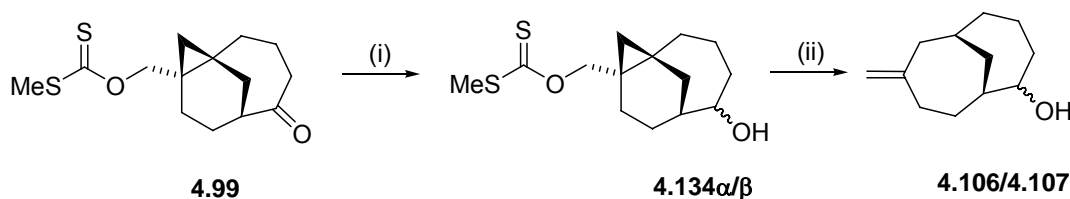
Scheme 4.22   Preparation and fragmentation of alcohol substrate **4.134α/β**.

Reagents and yields: (i) NaBH$_4$, EtOH, 30%; (ii) Bu$_3$SnH, AIBN, benzene.

Disappointingly, radical fragmentation of both alcohol stereoisomers **4.134α** and **4.134β** resulted in exclusive formation of the ring-expanded adduct, accompanied by a number of unidentified decomposition products. Identification of the fragmentation products **4.106** and **4.107** was made by comparison with the reduction products derived from the fragmentation–reduction protocol depicted in **Scheme 4.21**.

4.8.5   Substrate Modified Routes

The above studies indicated that the fragmentation of the cyclopropyl xanthate species **4.99** could not be controlled on a synthetically useful level with the formation of the cycloheptanyl radical **4.104** favoured both kinetically and thermodynamically over the desired methyl cyclohexane radical **4.101**.

In an effort to promote the desired C7-C13 *endo* cyclopropylcarbinyl fragmentation an alternative methodology was investigated which focused on stabilisation of the primary radical intermediate **4.101**.

4.8.5.1 Stabilised Cyclopropanes

The radical fragmentation pathway depicted in **Scheme 4.23** illustrates the transformation of the incipient primary cyclopropylcarbinyl radical **4.135** to either the C13 primary radical **4.136** or the C6 tertiary radical **4.137** *via* two competing pathways.

In the case of Y = H, it is evident that formation of the thermodynamically favourable tertiary radical **4.137** dominates *via* C6-C7 cleavage. If scission of the C6-C13 bond could be thermodynamically favoured, by stabilising the radical at the C13 position with an electron-withdrawing group (**4.136**, Y = EWG), productive generation of the desired carbocyclic skeleton **4.138** might be realised. Removal of the control group (Y) would then yield the desired carbocyclic core **4.102**. Towards this goal the preparation of a *gem*-dichlorocyclopropane species was investigated.
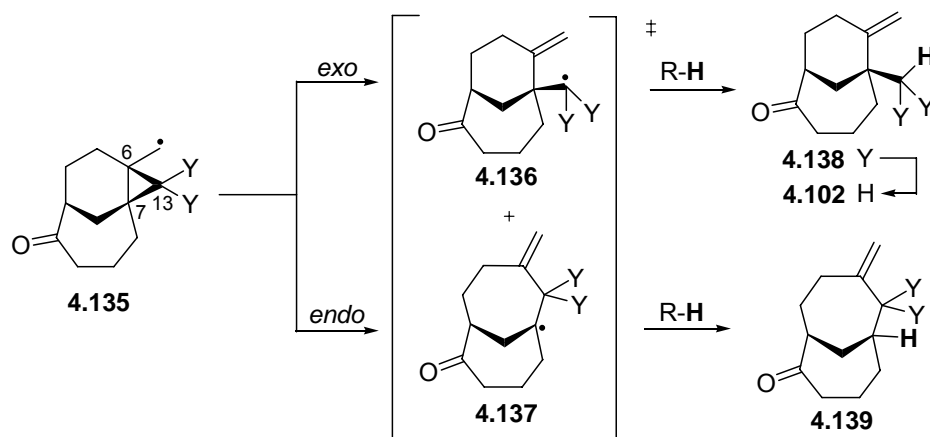
Scheme 4.23 Controlled radical fragmentation *via* inductive stabilisation at C13.

4.8.5.2 *gem*-Dichlorocyclopropane Preparation

A *gem*-dihalocyclopropane system was investigated on the basis of two assumptions. Firstly, it was anticipated that the electronegativity of the halide atoms would inductively the C13 primary radical derived from C6-C13 cleavage (**4.136**) and, secondly, that dehalogenation of the resultant

primary alkyl dihalide **4.138** could be effected under similar conditions to those required to cleave the initial cyclopropane structure.

Sydnes *et al.* reported the radical induced reduction of various 1,1-dihalo-2-haloalkylcyclopropanes.[139] Among these studies, the radical fragmentation of 1,1-dichloro-2-bromomethyl cyclopropane structures (**4.140**) were reported to give alkenes (**4.141**) derived from a cyclopropylmethyl → 3-butenyl radical rearrangement as depicted in **Figure 4.29**.
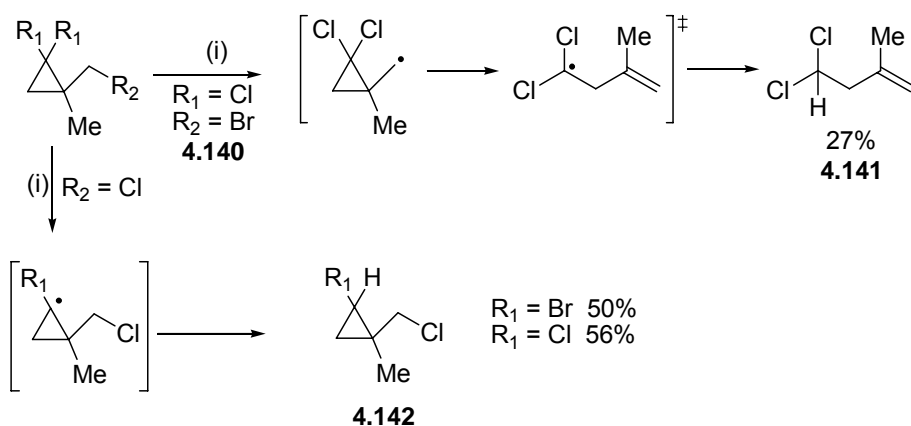
Figure 4.29 Radical fragmentation of *gem*-dihalocyclopropanes.

Reagents: (a) Bu$_3$SnH, AIBN.

The nature and regiochemistry of the halide incorporation is important to achieving this rearrangement as scission of the [Br-C] bond proceeded more readily than the [Cl-C] bond and the cyclopropyl position (R_1) was more reactive than the homomethyl position (R_2). For example, reductive dehalogenation of 1,1-dibromo- and 1,1-dichloro-2-chloroalkylcyclopropanes was observed to proceed exclusively at the cyclopropyl position with retention of the cyclopropane structure (**4.142**).

Within the context of **Scheme 4.23**, it was anticipated that radical fragmentation of the *gem*-dichlorocyclopropane species **4.135** (Y = Cl) would generate the stabilised primary dichloromethane species **4.136** (Y = Cl), with hydrogen capture yielding the desired bicyclo[4.3.1] ring structure **4.138** (Y = Cl). Additionally, it is known that exhaustive reduction of alkyl halides to the corresponding alkane can be achieved with excess tributyltin hydride under radical conditions.[140] It was hoped that these two processes, radical fragmentation-rearrangement (**4.135** → **4.138**) and halide reduction (**4.138** → **4.102**), could be conducted in tandem to reveal the desired *exo*-methylene C6-bridgehead methyl bicyclic structure **4.102**.

Towards this goal the *gem*-dichlorocyclopropane fragmentation precursors were prepared as depicted in **Scheme 4.24.**
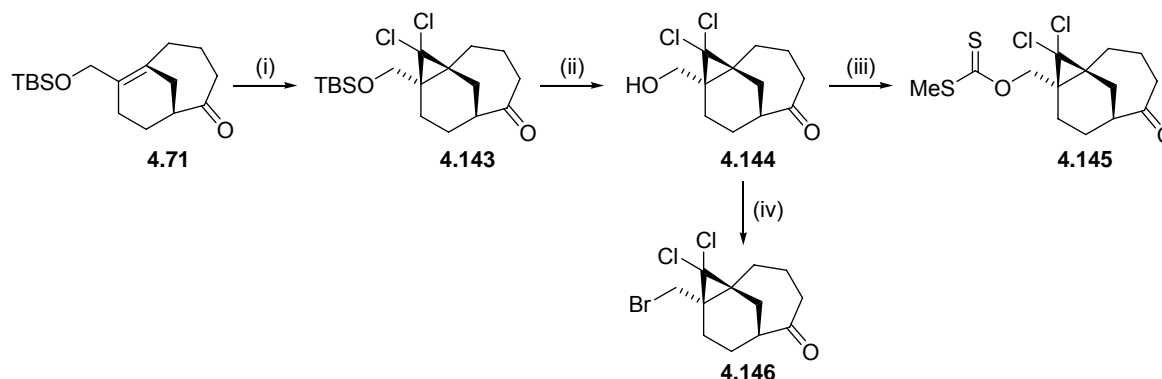
Scheme 4.24 Preparation of xanthate- and bromo-1,1-dichlorocyclopropanes **4.145** and **4.146**. Reagents and yields: (i) 50% NaOH, CHCl$_3$, TEBAC, 84%; (ii) TBAF (1.1 equiv), 94%; (iii) *(a)* NaH, THF, *(b)* imidazole, CS$_2$, *(c)* MeI, 64%; (iv) PPh$_3$.Br$_2$, CH$_2$Cl$_2$, 72%.

The synthetic route commenced with the clean installation of a *gem*-dichlorocyclopropane moiety in high yield *via* a dichlorocarbene addition to the $\Delta^{6,7}$ olefinic bond of **4.71** under phase-transfer conditions.[141] Removal of the TBS protecting group was readily achieved upon exposure to TBAF generating the free alcohol **4.144** which crystallised following silica column chromatography. X-ray crystallographic data obtained from a single large crystal confirmed the anticipated structure of **4.144 (Figure 4.30)**.

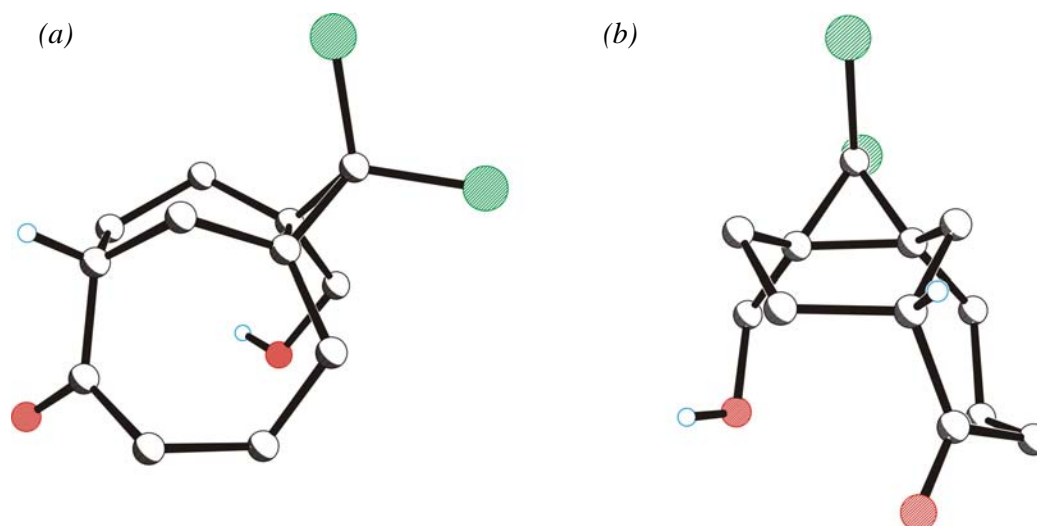**Figure 4.30** *(a)* Crystallographic structures determined for the dichloro-cyclopropane adduct **4.144**, [P-1, Z = 2, R = 2.6%]. *(b)* Orientation showing the convex nature of the bicyclo-[4.4.1.0^{1,3}]undecane core.

Inspection of the crystal structure confirms that electrophilic attack by the dichlorocarbene species had occurred exclusively from the convex face of **4.71** to yield a *gem*-dichlorocyclopropane (**Figure 4.26**-*a*). The geometrical conformation closely resembles that previously observed for **3.84** (**Figure 3.33b**).

The close proximity of the C7 homomethyl alcohol to the C2 carbonyl on the concave face of the carbocyclic skeleton is illustrated in **Figure 4.30**-*b*. This observation provides support for the proposed mechanism of chelation-directed *exo*-methylene formation while attempting to cyclopropanate the MOM protected $\Delta^{6,7}$ olefinic adduct **4.69** (see **Figure 4.18**).

The homomethyl alcohol functionality of **4.144** was subsequently converted to the xanthate ester **4.145** or the homomethyl bromide **4.146** in high yield. No decomposition products were observed during these transformations.

4.8.5.3   Radical Fragmentation of *gem*-Dichlorocyclopropane Adducts

Radical fragmentation of the *gem*-dichlorocyclopropane structure was initially conducted on the xanthate ester **4.145** under thermal initiation conditions (Bu$_3$SnH/AIBN) (**Scheme 4.25**).

4.145   **4.102** R = H   **4.104** R = H
                   4.147 R = Cl   **4.148** R = Cl
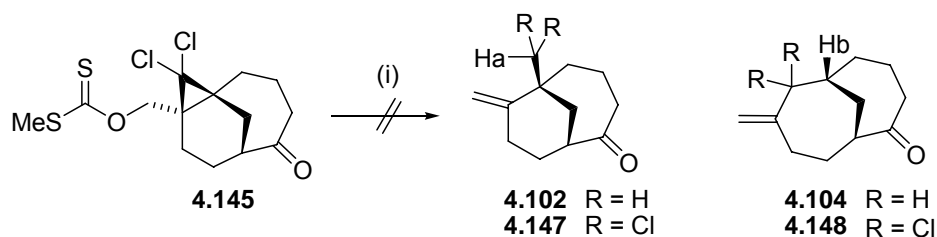
Scheme 4.25   Radical fragmentation xanthate **4.145**.

Reagents: (i) Bu$_3$SnH (3 equiv.), AIBN, toluene, reflux.

Exposure of **4.145** to thermally initiated radical conditions with three equivalents of tributyltin hydride resulted in the generation of a complex mixture of products, as assessed by ^{1}H NMR spectroscopy. No trace of the fully reduced adduct **4.102** (R = H), or the anticipated intermediates derived from cyclopropylcarbinyl fragmentation in the absence of reductive dehalogenation **4.147** and **4.148** were found. Critically, a singlet ascribable to the dichloromethylene proton (**Scheme 4.25**- Ha) arising from C6-C13 *exo* fragmentation could not be discerned. Increasing the quantity of Bu$_3$SnH to ten equivalents did not result in an appreciable improvement in the product distribution or the appearance of the fully dehalogenated adduct **4.102**. It is probable that the rate of xanthate cleavage is slower than the reductive

dehalogenation of the *gem*-dichlorocyclopropane substituents, resulting in the possibility of alternative cyclopropyl fragmentation pathways.

The thermally initiated radical fragmentation of bromo *gem*-dichlorocyclopropane **4.146** in the presence of excess tributyltin hydride and AIBN was successful in regioselectively cleaving the cyclopropane bond, as assessed by ^{1}H NMR spectroscopy. Disappointingly, the exclusive product isolated from this reaction was assigned as the ring expanded adduct **4.148**, contaminated with co-eluting stannane residues (**Scheme 4.26**).
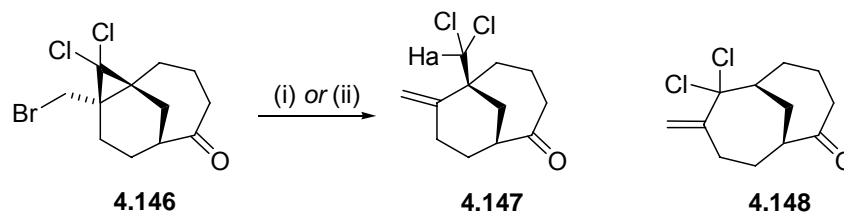
Scheme 4.26. Radical fragmentation of alkyl bromide **4.146.**

Reagents and yields: (i) Bu$_3$SnH (5 equiv), AIBN (5 mol %), toluene, 80°C, **4.148**, 100% conversion *via* ^{1}H NMR; (ii) Zn (10 equiv), cat. AcOH, EtOH, reflux, **4.148**, 83%.

The reaction of **4.146** with activated zinc powder, in the presence of a trace amount of acetic acid, similarly delivered near exclusive formation of the *endo*-fragmentation adduct **4.148**. A minor product was also observed under these reactions conditions, with similar polarity and elution characteristics to **4.148**. However, this adduct did not exhibit the anticipated singlet ascribable to the dichloromethylene proton Ha of **4.147** and is presumably derived from mono-dechlorination of the adduct **4.148**.

4.9   Summary of Cyclopropylcarbinyl Radical Fragmentations Within the Bicyclo[4.3.1]decane Framework

A succinct and high yielding route to differentially substituted 1,3-dienes was developed that utilised an EYCM reaction between ethylene and a readily prepared alkyne. These diene systems were advanced to form homomethyl IMDA triene precursors that were subjected to thermal cyclisation conditions.

In contrast to the 7-alkoxy-triene systems investigated in **Chapter Three**, the homomethyl IMDA adducts were not prone to $\Delta^{6,7} \rightarrow \Delta^{7,8}$ olefinic migration when conducted under thermal conditions allowing the clean isolation of $\Delta^{6,7}$-bridgehead olefinic adducts. These results, in conjunction with the observed acid stability of the homomethyl IMDA adducts, lends support to the hypothesis that the previously observed migration proceeded *via* a transient oxonium-intermediate.

Investigation of the radical-induced fragmentation of the bicyclo[4.1.0]heptanylmethyl system embedded within a bicyclo[4.3.1]decane framework revealed that ring expansion adducts, derived from a C6-C7 *endo*-fragmentation, dominate adducts derived from the desired C6-C13 *exo*-fragmentation.

Various synthetic approaches including modification of the reaction conditions, modification of the substrate and endeavours to favourably stabilise the primary radical derived from *exo* cleavage were unsuccessful.

The preferential *endo*-fragmentation of **4.99** and it's related analogues (**4.134** and **4.146**) can probably be traced to a number of factors. These include, principally, the stability of the tertiary intermediate **4.103** following endocyclic cleavage and possibly the conformational pre-alignment of the C12 SOMO radical orbital with the C6-C7 *endo* cyclopropane bond.

4.10   References for Chapter Four

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Chapter Five

Summary of Research and Future Studies

While the total synthesis of the nakafuran and florlide families of natural products has not been achieved, a number of key issues have been addressed. The information gained from this research allows some conclusions to be reached and permits the development of a refined synthetic strategy directed towards total syntheses of these natural products.

5.1   Nakafuran Synthesis – Summary

It was established that the type II IMDA reaction provides a convenient and succinct route to the preparation of bicyclo[4.3.1]decene ring systems with variable functionality at the C7 and C8 carbons from acyclic precursors (**Figure 5.1**).

Preparation of vinyl stannane coupling fragments *via* the hydrostannylation of their respective alkyne precursors was investigated under radical initiated, palladium-catalysed, stannylcupration and hydroiodination/transmetallation protocols. These differing methodologies were observed to give products with distinct regio- and stereoselectivities.

Preparation of the analogous vinyl iodide species *via* hydroiodination with the reagent derived from TMS-Cl/NaI/H_2O was hampered by competing olefinic migration, halogenation reactions and low yields. The use of the reagent derived from TMS-I/MeOH at low temperature was found to circumvent many of these problems, proceeding in high yield, to give excellent regio-, chemio- and stereoselectivities.
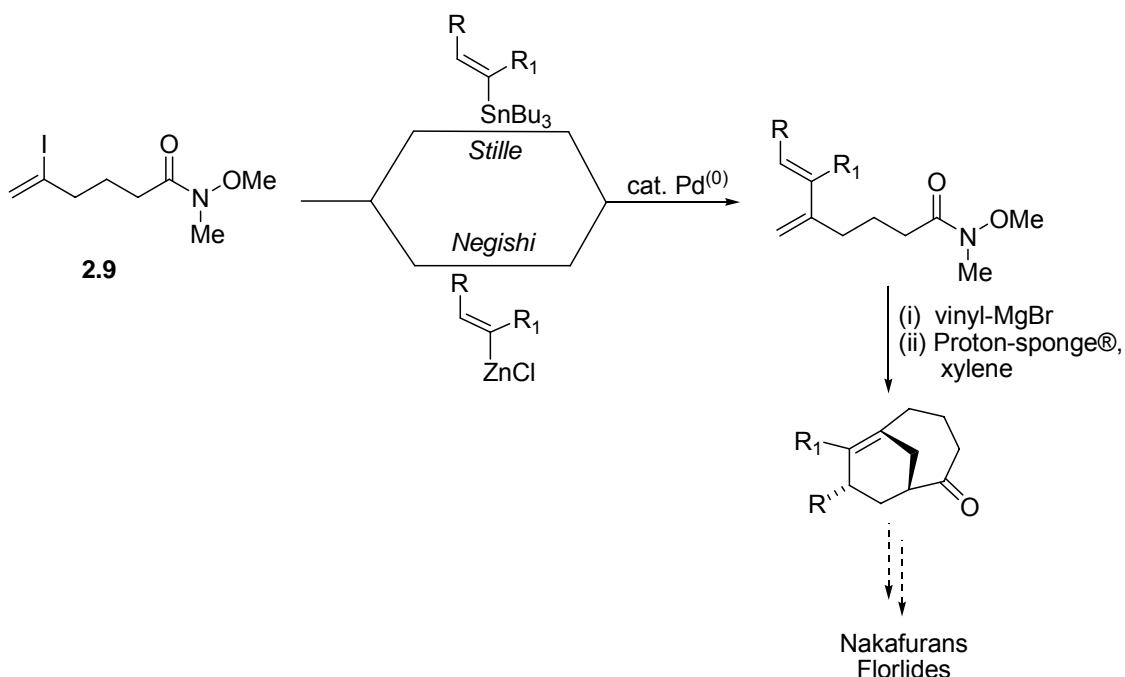
Figure 5.1   Development of a succinct route to bicyclo[4.3.1]decene ring systems.

The prepared fragments were successfully coupled utilising palladium-catalysed cross-coupling methodology to give access to the desired diene amide systems. A remarkably high yielding one-pot synthesis of substituted diene systems *via* a Negishi coupling protocol was developed. This organozinc methodology constitutes a considerable advance over the analogous organotin (Stille) coupling methodology in terms of the preparation of the coupling partners, purification issues and synthetic yield.

Whilst the IMDA cyclisation of the above triene systems proceeded under thermal conditions in high yield, the 7-alkoxy-cyclised adducts were susceptible to a facile $\Delta^{6,7} \rightarrow \Delta^{7,8}$ olefinic migration in the presence of trace amounts of acid. This isomerisation hindered the planned synthetic approach. The rigorous elimination of acidic species with greater than stoichiometric quantities of Proton-sponge® enabled the isolation of the desired $\Delta^{6,7}$ IMDA adduct with excellent regiocontrol. However, somewhat disappointingly, neither the $\Delta^{6,7}$ IMDA adduct, the $\Delta^{7,8}$ IMDA adduct nor cyclopropanated derivatives could be coerced to undergo selective alkylation at the C3 carbon centre.

Molecular modelling studies performed upon the IMDA adducts implied that a critical difference existed between these bicyclo[4.3.1]decene species and the bicyclo[5.3.1]undecene ring system from which analogue was drawn when formulating the original synthetic plan. Specifically, the

7-methoxy-IMDA adduct **1.68** adopts a unique conformational geometry in which unfavourable carbonyl-hydrogen dihedral angles thwart the regioselective deprotonation under kinetic conditions or the establishment of the anticipated non-bridgehead enolate under thermodynamic conditions.

5.2   Florlide Synthesis - Summary

The observation that $\Delta^{6,7} \rightarrow \Delta^{7,8}$ olefinic migration occurred with the 7-alkoxy substituted IMDA adducts **1.68** and **1.79** and not with the vinyl IMDA adduct **3.40** lead to the hypothesis that the intermediacy of a C7-oxonium ion may facilitate this rearrangement with relief of bridgehead torsional strain providing the thermodynamic impetus for this isomerisation. Following this rationale, an intermediate was envisaged (**3.70**) that saw substitution of the 7-alkoxy moiety by a homomethyl group, which was anticipated to display diminished tautomeric ability (**Figure 5.2**).
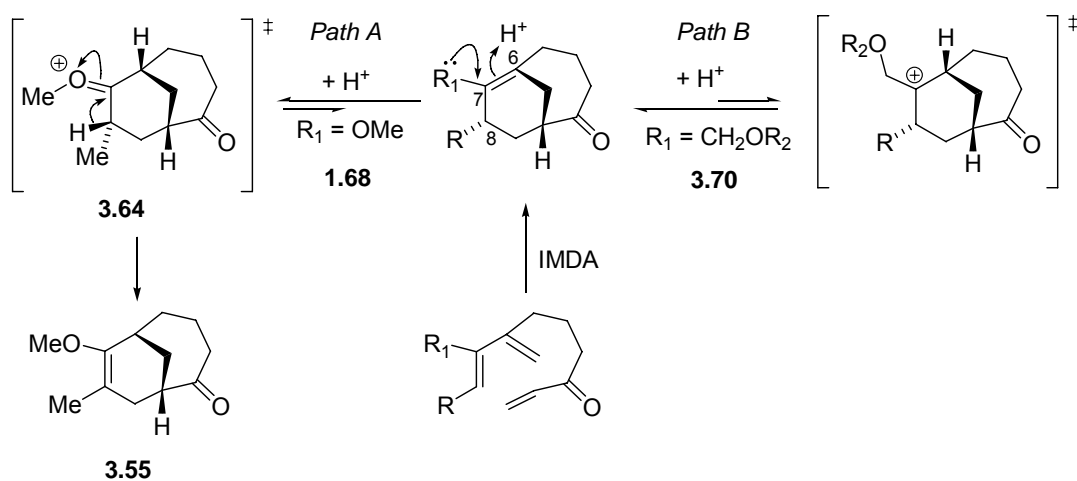

Figure 5.2   Olefinic migration *via* an oxonium intermediate *(Path A) vs* carbocation formation for the homomethyl analogue *(Path B)*.

Initial attempts to synthesise these homomethyl triene precursors *via* either Stille or Negishi coupling methodology were hampered by decomposition of the allylic coupling fragments. An alternative strategy that made use of recently developed enyne metathesis chemistry, however, was successful in generating these 1,3-disubstituted diene systems in excellent yield from simple alkyne precursors. The subsequently derived $\Delta^{6,7}$ IMDA adducts were shown to be considerably more stable to acidic conditions than the analogous 7-alkoxy-derivatives. This synthetic

observation lends support to the postulated involvement of an oxonium-type intermediate (**3.64**) in the facile olefinic migration previously observed.

The homomethyl IMDA adducts were advanced through subsequent synthetic steps to generate a range of $\Delta^{6,7}$-cyclopropane derivatives. Ultimately however, the *exo*-cyclopropylcarbinyl fragmentation, devised to establish the 6-methyl-bicyclo[4.3.1]decane ring system **4.102**, was not synthetically viable. The predominant formation of the bicyclo[4.4.1]undecane system **4.104** *via* *endo*-cleavage was observed, presumably due to preferential stabilisation afforded by the *endo*-tertiary radical relative to the *exo*-primary radical (**Figure 5.3**).
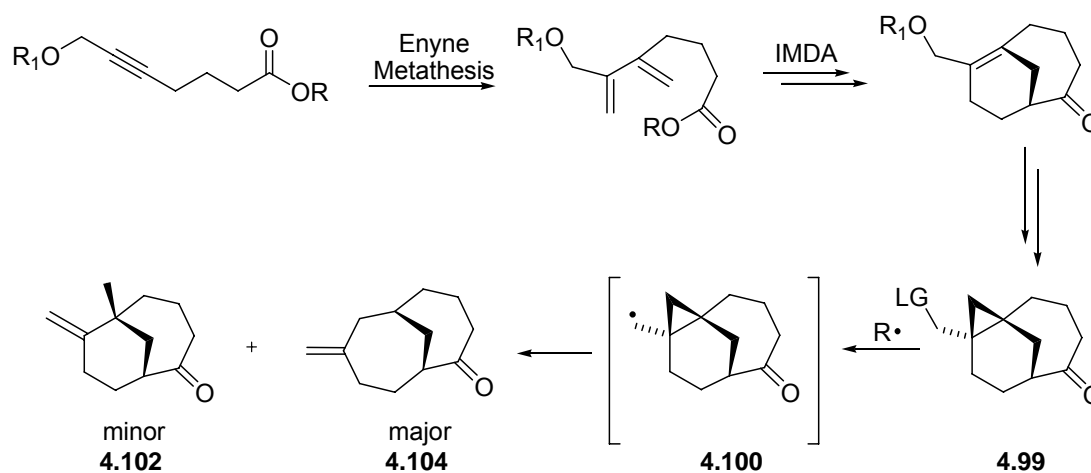
Figure 5.3   Enyne metathesis and cyclopropylcarbinyl fragmentation.

Molecular modelling studies performed upon the radical intermediate **4.100**, in conjunction with literature studies on the parent bicyclo[4.1.0]heptanylmethyl radical **4.116**, indicated a preference for *endo*-bond cleavage.[1]

Synthetic efforts to increase the ratio of **4.102** relative to **4.104** *via* modification of the reaction conditions and modification of the substrate to favourably stabilise the primary radical derived from *exo*-cleavage were unsuccessful.

5.3   *Nakafuran Synthesis – Future Studies*

5.3.1   Side Chain Pre-Inclusion

From the preceding studies it is evident that, in order to complete the synthesis of the nakafuran systems it will be necessary to incorporate the C3 side-chain functionality prior to the type II IMDA reaction. With the pre-inclusion of appropriate substituents upon the diene **1.70**, this strategy should be applicable to the installation of both the desired furan and C6-bridgehead methyl functionality, intersecting with the originally envisaged retrosynthetic plan (**Figure 5.4**).
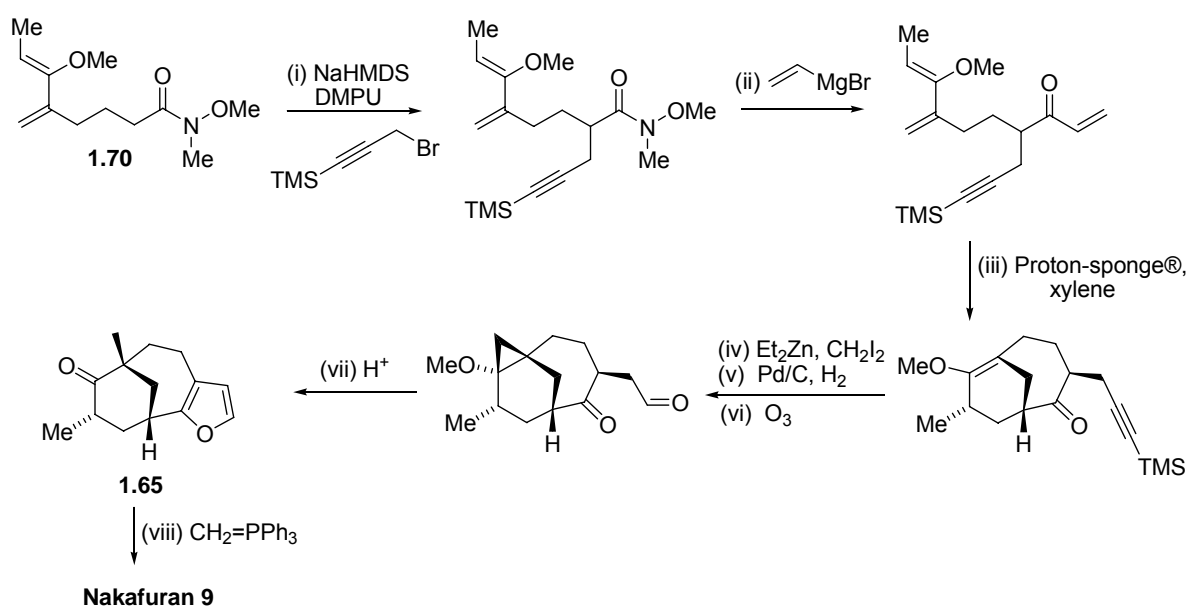
Figure 5.4   Proposed modified synthetic route incorporating pre-inclusion of the C3 sidechain.

5.3.2   Diene-Dienophile Transposition

The synthetic problems encountered within this thesis, to a large extent, were derived from the need to regioselectively install the $\Delta^{6,7}$ bridgehead olefin and then subsequently to effect an *exo*-bond selective cyclopropyl-ring opening to establish the C6 bridgehead methyl group. In theory, both of these issues could be eliminated by the transposition of the diene and dienophile functionality within the triene tether.

Figure 5.5   Proposed diene-dienophile transposition route.

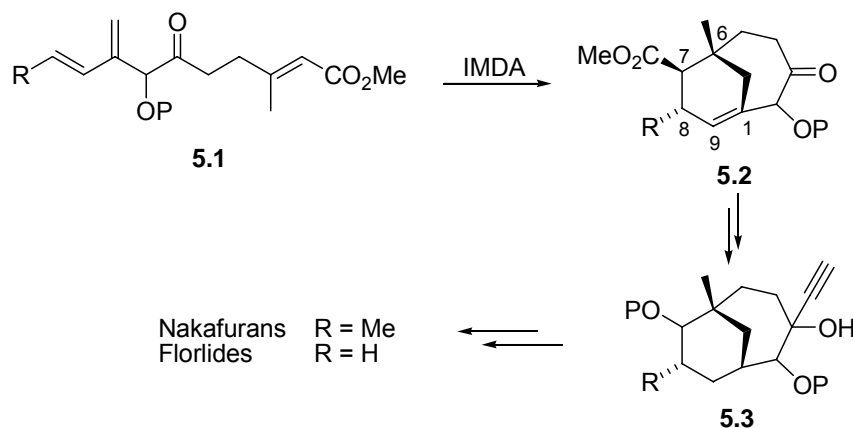As depicted in **Figure 5.5**, an IMDA cyclisation of the triene system **5.1** would generate the bicyclo[4.3.1]decane system with a $\Delta^{1,9}$ bridgehead olefin (**5.2**) whilst simultaneously installing the required C6 quaternary methyl group. As the $\Delta^{1,9}$-olefinic bond would ultimately be hydrogenated, *en route* to the targeted natural products, isomerisation of this intermediate would not present a synthetic concern. The installation of the furan moiety could be envisaged to proceed *via* a similar synthetic sequence to that utilised by White *et al.* in the reported synthesis of 2,3-dihydropallescensin **1.35** (**Scheme 1.5**).[2]

In support of this proposed synthetic route, recent work by Chan *et al.* demonstrated the feasibility of an IMDA reaction on a similar system (**5.4**) to give the $\Delta^{1,9}$-olefinic adduct (**5.5**) as a single product in high yield. No isomerisation of the olefinic bond was reported (**Figure 5.6**).[3]
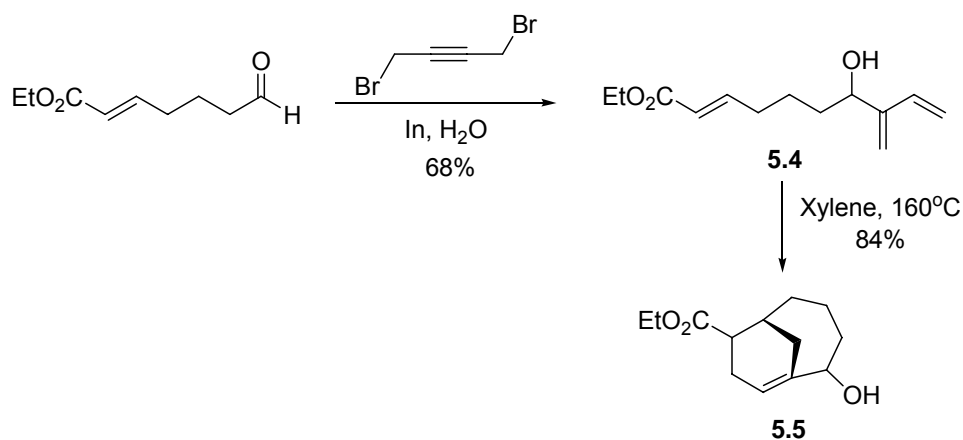

Figure 5.6   Illustration of the principle of diene-dienophile transposition from the work of Chan *et al.*

5.4 *Florlide Synthesis – Synthetic Application of the endo-Selective Cleavage*

Bicyclo[4.4.1]undecane ring systems are rare in nature. To the best of the author's knowledge only four natural products have been isolated that contain this structural motif within their carbocyclic framework. The unusual cyclocitrinols (**5.6-5.9**), examples of C25 steroids containing a bicyclo[4.4.1] A/B ring system, were isolated from both the terrestrial and marine fungus *Penicillium citrinum*[4] and the terrestrial fungus *Penicillim janthinellum*[5] (**Figure 5.7**). The absolute stereostructure was established *via* a combination of X-ray crystallographic analysis and application of modified Mosher's method[6] upon the acetyl adduct **5.8**, resulting in a revision of the previously ascribed structure.[7] A tentative biosynthesis was proposed based upon the rearrangement of ergosterol 5,8-endoperoxide which co-occurred in the fermentation broth.[5]

(+) **5.6** cyclocitrinol A (+) **5.7** R = H isocyclocitrinol A (+) **5.9** Neocyclocitrinol
(+) **5.8** R = Ac 22-acetylisocyclocitrinol
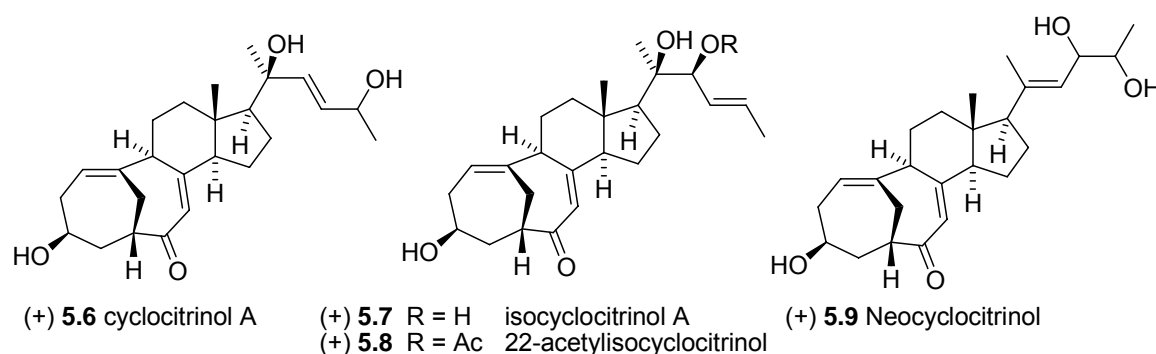
Figure 5.7 Novel steroids containing a bicyclo[4.4.1]undecane ring system.

Given the demonstrated tendency of the bicyclo[4.1.0]heptanylmethyl radical **4.100** to ring open *via* an *endo*-cleavage it may be possible to incorporate this rearrangement in the design of a concise synthesis of these novel steroids (**Figure 5.8**).
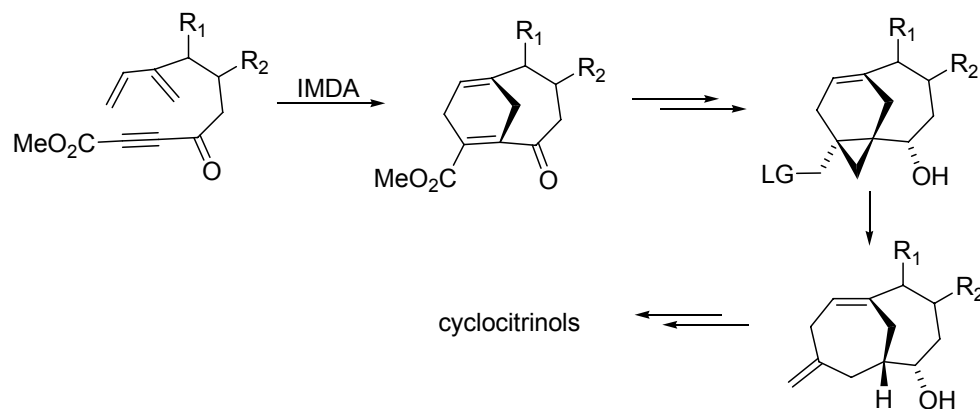
Figure 5.8 Potential application of radical *endo*-cleavage to the synthesis of the cyclocitrinols.

5.5   *References for Chapter Five*

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Chapter Six

Experimental Details

6.1   General Experimental

6.1.1 Reagents and Solvents

Reagents and solvents used in reactions were purified according to well-established procedures.[1] In particular, anhydrous tetrahydrofuran (THF) and diethyl ether (Et$_2$O) were freshly distilled from sodium benzophenone ketyl immediately prior to use. Toluene, dichloromethane (CH$_2$Cl$_2$), pyridine, *N,N*-diisopropylamine, acetonitrile (MeCN), triethylamine (NEt$_3$), *N,N*-diisopropyl–*N*-ethylamine (Hünig's base), 1,2-dimethoxyethane (DME), hexamethylphosphoramide (HMPA) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(*1H*)-pyrimidinone (DMPU) were freshly distilled from calcium hydride. 1,2-Dichloroethane (DCE) was distilled from phosphorous pentoxide and stored over 4Å molecular sieves under an argon atmosphere. Acetone was dried over activated 4Å molecular sieves for 24 h, then distilled into a dry vessel under an argon atmosphere. *N,N*-Dimethylformamide (DMF) and dimethylsulfoxide (DMSO) were sequentially dried over two batches of freshly activated 4Å molecular sieves (2 x 24 h), before being stored under argon over a third batch of 4Å molecular sieves. Prior to use, the DMF solvent was evacuated (~0.1 mmHg) for 15 min to remove residual dimethylamine. Anhydrous methanol and ethanol were distilled from their respective magnesium alkoxides and stored over 4Å molecular sieves under an argon atmosphere. Dry 1-methyl-2-pyrrolidinone (NMP) was purchased from Aldrich, stored under nitrogen or argon and used without further purification. Petroleum ether used consisted of the fraction with a boiling range of 50-70°C.

Solutions of *n*-butyllithium and *t*-butyllithium in hexanes were titrated in THF with standardised 2-butanol, using 1,10-phenanthroline as an indicator.[2] Solutions of lithium-, sodium- and potassium bis(trimethylsilyl)amide were titrated with 2-butanol using 2,2'-bipyridine as an indicator[3]. Copper(I) iodide was purified by refluxing in CH$_2$Cl$_2$ in a Soxhlet apparatus for 24 h, and stored in the dark under an argon atmosphere. Trimethylsilyl chloride (TMSCl) and boron

trifluoride diethyl etherate ($BF_3.OEt_2$) were distilled from calcium hydride. Chloromethyl methyl ether (MOM-Cl) was prepared according to the literature procedure[4] and stored in the freezer.

The palladium catalysts [$Pd(PPh_3)_2Cl_2$, $Pd(PPh_3)_4$, $Pd_2(dba)_3$, $Pd(AsPh_3)_2Cl_2$ and $Pd(MeCN)_2Cl_2$],[5,6] $CuBr.SMe_2$[6] and $Mo(tert\text{-}BuNC)_3(CO)_3$[7] were prepared according to literature procedure. Copper thiophene carboxylate (CuTC) was prepared *via* the method of Liebeskind *et al.*[8] 2,2'-Azobisisobutyronitrile (AIBN) was prepared according to literature methods and stored in the freezer.[9] The Dess-Martin periodinane (DMP) was prepared by the modified methods of Ireland and Liu.[10] Diethylzinc (Et_2Zn) was prepared as detailed by Foster and Cole-Hamilton[11] on a 0.2 mol scale to yield pure diethylzinc (20.77 g, 0.168 mol, 84%) which was dissolved in distilled toluene to give a ~1.2 M stock solution and stored at -8°C under Ar. 1,1-Diethoxy-2-bromoethane and 1,1-diethoxy-2-iodoethane were prepared *via* literature methods.[12,13] The MOM, THP and benzyl protected acetaldehydes **3.79a-3.79c** were prepared *via* ozonolysis of their respective bis-protected-1,4-but-2-ene precursors.[14] Grubbs 2nd generation catalyst, **4.25** was purchased from Strem or Aldrich and stored under an argon atmosphere at 0°C. Allyl(chloro)dimethylsilane was prepared *via* the method of Chihi and Weber.[15]

Unless otherwise stated, all reactions were performed in oven- or flame-dried glassware under an atmosphere of argon or nitrogen with the reaction temperature referring to the external bath temperature. All organic extracts were washed with brine and dried over anhydrous sodium sulfate. After filtration of the solutions to remove solids, the solvents were evaporated under reduced pressure on a Büchi rotary evaporator (~12 mmHg). When necessary, a high-vacuum pump (~0.1 mmHg) was used to remove the last traces of solvent from purified compounds. Evaporation under an inert atmosphere was achieved using a three way tap connected to a vacuum source and an inert atmosphere.

6.1.2 Chromatography and Small-Scale Distillation

Analytical thin-layer chromatography (TLC) was conducted on aluminium-backed Merck Kieselgel KG60F$_{254}$ silica plates, plastic-backed Macherey-Nagel Polygram® SIL G/UV$_{254}$ silica plates or Fluka aluminium-backed alumina type H plates. The developed TLC plates were visualised under short- or long-wave ultraviolet (UV) light, and/or exposure to iodine in a vapour chamber followed by staining with aqueous potassium permanganate or a phosphomolybdic acid (PMA) dip.

Flash chromatography was routinely carried out upon Merck Silica 60 (40-63 μm) using the procedure of Still *et al.*[16] For acid sensitive compounds, chromatography was performed with 1% NEt₃ in the eluting solvent on basified silica, prepared by the addition of NEt₃ to a slurry of silica in the eluting solvent until the odour of NEt₃ could be discerned. Alumina flash chromatography was performed on Laporte Alumina, Grade H (100-200 mesh). Solvents used for chromatography were purified by simple distillation.

Small scale (bulb-to-bulb) distillation was performed under low vacuum (~10-12 mmHg) or high vacuum (~0.1 mmHg) in a Büchi Kugelrohr apparatus.

6.1.3 Spectroscopic Techniques

The ^{1}H NMR spectra were obtained on either a Varian UNITY 300 or Varian INOVA 500 spectrometer, operating at 300 MHz and 500 MHz respectively at 23°C. The ^{13}C NMR were recorded on a Varian UNITY 300 NMR spectrometer operating at 75 MHz, typically with a delay (d1) of 1-3 seconds. 2D NMR experiments were carried out on a Varian INOVA 500 spectrometer fitted with an Inverse Detection Probe and Pulsed Field Gradient Driver, operating at 500 MHz. Assignments of H and C signals were determined on the basis of COSY, TOCSY, HSQC, HMBC or CIGAR experiments. In some cases difference-NOE or 1D NOESY experiments were employed if uncertainty regarding structural assignments remained. Due to non-first order coupling between the diastereotopic protons in the bicyclic[4.3.1]carbocyclic adducts, peaks are listed over the range which they occur in ppm and are characterised according to the following designations: s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet), m (multiplet) or combinations thereof.

Chemical shifts are reported in parts per million (ppm) on the δ scale, and were referenced to residual protonated solvent peaks: CDCl₃ referenced to C*H*Cl₃ at δ_H 7.25 and *C*DCl₃ at δ_C 77.0; C₆D₆ at δ_H 7.27 and δ_C 128.3. Tetramethylsilane (TMS) was used as an internal standard at δ_H 0.0. For acid sensitive compounds 0.2% v/v C₅D₅N (deuteriopyridine) was added to the CDCl₃ solvent.

Infrared spectra (IR) were obtained on a Shimadzu FTIR-8201 PC spectrometer. Spectra of oils were run neat on KBr plates. Solid materials were dissolved in a minimum of CH_2Cl_2, applied to

the plates as a solution and then evaporated under a N_2 stream. Values of selected peaks are reported in wavenumbers (cm^{-1}).

High Resolution Electron Impact Mass Spectra (HREIMS) was conducted on a Kratos MS80RFA Mass Spectrometer operating in electron ionisation (EI) mode at 70 eV, using a 4 kV accelerating potential and 250°C source temperature.

High Resolution Electrospray Ionisation Mass Spectra (HRESIMS) were obtained from a Micromass LCT spectrometer, with a probe voltage of 3200 V and temperature of 150°C. A nebuliser gas flow of 160 L/hr and desolvation gas flow of 520L/hr were used in conjunction with a source temperature set at 80°C. The carrier solvent was 50% MeCN/H_2O at 20 μL/min (for direct injection mode). A 10 μL injection of sample was made from a 10 μg/mL solution. Positive ESI mass spectra were recorded after the addition of sodium iodide or formic acid to the sample prior to analysis. Only molecular ions (M^+) and other major fragments are reported.

Melting points (mp) were obtained using a Büchi 510 Cambridge Instruments Gallen™ III hot stage melting point apparatus and are uncorrected.

6.1.4 Nomenclature

The nomenclature used in this thesis is in accordance with the IUPAC recommendations.[17] In some circumstances, due to the need for consistency and clarity, the naming of some compounds described in this dissertation deviates from IUPAC nomenclature. This in no way creates an ambiguity in the naming of compounds, and is in accord with the IUPAC recommendations in such a situation. The bicyclo[4.3.1]dec-6-en-2-one core **3.40** will be used as the basis for all derivatives regardless of functional groups.
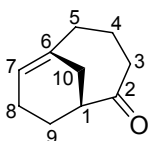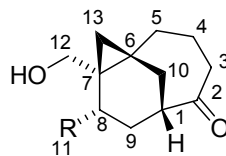
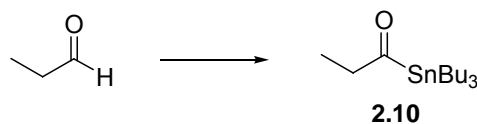**3.40**   **4.74**

For example **4.74** (R = H)

IUPAC: 3-Hydroxymethyl-tricyclo[4.4.1.0^{1,3}]undecan-7-one

This Thesis: 7-Hydroxymethyl-tricyclo[4.3.1.1^{6,7}]undecan-2-one

6.2   Experiments Described in Chapter Two

**1-(Tributylstannyl)propan-1-one (2.10)**

2.10

Acyl stannane **2.10** was prepared *via* the method of Migita *et al.*[18] in variable yield (20-54%) and stored under an Ar atmosphere protected from light at -8°C. This material was unstable with respect to light, oxygen and prolonged heating. Values from the ^{1}H NMR spectrum of the distilled adduct were in close agreement with the reported values.[18]

^{1}H NMR (500 MHz, CDCl$_3$): δ 0.87-0.94 (m, 9H), 1.28-1.39 (m, 6H), 1.47-1.57 (m, 9H), 1.47-1.67 (m, 6H), 2.61 (q, *J* = 7.3 Hz, 2H).

LRMS (GCMS/EI): calc. C$_{15}$H$_{32}$OSn: 348.1475; obs. 291 (C$_{11}$H$_{23}$OSn; M$^+$ - *n*-Bu, calc. 291); 307 (C$_{11}$H$_{23}$O$_2$Sn; oxidation product EtCO-O-SnBu$_3$ – *n*-Bu, calc. 307).

1-Phenylbutane-1,2-dione (2.17) and 1-(4-Methoxyphenyl)butane-1,2-dione (2.18)

2.10   R = H   **2.17**
                                                                              = OMe   **2.18**
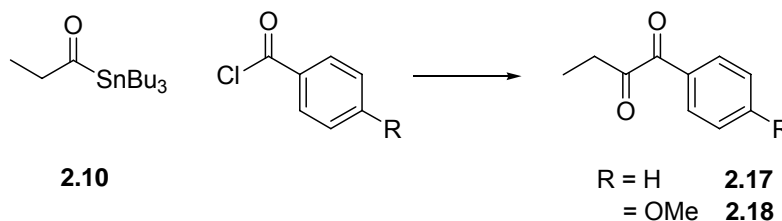
Acyl stannane **2.10** (200 mg, 0.58 mmol, 1.1 equiv), benzoyl chloride (74 mg, 0.52 mmol) and Pd(PPh$_3$)$_2$Cl$_2$ (20 mg, 5 mol %) were dissolved in toluene (5 mL) in a Pyrex tube. The mixture was subjected to a freeze/pump/thaw cycle (x 3), sealed under an argon atmosphere and heated at 100°C for 16 h protected from light. Upon the observed precipitation of palladium black within the solution, the tube was carefully opened, quenched with saturated aqueous KF solution and extracted with Et$_2$O (10 mL x 3). The solvent was removed under reduced pressure and the residue purified by flash chromatography on silica gel, eluting with 5% EtOAc/petroleum ether, to give the α,β-diketone **2.17** as a colourless oil (34.5 mg, 66%).

An identical method was used to prepare the methoxy-adduct **2.18**: Acyl stannane **2.10** (200 mg, 0.58 mmol, 1.1 equiv), 4-methoxybenzoyl chloride (89 mg, 0.52 mmol) and Pd(PPh$_3$)$_2$Cl$_2$ (20 mg, 5 mol %) were reacted in toluene to give, after purification, **2.18** as a colourless oil (51.2 mg, 51%).

2.17: ^{1}H NMR (500 MHz, CDCl$_3$): δ 1.19 (t, J = 7.2 Hz, 3H), 2.91 (q, J = 7.2 Hz, 2H), 7.49 (t, J = 7.8 Hz, 1H), 7.63 (m, 2H), 7.97 (d, J = 8.4 Hz, 2H).[19]

2.18: ^{1}H NMR (500 MHz, CDCl$_3$): δ 1.17 (t, J = 7.3 Hz, 3H), 2.89 (q, J = 7.3 Hz, 2H), 3.87 (s, 3H), 6.95 (d, J = 8.9 Hz, 2H), 7.96 (d, J = 8.8 Hz, 2H).

1-Methoxypropyne (2.12)

2.12
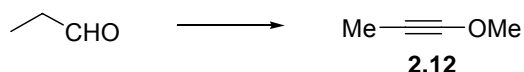
Adapted from the method of Nooi and Arens.[20]

A stirred solution of distilled propionaldehyde (108.2 mL, 1.5 mol) and methanol (60.8 mL, 1.5 mol) was saturated with anhydrous HCl gas (3 equiv) under cooling in an ice/NaCl salt bath (-10°C). Upon completion, the organic layer was separated from the lower aqueous layer and dried over CaCl$_2$ and filtered to afford a light yellow oil (150.9 g, 93%). This liquid was stirred vigorously at 0°C in a flask equipped with a pressure-equalising dropping funnel and a drying tube. Bromine (69.5 mL, 1.35 mol, 1 equiv), purified by shaking with conc. sulfuric acid, was added sufficiently slowly to allow decolourisation of the solution. The HCl gas generated was vented through the drying tube. Following complete addition, a small amount of anhydrous CaCl$_2$ was added and remaining HCl gas removed by gentle evacuation at 0°C. The light yellow solution was filtered to remove residual CaCl$_2$ and added over 30 min to a refluxing solution of *N,N*-diethylaniline (330 mL, 2.0 mol, 1.5 equiv) and benzene (200 mL). This solution was heated at 120°C for 12 h, resulting in the formation of a black solution. The cooled reaction mixture, which solidified, was quenched by vigorously shaking with a mixture of ice (600 g), conc. aqueous HCl solution (150 mL) and Et$_2$O (200 mL). The aqueous phase was extracted with Et$_2$O (3 x 150 mL) and the combined organic fractions washed successively with 2 M aqueous HCl solution (100 mL) until the aqueous extract was colourless, with water (100 mL) until neutral and dried over MgSO$_4$. Evaporation of the excess organic solvent was performed *in vacuo* such that the bath temperature did not exceed 30°C. The resultant crude product was fractionally distilled under reduced pressure through a Vigreux column to separate the *cis-* and *trans*-1-methoxy-2-bromopropenes (*cis*: 45-48°C / 20 mmHg; *trans*: 56-62°C / 20 mmHg). Fractions composed primarily of the *trans* species, as assessed by ^{1}H NMR spectroscopy, were combined and added to freshly powdered KOH (5 equiv) and heated with care to effect distillation until the reaction vessel was dry. A light vacuum was applied to ensure complete removal of the distillate. The received fractions were dried over MgSO$_4$ and redistilled in a well-lagged 30 cm Vigreux column to yield a colourless liquid (34.4 g, 51% over 4 steps).
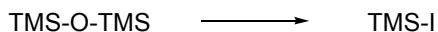
bp: 66.5 / 760 mmHg; (lit. 65.7-66.3°C / 760 mmHg).[20]

FTIR (film, KBr, cm^{-1}): 2946, 2934, 2287, 1457, 1260, 1175, 1055, 962, 722.

^{1}H NMR (500 MHz, CDCl$_3$): δ 1.70 (t, J = 1.5 Hz, 3H), 3.79 (d, J = 1.5 Hz, 3H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 1.2, 31.4, 64.9, 89.6.

Iodotrimethylsilane[21]

<div align="center">TMS-O-TMS ⟶ TMS-I</div>


A flame-dried two-necked 100 mL flask equipped with a magnetic stirring flea, a wide bore reflux condenser and a solid addition tube was assembled such that all glass joints were wrapped internally with Teflon tape. The reaction vessel was charged with aluminium powder (5.6 g, 0.21 mol), hexamethyldisiloxane (21.2 mL, 0.1 mol) and sparged with argon gas for 2 min. The mixture was heated to 60°C and solid iodine (50.8 g, 0.2 mol) was introduced in small portions such that the vigorously exothermic reaction was controlled. Upon complete addition, the temperature was increased to 140°C and the solution refluxed for 1.5 h. The mixture was cooled sufficiently to allow replacement of the addition tube with a one-piece distillation apparatus, and the reflux condenser with a glass stopper. Distillation was effected *via* heating with a flame to yield a colourless distillate which was collected over freshly abraded and cut copper foil pieces. Upon completion the collection vessel was sealed with a Telfon tape wrapped glass stopper and the iodotrimethylsilane (29.5 g, 74%) stored in the freezer wrapped in aluminium foil over self-indicating granular silica desiccant.

CAUTION: Iodotrimethylsilane is moisture-sensitive, light-sensitive and extremely corrosive. It should be handled with care, out of direct sunlight and ideally in a darkened environment. The reaction vessel used to prepare TMSI should be carefully quenched at 0°C with the portion-wise addition of ice chips which results in a vigorous exotherm and the evolution of acidic gases.

5-Hexyn-1-ol (2.53)
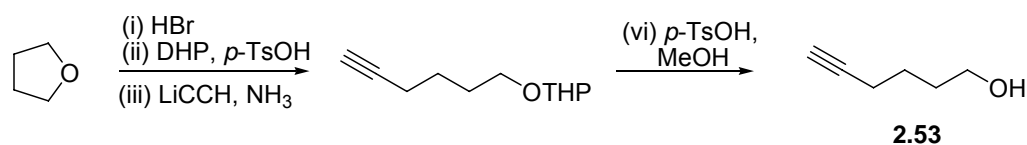
Prepared *via* the addition of lithium acetylide to 2-(4-bromobutoxy)-tetrahydro-2*H*-pyran at -33°C on a 1.25 mol scale as described in detail by Brandsma.[22] Hydrolysis of the THP protecting group was performed in aqueous methanol with catalytic *p*-TsOH. Work-up and distillation yielded **2.53** as a colourless oil. The yield was 87% for the 3 steps.

2-(Hex-5-ynyloxy)-tetrahydro-2*H*-pyran

FTIR (KBr, cm^{-1}): 3298, 2943, 2870, 1439, 1354, 1200, 1138, 1123, 1076, 1034, 988, 633.

^{1}H NMR (500 MHz, CDCl$_3$): δ 1.49-1.87 (m, 14H), 1.95 (t, *J* = 2.5 Hz, 2H), 2.23 (td, *J* = 7.0, 2.5 Hz, 2H), 3.41 (dt, *J* = 10.0, 6.0 Hz, 1H), 3.48-3.53 (m, 1H), 3.76 (dt, *J* = 10.0, 6.0 Hz, 1H), 3.86 (m, 1H), 4.58 (t, *J* = 4.0 Hz, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 18.1, 19.5, 25.2, 25.4, 28.7, 30.6, 62.1, 66.7, 68.3, 84.2, 98.6.
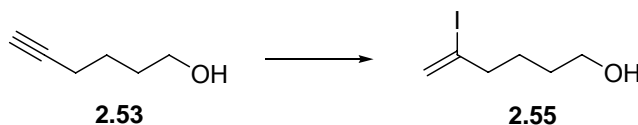
5-Hexyn-1-ol (2.53)[22]

bp: 76-77°C / 12 mmHg; (lit. 73-75°C / 15 mmHg).

FTIR (film, KBr, cm^{-1}): 3298, 2943, 2870, 1435, 1456, 1063, 1038, 991, 640.

^{1}H NMR (500 MHz, CDCl$_3$): δ 1.53-1.64 (m, 2H), 1.65-1.70 (m, 2H), 1.95 (t, *J* = 2.0 Hz, 1H), 2.22 (dt, *J* = 2.5, 7.0 Hz, 2H), 3.66 (t, *J* = 6.5 Hz, 2H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 17.8, 24.5, 31.2, 61.4, 68.4, 84.1.

5-Iodohex-5-en-1-ol (2.55)[23]

Chlorotrimethylsilane (7.77 mL, 0.061 mol) was added dropwise to a solution of dry NaI (9.18 g, 0.061 mol) dissolved in MeCN (80 mL) and the resultant white solution stirred for 5 min. Water (558 μL, 0.0306 mol) was added dropwise to generate a yellow solution, followed after 5 min by the rapid addition of **2.53** (5 g, 0.051 mol). The reaction was stirred for 2 h at room temperature protected from light. The mixture was quenched with a 1:1 solution of saturated aqueous NaHCO$_3$ and saturated aqueous Na$_2$S$_2$O$_3$ and extracted with Et$_2$O (100 mL x 3). The solvents were removed under reduced pressure and the residue purified by flash chromatography on silica gel, eluting with 20% EtOAc/petroleum ether, to give the vinyl iodide **2.55** as a yellow oil, (5.43 g, 47%).
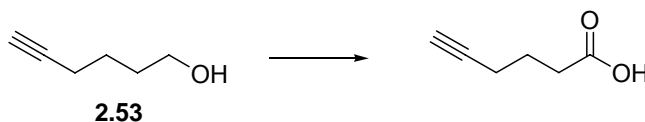
FTIR (KBr, cm^{-1}): 3342, 2939, 2866, 1616, 1429, 1175, 1121, 1063, 893.

^{1}H NMR (500 MHz, CDCl$_3$): δ 1.53-1.60 (m, 4H), 2.40 (t, J = 7.0 Hz, 2H), 3.64 (dt, J = 2.5, 6.5 Hz, 2H), 5.68 (d, J = 1.0 Hz, 1H) 6.02 (t, J = 1.5 Hz, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 25.2, 31.0, 44.8, 62.1, 112.1, 125.5.

HRMS (EI): calc. for C$_6$H$_{11}$IO: 225.9855; obs. 207.9750 (C$_6$H$_9$I; M$^+$ - H$_2$O, calc: 207.9748), 99.0809 (C$_6$H$_{11}$O; M$^+$ - I, calc: 99.0810).

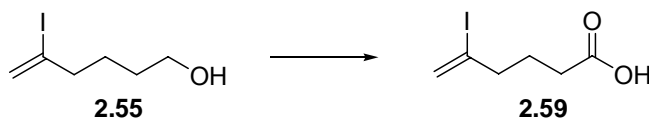### 5-Hexynoic acid[24]

2.53

Alcohol **2.53** (6.22 g, 0.063 mol) in acetone (300 mL) at 0°C was stirred rapidly by mean of a mechanical stirrer whilst Jones' reagent (2.775 M solution) was added dropwise until a noticeable retention of an orange colour (~1.15 equiv) was observed. Excess Jones' reagent was added (0.05 equiv) and the reaction stirred for 2 h at room temperature. The reaction was quenched at 0°C *via* the addition of isopropyl alcohol causing the precipitation of a fine green powder. The mixture was filtered though a plug of Celite® and the solid residues washed with acetone (4 x 25 mL). The combined organic layers were evaporated to yield a green oil, which was dissolved in EtOAc (50 mL) and the solution washed with H$_2$O until colourless. Evaporation yielded 5-hexynoic acid as a colourless oil (7.29 g, 99%).

bp: 74°C / 0.1 mmHg, (lit. 95-96°C / 6 mmHg).[25]

FTIR (KBr, cm^{-1}): 3298, 2947, 2918, 1711, 1414, 1246, 644.

^{1}H NMR (500 MHz, CDCl$_3$): δ 1.85 (m, 2H), 1.97 (t, J = 2.6 Hz, 1H), 2.28 (dt, J = 2.6, 6.9 Hz, 2H), 2.51 (t, J = 7.5 Hz, 2H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 17.5, 23.1, 32.4, 69.2, 82.9, 179.1.

5-Iodohex-5-enoic acid (2.59)

The Jones' oxidation of **2.55** was performed *via* the method described for the preparation of 5-hexynoic acid. The vinyl iodide **2.55** (1.02 g, 4.5 mmol) was converted quantitatively to **2.59** (1.08 g, 100%) which was isolated as a colourless oil.

FTIR (KBr, cm^{-1}): 3433, 2943, 1709, 1620, 1427, 1412, 1276, 1246, 1207, 1173, 899.

^{1}H NMR (500 MHz, CDCl$_3$): δ 1.87 (qn, 2H), 2.37 (t, J = 7.4 Hz, 2H), 2.46 (t, J = 7.1 Hz, 2H), 5.75 (s, 1H), 6.07 (s, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 23.6, 32.0, 43.9, 110.5, 126.3, 179.2.

HRMS (EI): calc for C$_6$H$_9$IO$_2$: 238.9569; obs. 238.9583.

N-Methoxy-N-methylhex-5-ynamide (2.54)
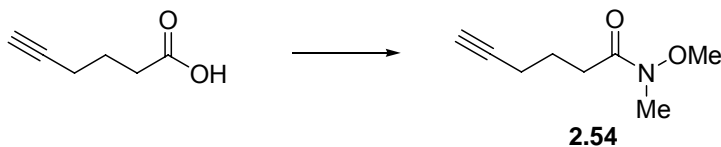
Oxalyl chloride (10.73 mL, 123.1 mmol) was added dropwise to a solution of 5-hexynoic acid (6.90 g, 61.5 mmol) dissolved in CH$_2$Cl$_2$ (250 mL) at 0°C, followed by the addition of 4 drops of dry DMF. The solution was warmed to room temperature and stirred for 1 h protected with a CaCl$_2$ drying tube. The mixture was briefly heated until no more bubbles were observed, cooled to room temperature and the excess solvent and oxalyl chloride removed under reduced pressure to yield a yellow oil. This oil was redissolved in CH$_2$Cl$_2$ (250 mL) and cooled to 0°C before N,O-dimethylhydroxylamine hydrochloride (6.6 g, 67.7 mmol) was added in one portion and stirred into the solution. Pyridine (14.75 mL, 0.148 mol) was added dropwise over 5 min and the reaction mixture allowed to warm to room temperature over 3 h. Evaporation of the solvent gave a white crystalline solid that was dissolved in Et$_2$O/CH$_2$Cl$_2$ (2:1) (300 mL) and the organic layer washed successively with 1 M aqueous HCl solution (3 x 100 mL), saturated aqueous NaHCO$_3$ solution (100 mL) and brine. The solvent was removed under reduced pressure and the residue purified by flash chromatography on silica gel, eluting with 20% EtOAc/petroleum ether, to give amide **2.54** as a colourless oil (7.86 g, 82%).
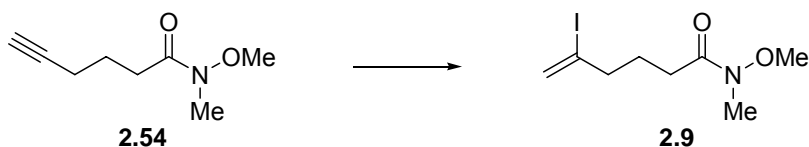
bp: 93-95°C / 0.1 mmHg.

FTIR (KBr, cm^{-1}): 3296, 3254, 2941, 1661, 1418, 1387, 1180, 995, 669.

^{1}H NMR (500 MHz, CDCl$_3$): δ 1.86 (qn, 2H), 1.96 (t, J = 2.5 Hz, 1H), 2.29 (td, J = 2.5, 7.0 Hz, 2H), 2.58 (t, J = 7.0 Hz, 2H), 3.18 (s, 3H), 3.69 (s, 3H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 17.6, 22.9, 30.1, 31.9, 60.9, 68.7, 83.5, 173.6.

HRMS (EI): calc for C$_8$H$_{13}$NO$_2$: 155.0946; obs. 155.0946.

5-Iodo-*N*-methoxy-*N*-methylhex-5-enamide (2.9)

Iodotrimethylsilane (13.6 mL, 0.096 mol, 3 equiv) was added dropwise to a solution of **2.54** (5 g, 0.032 mol) and dry MeOH (3.92 mL, 0.096 mol, 3 equiv) dissolved in CH$_2$Cl$_2$ (125 mL) at -78°C. The mixture was stirred for 20 min at -78°C and then allowed to warm to room temperature wrapped in aluminium foil over 3 h. The mixture was poured into a solution comprised of water (90 mL), saturated aqueous NaHCO$_3$ (90 mL) and saturated aqueous Na$_2$S$_2$O$_3$ (20 mL) and extracted with CH$_2$Cl$_2$ (50 mL x 2). The organic solvent was removed under reduced pressure to give 9.06 g of a crude product composing of **2.9** and **2.54** in a ratio of 4:1 (as assessed *via* ^{1}H NMR spectroscopy). Kugelrohr distillation led to the isolation of the starting alkyne **2.54** (1.23 g, 24%; 95°C/0.1 mmHg) and then pure vinyl iodide **2.9** as an orange oil (6.98 g, 76%, [100 % b.r.s.m.]; 103°C/0.1 mmHg).

From 2.7 via tributyltin-iodine exchange.

A solution of iodine (45.8 mg, 0.18 mmol, 2 equiv) in CH$_2$Cl$_2$ (3 mL) was added dropwise to the stannane **2.7** (40.2 mg, 0.09 mmol) dissolved in CH$_2$Cl$_2$ (10 mL) at 0°C such that the purple colour disappeared after the addition of each drop. Upon the attainment of a faint orange colour the solution was stirred at 0°C for 30 min, at which point TLC indicated complete conversion. The solution was quenched *via* the addition of saturated aqueous Na$_2$S$_2$O$_3$ solution (10 mL) and extracted with Et$_2$O (10 mL x 3). The solvents were removed under reduced pressure and the residue purified by flash chromatography on silica gel, eluting with 30% EtOAc/petroleum ether, to give vinyl iodide **2.9** as a colourless oil (26 mg, 100%).

From **2.59** *via amidation.*

The amidation of **2.59** was performed *via* the method described for the preparation of *N*-methoxy-*N*-methylhex-5-ynamide **2.54**. As such, **2.59** (3.68 g, 15.4 mmol) was first converted to the acid chloride *via* the action of oxalyl chloride (2.68 mL, 30.7 mmol, 2 equiv) and a catalytic amount of DMF (2 drops). Subsequent reaction with *N,O*-dimethylhydroxylamine hydrochloride salt (1.80 g, 18.4 mmol, 1.2 equiv) in the presence of pyridine (3.7 mL, 36.8 mmol, 2.4 equiv), followed by aqueous work-up, resulted in the isolation of **2.9** as a colourless liquid (3.92 g, 89%).

bp: 103-105°C / 0.1 mmHg.

FTIR (KBr, cm^{-1}): 2937, 1665, 1616, 1418, 1387, 1178, 1117, 995, 897.

^{1}H NMR (500 MHz, CDCl$_3$): δ 1.85 (qn, 2H), 2.41 (t, *J* = 7.0 Hz, 2H), 2.46 (t, *J* = 7.0 Hz, 2H), 3.17 (s, 3H), 3.67 (s, 3H), 5.71 (s, 1H), 6.05 (d, *J* = 1.5 Hz, 1H). (500 MHz, C$_6$D$_6$): δ 1.97 (qn, 2H), 2.30 (m, 2H), 2.38 (t, *J* = 7.0 Hz, 2H), 2.95 (s, 3H), 3.10 (s, 3H), 5.65 (s, 1H), 5.81 (s, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 23.4, 29.6, 31.9, 44.2, 61.0, 111.2, 125.7, 173.4.

HRMS (EI): calc. for C$_8$H$_{14}$INO$_2$: 283.0069; obs: 222.9620 (C$_6$H$_9$IO; M$^+$ - N(OMe)Me, calc: 222.9620); 156.1025 (C$_8$H$_{14}$NO$_2$, M$^+$ - I, calc: 156.1025).

Alkyne Hydrostannylation Reactions

The preparation of a number of vinyl stannane species was conducted *via* the hydrostannylation or metallostannylation of their respective alkyne precursors. Four general protocols were utilized as described below. The percentage yields refer to isolated yields of homogeneous material as assessed by ^{1}H NMR spectroscopy and TLC. Additional unique reactions that result in the overall hydrostannylation will be detailed independently.

Protocol A: **Radical Hydrostannylation**[26,27]

(a) Thermal initiation: Bu$_3$SnH (1.1 equiv) and AIBN (0.1 equiv) were added to a solution of the alkyne (1 equiv) in toluene and heated at 80°C for 8 h. The solution was cooled, concentrated *in vacuo* and the residue purified by flash chromatography on NEt$_3$-deactivated silica gel.

(b) Low and ambient temperature initiation: BEt$_3$ (5 mol %) was added in one portion to a solution of Bu$_3$SnH (1.1 equiv) and the alkyne (1 equiv) in toluene at 0°C. Dry air was introduced beneath the solvent surface *via* syringe, in 1 mL portions every 10 min, whilst the

reaction was monitored *via* TLC. Upon completion, the solution was concentrated *in vacuo* and the residue purified by flash chromatography on NEt_3-deactivated silica gel.

Protocol B: **Transition metal-catalysed**[28,29]

(a) Bu_3SnH (1.05 equiv) was added dropwise to a solution of the alkyne (1 equiv) and the palladium catalyst (2 mol %) in THF at room temperature over 2 min. Completion of the reaction was signified by a darkening of the solution and the evolution of H_2 gas. The solutions were stirred for an additional 2 h, concentrated *in vacuo* and the residue purified by flash chromatography on NEt_3-deactivated silica gel.

(b) Bu_3SnH (3 equiv) was added in one portion to a solution of the alkyne (1 equiv), Mo(*t*-BuNC)$_3$(CO)$_3$ (2 mol %) and hydroquinone (10 mol %) in THF at room temperature and mixture stirred for 6 h. The reaction was monitored *via* TLC and ^1H NMR spectroscopy of sample aliquots. Upon completion, the solution was concentrated *in vacuo* and the residue purified by flash chromatography on NEt_3-deactivated silica gel.

Protocol C: **Lower order stannylcupration: $Bu_3SnCu.Me_2S$ (2.61)**[30]

A solution of $Bu_3SnCu.Me_2S$ was prepared *via* the following protocol: *n*-BuLi (1 equiv of a 1.6 M solution in hexanes) was added dropwise to a solution of $(Bu_3Sn)_2$ (1 equiv) in THF at 0°C. The solution was stirred for 15 min at 0°C and then cooled to -48°C. Solid $CuBr.Me_2S$ was added in one portion and the mixture was stirred at -48°C for 10 min to give a dark red solution before being cooled to -78°C.

To this stannylation reagent was added the alkyne substrate (0.5 equiv) in a mixture of THF and dry MeOH (60 equiv) and the solution allowed to stir at -78°C for 12 h. Quenching was performed *via* the addition of a saturated aqueous solution of NH_4Cl/NH_4OH (5:1) and Et_2O and the resultant biphasic mixture stirred vigorously for 1 h. The solution was extracted with Et_2O (x 3) and the organic layer washed with saturated aqueous NH_4Cl/NH_4OH (5:1) and then H_2O. The solution was concentrated *in vacuo* and the residue purified by column chromatography on NEt_3-deactivated silica gel.

For successful reaction it is necessary to ensure that the $CuBr.Me_2S$ complex is of a white crystalline form; a pink colouration indicates evaporation of Me_2S and decomposition to insoluble Cu$^{(I)}$ and Cu$^{(II)}$ salts.[6] When performing stannylcupration reactions, a colour change from yellow (stannyllithium) to dark red/black (stannylcuprate) is a good indicator of the successful preparation of the desired Cu-Sn species. The formation of a green or brown solution represents unfavourable speciation in solution and results in diminished yield or reaction failure.

***Protocol D*: Higher order stannylcupration: Bu₃Sn(Bu)Cu(CN)Li₂ (2.45)**[31]

(a) Thermodynamic: *n*-BuLi (2.2 equiv of a 1.6 M solution in hexanes) was added to a suspension of CuCN (1.1 equiv) in THF at -78°C. The solution was warmed to -40°C and stirred for 30 min before cooling to -78°C. Bu₃SnH (2.2 equiv) was added and the solution stirred at -40°C for 30 min. The solution was cooled to -78°C and the alkyne (1 equiv) added *via* cannula as a solution in THF, before stirring for 2 h at -78°C. MeOH (30 equiv) was added and the solution stirred for an additional 6 h at -78°C. Quenching was performed at -78°C *via* the addition of a saturated aqueous solution of NH₄Cl/NH₄OH (5:1) and Et₂O and the mixture allowed to warm to room temperature with vigorous stirring. The solution was extracted with Et₂O (x 3) and the organics washed with saturated aqueous NH₄Cl/NH₄OH (5:1) solution and then H₂O. The solution was concentrated *in vacuo* and the residue purified by column chromatography on NEt₃-deactivated silica gel.

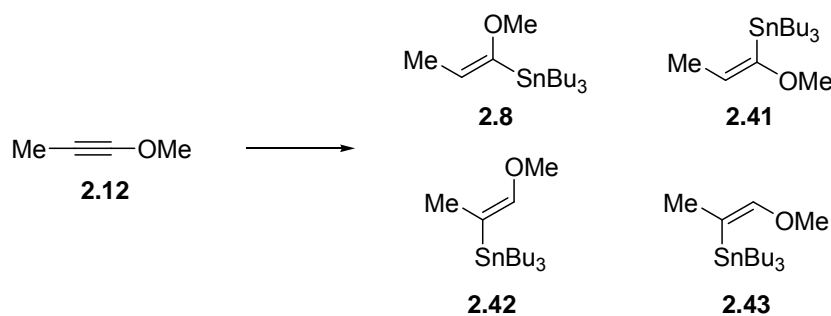*(b)* Kinetic: Identical procedure to *(a)* except that the alkyne is added in a solution of THF/MeOH (30 equiv) to prevent equilibration of the intermediate vinyl cuprate species.

(*E*)-Tributyl(1-methoxyprop-1-enyl)stannane (2.8), **(*Z*)-Tributyl(1-methoxyprop-1-enyl)-stannane (2.41)**, **(*E*)-Tributyl(1-methoxyprop-1-en-2-yl)stannane (2.42) and (*Z*)-Tributyl(1-methoxyprop-1-en-2-yl)stannane (2.43)**

Using *Protocol A-a* (80°C, 12 h); stannylation of **2.12** (140 mg, 2 mmol) in toluene (10 mL) led to the isolation of a mixture of products in the ratio 21 (**2.8**): 36 (**2.41**): 12 (**2.42**): 30 (**2.43**) in 92% combined yield (665 mg).

Using *Protocol A-b* (23°C, 2 h); stannylation of **2.12** (70 mg, 1 mmol) in toluene (5 mL) led to the isolation of a mixture of products in the ratio 66 (**2.41**): 34 (**2.43**) in 94% combined yield (342 mg).

Using *Protocol B-a* (23°C, 30 min); stannylation of **2.12** (140 mg, 2 mmol) in THF (6 mL) gave a mixture of products in the ratio 30 (**2.8**): 70 (**2.42**) as assessed by ¹H NMR spectroscopy.

Stannylation of **2.12** (70 mg, 1 mmol) in THF (3 mL) with the slow addition of Bu$_3$SnH (275 mg in 700 μL of THF, 0.95 equiv added over 30 min *via* syringe pump) led to the isolation of **2.42** as the sole observable product (320 mg, 96%).

Using *Protocol D-a*; stannylcupration of **2.12** (35 mg, 0.5 mmol) in THF (5 mL) led to the isolation of the single isomer **2.42** (178 mg, 99%).

Using *Protocol D-b;* stannylcupration of **2.12** (35 mg, 0.5 mmol) in THF (5 mL) gave a mixture of products in the ratio 23 (**2.8**): 77 (**2.42**) as assessed by ^{1}H NMR spectroscopy.

Hydroiodination – Transmetallation reaction
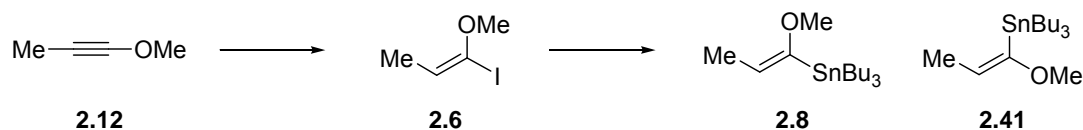
Iodotrimethylsilane (1.28 mL, 9 mmol) was added dropwise to a solution of **2.12** (700 mg, 10 mmol) and dry MeOH (365 μL, 9 mmol) in CH$_2$Cl$_2$ (25 mL) at -78°C (internal temperature). The solution was stirred for 20 min at -78°C and then warmed to room temperature over 1 h, protected from light with aluminium foil. The solvent was evaporated off at 5°C under an inert atmosphere to leave a pale yellow oil. Freshly distilled Et$_2$O (45 mL) was added and the vessel cooled to -94°C. *t*-Butyllithium (13.2 mL of a 1.5 M solution in hexane, 19.8 mmol, 2.2 equiv) was added dropwise and the solution stirred for 20 min at -94°C. Tributyltin chloride (2.69 mL, 9.9 mmol) was added dropwise and the reaction mixture slowly allowed to warm to room temperature in the cold bath over 8 h. The mixture was quenched with H$_2$O (100 mL) and extracted with Et$_2$O (3 x 50 mL). The solvent was removed under reduced pressure and the residue purified by flash chromatography on NEt$_3$-basified silica gel, eluting with 100% pentane, to give first **2.41** and then **2.8** as a colourless oil (2.83 g, 87%).

(E)-1-Iodo-1-methoxyprop-1-ene (2.6)

A pale yellow oil which is stable at ambient temperature under an Ar atmosphere but readily decomposes to release iodine vapour upon exposure to atmospheric moisture.

FTIR (KBr, cm^{-1}): 2931, 2361, 2342, 1641, 1456, 1306, 1190, 1103, 1074, 918, 669.

^{1}H NMR (500 MHz, CDCl$_3$): δ 1.61 (d, *J* = 6.9 Hz, 3H), 3.43 (s, 3H), 5.34 (q, *J* = 6.9 Hz, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 13.2, 60.9, 113.7, 120.8.

LRMS (GCMS): calc for C$_4$H$_7$IO: 197.9542; obs. 198 (M$^+$), 127 (I$^+$), 71 (M$^+$-I).

(E)-Tributyl(1-methoxyprop-1-enyl)stannane (2.8)

Rf: 0.34 (Pentane).

FTIR (KBr, cm^{-1}): 2959, 2928, 2874, 2855, 1456, 1197, 1113, 667.

^{1}H NMR (500 MHz, CDCl$_3$): δ 0.89 (t, J = 7.5 Hz, 9H), 0.93 (m, 6H), 1.32 (m, 6H), 1.50 (m, 6H), 1.64 (d, J = 6.5 Hz, 3H), 3.54 (s, 3H), 4.63 (m, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 10.4, 10.9, 13.6, 27.3, 29.0, 59.5, 117.0, 164.6.

HRMS (EI): calc. for C$_{16}$H$_{34}$OSn: 362.1632; obs. 305.0931 (C$_{12}$H$_{25}$OSn; M$^+$ - Bu, calc: 305.0927).

(Z)-Tributyl(1-methoxyprop-1-enyl)stannane (2.41)

Rf: 0.47 (Pentane).

FTIR (KBr, cm^{-1}): 2957, 2930, 2874, 2855, 1612, 1464, 1194, 1138, 1090, 988, 692.

^{1}H-NMR (500 MHz): δ 0.88 (t, J = 7.5 Hz, 9H), 0.96 (m, 6H), 1.31 (m, 6H), 1.51 (m, 6H), 1.59 (d, J = 6.5 Hz, 3H), 3.44 (s, 3H), 5.26 (t of q, J = 6.5 Hz, $^3J_{\text{Sn-H}}$ = 46.5 Hz, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 10.1, 13.7, 14.3, 27.3, 29.1, 54.7, 105.4, 166.4.

HRMS (EI): calc. for C$_{16}$H$_{34}$OSn: 362.1632; obs. 305.0927 (C$_{12}$H$_{25}$OSn; M$^+$ - Bu, calc: 305.0927).

(E)-Tributyl(1-methoxyprop-1-en-2-yl)stannane (2.42)

FTIR (KBr, cm^{-1}): 2957, 2926, 1622, 1464, 1211, 1128, 1103.

^{1}H NMR (500 MHz, CDCl$_3$): δ 0.84-0.89 (m, 15H), 1.27-1.34 (m, 6H), 1.44-1.51 (m, 6H), 1.74 (d, J = 1.3 Hz, 3H), 3.60 (s, 3H), 5.62 (tdd, J = 0.4, 1.68 Hz, $^3J_{\text{Sn-H}}$ = 33.0 Hz, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 9.0, 11.2, 13.7, 27.4, 29.1, 58.9, 108.5, 149.8.

HRMS (EI): calc. for C$_{16}$H$_{34}$OSn: 362.1632; obs. 305.0927 (C$_{12}$H$_{25}$OSn; M$^+$ - Bu, calc: 305.0927).

(Z)-Tributyl(1-methoxyprop-1-en-2-yl)stannane (2.43)

^{1}H NMR (500 MHz, CDCl$_3$): δ 0.89 (t, J = 7.4 Hz, 15H), 0.96 (m, 6H), 1.31 (m, 6H), 1.49 (m, 6H), 1.72 (s, 3H), 3.45 (s, 3H), 6.41 (t, $^3J_{\text{Sn-H}}$ = 45.1 Hz, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 9.5, 9.9, 27.4, 27.5, 29.3, 58.3, 111.3, 152.0.

5-(Tributylstannyl)hex-5-en-1-ol (2.56) and (E)-6-(Tributylstannyl)hex-5-en-1-ol (2.60)
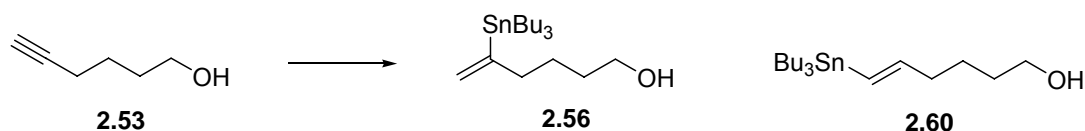
Using *Protocol B-a* (23°C, 30 min); stannylation of **2.53** (98 mg, 1 mmol) in THF (3 mL) gave a mixture of products in a ratio of 1 (**2.56**): 2 (**2.60**) in 93% isolated combined yield (362 mg).

Using *Protocol C*; stannylcupration of **2.53** (50 mg, 0.51 mmol) led to the isolation of **2.56** (89.5 mg, 45%) and **2.60** (22 mg, 11%).

Using *Protocol D-a*; stannylcupration of **2.53** (22.3 mg, 0.23 mmol) led to the isolation of **2.56** (64 mg, 73%) and **2.60** (13 mg, 15%).

5-(Tributylstannyl)hex-5-en-1-ol (2.56)[31]

FTIR (KBr, cm^{-1}): 3333, 2957, 2928, 2872, 2855, 1464, 1456, 1070, 912.

^{1}H NMR (500 MHz, CDCl$_3$): δ 0.88 (t, J = 7.5 Hz, 12H), 1.20 (t, J = 5.5 Hz, 2H), 1.30 (m, 6H), 1.39-1.59 (m, 10H), 2.26 (dt, J = 7.5 Hz, $^3J_{Sn-H}$ = 23.0 Hz, 2H), 3.64 (dd, J = 6.5, 12.0 Hz, 2H), 5.10 (t of t, J = 3.0 Hz, $^3J_{Sn-H}$ = 32.0 Hz, 1H), 5.66 (td, J = 3.0 Hz, $^3J_{Sn-H}$ = 70.0 Hz, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 9.5, 13.6, 25.5, 27.4, 29.1, 32.3, 40.0, 62.7, 125.1, 155.1.

HRMS (EI): calc. for C$_{18}$H$_{38}$OSn: 390.1945; obs. 333.1234 (C$_{14}$H$_{29}$OSn; M$^+$ - Bu, calc: 333.1240).

(E)-6-(tributylstannyl)hex-5-en-1-ol (2.60)

The ^{1}H NMR spectroscopic data obtained for **2.60** was in agreement with the reported literature values.[32]

1H-NMR (500 MHz): δ 0.88 (m, 15H), 1.26-1.62 (m, 16H), 2.16 (m, 2H), 3.65 (m, 2H), 5.8-6.0 (m, 2H).

N-Methoxy-N-methyl-5-(tributylstannyl)hex-5-enamide (2.7) and (E)-N-methoxy-N-methyl-6-(tributylstannyl)hex-5-enamide (2.62)
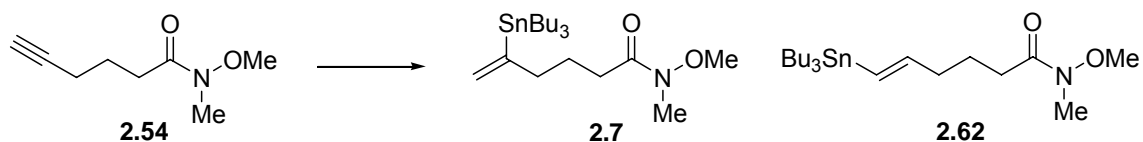
Using *Protocol B-a* (23°C, 30 min); stannylation of **2.54** (155 mg, 1 mmol) in THF (3 mL) led to isolation of **2.7** (138 mg, 31%) and **2.62** (253 mg, 57%).

Using *Protocol C*; stannylcupration of **2.54** (79.1 mg, 0.51 mmol) led to the isolation of **2.7** (72 mg, 32%) and **2.62** (23 mg, 10%).

Using *Protocol D-a*, stannylcupration of **2.54** (500 mg, 3.2 mmol) in THF (30 mL) and MeOH (27 equiv) led to the isolation of **2.7** (0.866 g, 61%) and **2.62** (0.284 g, 20%).

N-Methoxy-*N*-methyl-5-(tributylstannyl)hex-5-enamide (2.7)

FTIR (KBr, cm^{-1}): 2957, 2928, 2872, 2855, 1676, 1464, 1420, 1379, 999, 912.

^{1}H NMR (500 MHz, CDCl$_3$): δ 0.88 (t, *J* = 7.5 Hz, 9H), 1.30 (m, 6H), 1.47 (m, 6H), 1.72 (qn, 2H), 2.28 (t, *J* = 7.5 Hz, 2H), 2.39 (t, *J* = 7.5 Hz, 2H), 3.16 (s, 3H), 3.66 (s, 3H), 5.13 (t, $^3J_{\text{Sn-H}}$ = 70.0 Hz, 1H), 5.68 (t , $^3J_{\text{Sn-H}}$ = 30.0 Hz, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 9.4, 13.6, 24.1, 26.1, 27.0, 31.3, 32.1, 40.6, 61.1, 125.3, 154.6, 174.4.

HRMS (EI): calc for C$_{20}$H$_{41}$NO$_2$Sn: 447.2159; obs. 390.1455 (C$_{16}$H$_{32}$NO$_2$Sn; M$^+$ - Bu, calc: 390.1455).

(E)-N-Methoxy-*N*-methyl-6-(tributylstannyl)hex-5-enamide (2.62)

FTIR (KBr, cm^{-1}): 2955, 2928, 1674, 1462, 1416, 1381, 1177, 999.

^{1}H NMR (500 MHz, CDCl$_3$): δ 0.87 (m, 15H), 1.23-1.34 (m, 12H) 1.48 (m, 6H), 1.75 (qn, 2H), 2.16-2.34 (m, 2H), 2.42 (t, *J* = 7.5 Hz, 2H), 3.18 (s, 3H), 3.67 (s, 3H), 5.93 (m, 2H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 9.3, 13.6, 23.6, 27.3, 29.3, 31.1, 32.1, 37.2, 61.1, 128.1, 148.5, 174.5.

HRESIMS (E$^+$): calc for C$_{20}$H$_{41}$NO$_2$Sn: 448.2237 (MH$^+$); obs. 448.2238.

(Z)-N,6-Dimethoxy-*N*-methyl-5-methyleneoct-6-enamide (1.70)

Via Stille coupling: see Table **2.5** for a summary of the catalysts, additives, solvents and experimental conditions used. The optimised procedure is as follows:
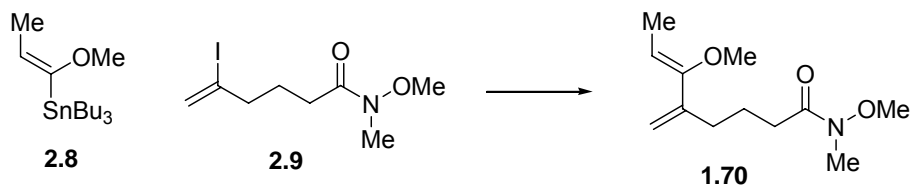
Stannane **2.8** (0.42 g, 1.15 mmol), vinyl iodide **2.9** (0.283 g, 1 mmol), Pd$_2$(dba)$_3$ (46 mg, 5 mol %), AsPh$_3$ (61 mg, 20 mol %) and CuI (38 mg, 20 mol %) were combined and evacuated at 0.2 mmHg for 30 min. Dry DMF (6 mL) was added and the mixture deoxygenated *via* subjection to

six freeze/pump/thaw cycles, wrapped in aluminium foil and stirred at 55°C for 16 h. At this time the solution was cooled and quenched *via* the addition of 100 mL of a solution comprised of saturated aqueous NH_4Cl and water (1:1) and extracted with Et_2O. The solvent was removed under reduced pressure and the residue purified by flash chromatography on NEt_3-basified silica gel, eluting with 20% EtOAc/petroleum ether with 1% NEt_3, to give **1.70** as a yellow oil (0.169 g, 73%).

Via Negishi coupling:
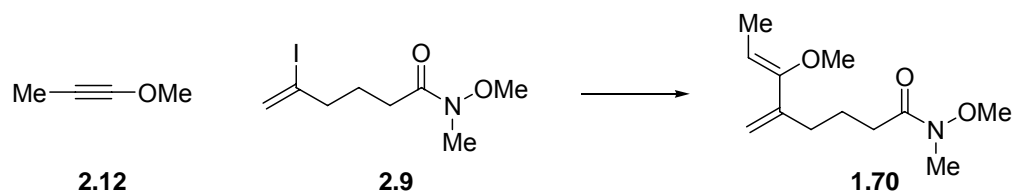
Into a 250 mL flask equipped with a three-way tap and a low-temperature thermometer, were added sequentially 1-methoxypropyne **2.12** (2.47 g, 35.3 mmol), dry CH_2Cl_2 (54 mL) and dry MeOH (859 μL, 21.2 mmol). After cooling to -80°C (internal temperature; maintained with a N_2/MeOH slush bath) the flask was protected from light with a foil shield and TMSI (3.02 mL, 21.2 mmol) added dropwise, with vigorous stirring, to give an orange solution. This solution was stirred at -78°C for 20 min and then allowed to warm to room temperature, protected in foil over 1 h. [Note: It is essential that the temperature should be maintained between -85°C to -75°C during the addition of TMSI. Within this temperature range addition can be relatively rapid ~1-2 mL/min. Above -70°C a noted exotherm is present upon the addition of each drop and results in the decomposition of the vinyl iodide species **2.6**, as evidenced by the formation of an dark orange solution upon the evaporation of the CH_2Cl_2 and the failure of the subsequent cross-coupling step].

The CH_2Cl_2 solvent was evaporated under reduced pressure (~20 mmHg, 5°C water bath) through the take-off adaptor, to give the vinyl iodide **2.6** as light yellow solution. Et_2O (108 mL) was added and the solution cooled to -100°C in a N_2/MeOH slush bath.

n-Butyllithium (13.25 mL of a 1.6 M solution in hexanes, 21.2 mmol) was added dropwise, ensuring that the temperature did not exceed -85°C. The solution was then stirred sequentially at -90°C for 50 min and at -40°C for 20 min. $ZnCl_2$ (25.4 mL of a 1 M solution in Et_2O, 25.4 mmol) [prepared by heating $ZnCl_2$ *in vacuo* at 0.1 mmHg with a flame until molten, allowing to cool under Ar and dissolving in freshly distilled Et_2O] was added, creating a white solution which was stirred at -30°C for 15 min. The vinylzinc species was transferred *via* cannula to a aluminium foil wrapped solution of the vinyl iodide **2.9** (2 g, 7.07 mmol) and Pd(PPh₃)₄ (408

mg, 0.35 mmol, 5 mol %) in THF (80 mL) and allowed to stir at room temperature for 16 h. The reaction mixture was concentrated *via* rotary evaporation to ~50 mL and quenched with the addition of a 10:1 solution of saturated aqueous NaHCO$_3$/saturated aqueous Na/K-tartrate (250 mL). The aqueous mixture was extracted with Et$_2$O (3 x 100 mL) and EtOAc (50 mL). The solvents were removed under reduced pressure and the residue purified by flash chromatography on alumina, eluting with 15% Et$_2$O/petroleum ether with 1% NEt$_3$, to give **1.70** as a yellow oil (1.56 g, 97%).

This reaction was successfully scaled to 10 g (35 mmol) of **2.9** to deliver **1.70** in excellent yield (7.6 g, 94%).

FTIR (KBr, cm^{-1}): 2939, 1666, 1605, 1416, 1385, 1304, 1080, 995, 899.

^{1}H NMR (500 MHz, CDCl$_3$): δ 1.69 (d, *J* = 7.0 Hz, 3H), 1.81 (qn, 2H), 2.20 (t, *J* = 7.5 Hz, 2H), 2.43 (t, *J* = 7.0 Hz, 2H), 3.17 (s, 3H), 3.51 (s, 3H), 3.66 (s, 3H), 4.92 (s, 1H), 5.21 (q, *J* = 7.0 Hz, 1H), 5.24 (d, *J* = 1.5 Hz, 1H); (500 MHz, C$_6$D$_6$): δ 1.78 (d, *J* = 7.0 Hz, 3H), 2.07 (qn, 2H), 2.35 (t, *J* = 7.0 Hz, 2H), 2.44 (t, *J* = 7.0 Hz, 2H), 2.99 (s, 3H), 3.13 (s, 3H), 3.46 (s, 3H), 5.08 (s, 1H), 5.34 (q, *J* = 7.0 Hz, 1H), 5.55 (d, *J* = 2.0 Hz, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 10.7, 23.2, 31.1, 31.9, 32.3, 58.7, 61.0, 109.8, 111.2, 141.5, 155.5, 174.2.

HRESIMS (E$^+$): calc for C$_{12}$H$_{21}$NO$_3$: 228.1599 (MH$^+$); obs. 228.1515.

N-Methoxy-N-methyl-5-methylene-6-oxo-octanamide (2.61)
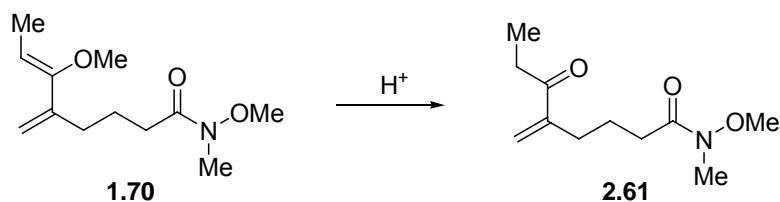
A noted degradation product was **2.61**, arising from the acidic hydrolysis of the methyl enol-ether of **1.70**. This hydrolysis was observed to occur readily during column chromatography on non-deactivated silica (i.e. not NEt$_3$ washed), in CDCl$_3$ (in the absence of deuteriopyridine) and upon exposure to acidic conditions (0.05 M aqueous HCl).
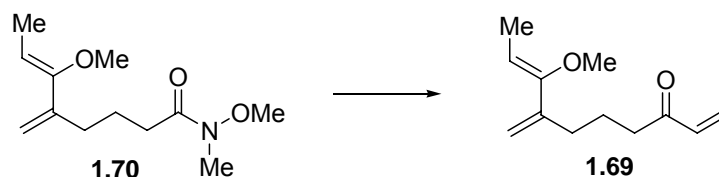
FTIR (KBr, cm^{-1}): 2939, 1676, 1460, 1416, 1385, 1178, 1103, 995, 941.

¹H NMR (500 MHz, CDCl₃): δ 1.08 (t, J = 7.3 Hz, 3H), 1.74 (qn, 2H), 2.31 (t, J = 7.8 Hz, 2H), 2.42 (t, J = 7.4 Hz, 2H), 2.70 (qn, J = 7.3 Hz, 2H), 3.16 (s, 3H), 3.66 (s, 3H), 5.75 (s, 1H), 6.00 (s, 1H).

¹³C NMR (75 MHz, CDCl₃): δ 8.2, 23.1, 30.2, 30.7, 31.2, 32.0, 61.0, 106.9, 123.6, 147.8, 202.2.

HRESIMS (E⁺): calc. for $C_{11}H_{19}NO_3$: 214.1443 (MH⁺); obs. 214.1445.

**_(Z)_-8-Methoxy-7-methylenedeca-1,8-dien-3-one (1.69)**

Vinylmagnesium bromide (6.42 mL of a 1 M solution in THF, 6.42 mmol, 2 equiv) was added dropwise to a solution of amide **1.70** (0.729 g, 3.21 mmol) in THF (50 mL) at 0°C and allowed to stir at room temperature for 12 h. The mixture was quenched *via* addition to a solution comprised of saturated aqueous NH₄Cl (100 mL) and H₂O (100 mL) and extracted with pentane (2 x 50 mL) and EtOAc (2 x 25 mL). The solvents were removed under reduced pressure to give a brown oil that was analytically pure upon inspection *via* ¹H NMR spectroscopy. The material could be purified by flash chromatography on alumina, eluting with 100% pentane with 1% NEt₃, to give **1.67** as a colourless oil (0.256 g, 73%).

FTIR (KBr, cm⁻¹): 2936, 1701, 1684, 1616, 1402, 1080, 964.

¹H NMR (500 MHz, CDCl₃): δ 1.71 (d, J = 7.0 Hz, 3H), 1.81 (qn, 2H), 2.19 (t, J = 7.5 Hz, 2H), 2.61 (t, J = 7.5 Hz, 2H), 3.52 (s, 3H), 4.91 (s, 1H), 5.20 (q, J = 7.0 Hz, 1H), 5.26 (d, J = 1.5 Hz, 1H), 5.82 (d, J = 10.5 Hz, 1H), 6.21 (d, J = 17.5 Hz, 1H), 6.35 (dd, J = 10.5, 17.5 Hz, 1H); (500 MHz, C₆D₆): 1.77 (d, J = 7.0 Hz, 3H), 1.89 (qn, 2H), 2.19 (t, J = 7.5 Hz, 2H), 2.28 (t, J = 7.0 Hz, 2H), 3.44 (s, 3H), 5.00 (s, 3H), 5.24 (q, J = 7.0 Hz, 1H), 5.29 (d, J = 10.5 Hz, 1H), 5.52 (d, J = 2.0 Hz, 1H), 5.95 (d, J = 17.5 Hz, 1H), 6.17 (dd, J = 10.5, 17.5 Hz, 1H).

¹³C NMR 75 MHz, CDCl₃): δ 10.7, 22.5, 32.1, 38.7, 58.7, 109.9, 111.5, 127.8, 136.4, 141.5, 155.5, 200.4; (75 MHz, C₆D₆): δ 11.0, 23.0, 32.6, 39.0, 58.5, 109.9, 111.9, 126.8, 136.8, 142.5, 156.4, 198.8.

HRMS (EI): calc. for $C_{12}H_{18}O_2$: 194.1307; obs. 194.1309.

(Z)-10-Methoxy-9-methylenedodec-10-en-5-one

1.70
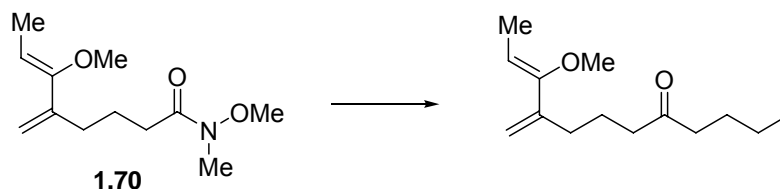
The butyl addition derivative of **1.70** was prepared for ^{1}H NMR spectroscopic comparison with the proposed product arising from conjugate addition of an ethyl group from Et$_2$AlCl to the α,β-unsaturated system of triene **1.69**.

n-Butyllithium (165 μL of a 1.6 M solution in hexanes, 0.26 mmol) was added dropwise to a solution of amide **1.70** (50 mg, 0.22 mmol) in THF (10 mL) at -78°C and stirred for 30 min. The reaction was warmed to room temperature and quenched with the addition of a saturated solution of aqueous NH$_4$Cl (50 mL) and extracted with EtOAc (20 mL x 3). The solvent was removed under reduced pressure and the residue purified by flash chromatography on NEt$_3$-basified silica gel, eluting with 10% EtOAc/petroleum ether with 1% NEt$_3$, to give the butyl addition adduct as a colourless oil (85.6 mg, 72%).

^{1}**H NMR** (500 MHz, C$_6$D$_6$): δ 0.92 (t, *J* = 7.3 Hz, 3H), 1.27 (m, 2H), 1.58 (qn, 2H), 1.79 (d, *J* = 6.9 Hz, 3H), 1.87 (m, 2H), 2.08 (t, *J* = 7.4 Hz, 2H), 2.12 (t, *J* = 7.2 Hz, 2H), 2.21 (t, *J* = 7.6 Hz, 2H), 3.46 (s, 3H), 5.03 (s, 1H), 5.29 (q, *J* = 6.9 Hz, 1H), 5.54 (s, 1H).

(l-Ethoxyetheny1)tributylstannane (2.51)

2.51
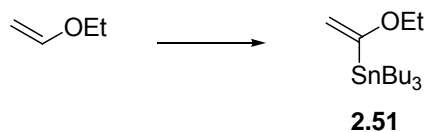
Prepared *via* the method of Gadwood *et al.*[33] with generation of the intermediate 1-lithio-1-ethoxyethene utilising the modification of Overmann *et al.*[34]

t-BuLi (10 mL of a 1.5 M solution in pentane, 15 mmol) was added dropwise over 5 min to a solution of ethyl vinyl ether (2.86 mL, 30 mmol) in THF (20 mL) at -78°C. The resultant solution was stirred at -78°C for 30 min and warmed to -22°C for 30 min causing the yellow solution to decolourise. The solution was cooled to -78°C and *n*-Bu$_3$SnCl (2.7 mL, 10 mmol) added dropwise over 5 min. After stirring at -78°C for 20 min the reaction was warmed to room temperature and quenched with water (10 mL). Hexane (100 mL) was added and the organic

phase washed with water (3 x 20 mL). The solvent was removed under reduced pressure and the residue purified by Kugelrohr distillation to give **2.51** as a colourless liquid (3.12 g, 86%).

b.p: 120-122°C / 0.1 mmHg; (lit. 75-85°C / 0.005 mmHg).[33]

**FTIR** (KBr, cm^{-1}): 2959, 2928, 1570, 1462, 1377, 1180, 1045, 968, 806, 691, 667.

^{1}H NMR (500 MHz, CDCl$_3$): δ 0.87-0.96 (m, 15H), 1.25 (t, J = 7.0 Hz, 3H), 1.33 (qn, 6H), 1.49-1.59 (m, 6H), 3.69 (q, J = 7.0 Hz, 2H), 4.04 (s, 1H), 4.67 (s, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 9.7, 13.6, 14.5, 27.2, 28.9, 61.9, 95.3, 172.8.

HRMS (EI): calc. for C$_{16}$H$_{34}$OSn: 362.1632; obs. 305.0932 (C$_{12}$H$_{25}$OSn, M$^+$ - Bu, calc: 305.0927).

6-Ethoxy-*N*-methoxy-*N*-methyl-5-methylenehept-6-enamide (1.81)

***Via Stille coupling*:** Coupling was conducted under the optimised conditions determined for the preparation of **1.70**.
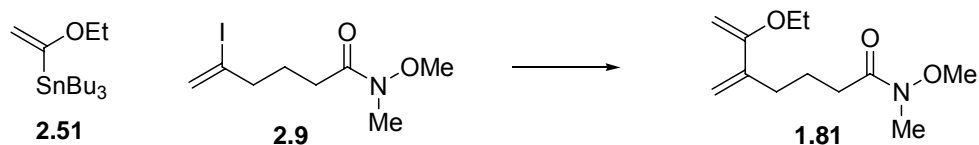
Stannane **2.51** (0.50 g, 1.38 mmol), vinyl iodide **2.9** (0.325 g, 1.15 mmol), Pd$_2$(dba)$_3$ (53 mg, 5 mol %), AsPh$_3$ (70 mg, 20 mol %) and CuI (44 mg, 20 mol %) were subjected to the previously described conditions. Work-up and purification of the crude material by flash chromatography on NEt$_3$-basified silica gel, eluting with 20% EtOAc/petroleum ether with 1% NEt$_3$, gave **1.81** as a yellow oil (0.165 g, 63%). The ethoxy-adduct **1.81** was observed to be more prone to acid-catalysed hydrolysis than the analogous methoxy-adduct **1.70**.

Via Negishi Coupling:
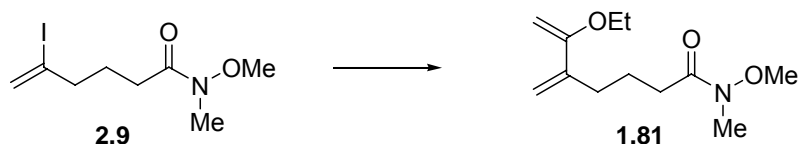
t-BuLi (14.13 mL of a 1.5 M solution in pentane, 21.2 mmol, 3 equiv) was added dropwise to a solution of ethyl vinyl ether (13.49 mL, 0.143 mol, 20 equiv) in THF (60 mL) at -78°C to

generate a bright yellow solution which was warmed to room temperature over 1 h. $ZnCl_2$ (3.37 g in 20 mL of THF, 27 mmol, 3.5 equiv) was added *via* cannula and the solution stirred at room temperature for 40 min. Vinyl iodide **2.9** (2 g, 7.06 mmol) and $Pd(PPh_3)_4$ (400 mg, 0.34 mmol, 5 mol %) dissolved in 10 mL of THF) was added *via* cannula and the solution stirred for 14 h at room temperature. The reaction was quenched *via* the addition of a 10:1 mixture of saturated aqueous $NaHCO_3$/ Na/K-tartrate solution (200 mL) and extracted with Et_2O (3 x 50 mL) and EtOAc (50 mL). The solvents were removed under reduced pressure and the residue purified by flash chromatography on NEt_3-basified silica, eluting with 25% EtOAc/petroleum ether with 1% NEt_3, to give **1.81** as a yellow oil (1.56 g, 99%).
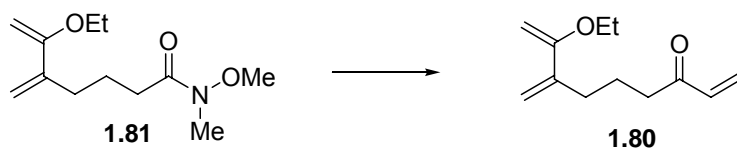
FTIR (KBr, cm^{-1}): 2978, 2937, 1168, 1586, 1479, 1461, 1414, 1383, 1198, 1177, 1069.

^{1}H NMR (500 MHz, C_6D_6): δ 1.19 (t, *J* = 7.0 Hz, 3H), 2.14 (qn, *J* = 7.4 Hz, 2H), 2.45 (t, *J* = 6.2 Hz, 2H), 2.50 (t, *J* = 7.6 Hz, 2H), 2.98 (s, 3H), 3.11 (s, 3H), 3.58 (q, *J* = 7.0 Hz, 2H), 4.17 (s, 1H), 4.64 (s, 1H), 5.16 (s, 1H), 5.93 (s, 1H).

^{13}C NMR (75 MHz, C_6D_6): δ 14.9, 24.4, 30.9, 31.8, 32.5, 33.6, 61.0, 63.2, 83.9, 113.2, 144.0, 160.4.

HRESIMS (E$^+$): calc for $C_{12}H_{21}NO_3$: 228.1599 (MH$^+$); obs. 228.1599.

8-Ethoxy-7-methylenenona-1,8-dien-3-one (1.80)

Vinylmagnesium bromide (3.94 mL of a 1 M solution in THF, 3.94 mmol, 2 equiv) was added dropwise to a solution of **1.81** (0.447 g, 1.97 mmol) in THF (40 mL) at 0°C and allowed to stir at room temperature for 2 h. The reaction was quenched with addition of saturated aqueous NH_4Cl solution (100 mL) and extracted with EtOAc (3 x 30 mL). The solvent was removed under reduced pressure to quantitatively return **1.80** as a pale brown oil that was analytically pure upon inspection *via* ^{1}H NMR spectroscopy. The residue could be purified by flash chromatography on alumina eluting with 99% pentane:1% NEt_3 to give **1.80** as a colourless oil, but in considerably reduced yields (0.249 g, 65%).

FTIR (KBr, cm^{-1}): 2930, 1707, 1682, 1443, 1367, 1178, 1113.

¹H NMR (500 MHz, CDCl₃) δ 1.19 (t, *J* = 7.0 Hz, 3H), 1.95 (qn, 2H), 2.28 (t, *J* = 7.0 Hz, 2H), 2.34 (t, *J* = 7.5 Hz, 2H), 3.58 (q, *J* = 7.0 Hz, 2H), 4.14 (s, 1H), 4.54 (d, *J* = 2.5 Hz, 1H), 5.07 (s, 1H), 5.27 (dd, *J* = 1.0, 10.5 Hz, 1H), 5.90 (d, *J* = 2.5 Hz, 1H), 5.93 (dd, *J* = 1.0, 17.5 Hz), 6.15 (dd, *J* = 10.5, 17.5 Hz, 1H); (500 MHz, C₆D₆) δ 1.19 (t, *J* = 7.0 Hz, 3H), 1.95 (m, 2H), 2.29 (t, *J* = 7.2 Hz, 2H), 2.34 (t, *J* = 7.6 Hz, 2H), 3.58 (q, *J* = 7.0 Hz, 2H), 4.15 (s, 1H), 4.54 (d, *J* = 2.3 Hz, 1H), 5.07 (s, 1H), 5.27 (dd, *J* = 1.2, 10.6 Hz, 1H), 5.90 (d, *J* = 2.2 Hz, 1H), 5.93 (dd, *J* = 1.2, 17.6 Hz, 1H), 6.15 (dd, *J* = 10.6, 17.6 Hz, 1H).

¹³C NMR (75 MHz, C₆D₆): δ 14.9, 24.4, 31.8, 32.5, 33.6, 61.0, 63.2, 83.9, 113.2, 144.0, 160.4.

HRMS calc. for $C_{12}H_{18}O_2$: 194.1307; obs. 194.1310.

N-Methoxy-N-methyl-5-methylenehept-6-enamide (2.66)


2.9 → **2.66**
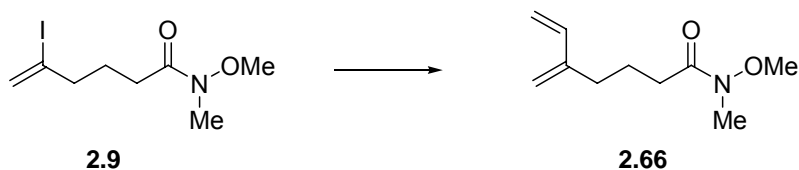
Vinylmagnesium bromide (5.3 mL of a 1 M solution in THF, 5.3 mmol) was added dropwise to a solution of ZnCl₂ (6.18 mL of a 1 M solution in Et₂O, 6.2 mmol) in THF (25 mL) at 0°C and allowed to stir at room temperature for 1 h. The resultant vinyl zinc species was added *via* cannula to a solution of vinyl iodide **2.9** (0.5 g, 1.77 mmol) and Pd(PPh₃)₄ (120 mg, 0.103 mmol, 5 mol %) in THF (5 mL) and stirred at room temperature for 12 h. The reaction was quenched *via* the addition of a 10:1 mixture of saturated aqueous NaHCO₃/ Na/K-tartrate solution (100 mL) and extracted with Et₂O (2 x 30 mL) and EtOAc (30 mL). The solvents were removed under reduced pressure and the residue purified by flash chromatography on alumina, eluting with 20% Et₂O/petroleum ether, to give **2.66** as a yellow oil (0.267 g, 83%).

FTIR (KBr, cm⁻¹): 2939, 2341, 1666, 1416, 1385, 1180, 995, 899.

¹H NMR (500 MHz, C₆D₆): δ 2.07 (qn, 2H), 2.38 (t, *J* = 7.5 Hz, 2H), 2.42 (t, *J* = 6.5 Hz, 2H), 2.98 (s, 3H), 3.12 (s, 3H), 5.08 (s, 2H), 5.10 (d, *J* = 10.5 Hz, 1H), 5.43 (d, *J* = 17.5 Hz, 1H), 6.46 (dd, *J* = 10.5, 17.5 Hz, 1H).

¹³C NMR (75 MHz, C₆D₆): δ 23.7, 31.7, 31.0, 32.5, 61.0, 114.0, 116.5, 139.5, 146.8, 174.4.

HRESIMS (E⁺): calc for $C_{10}H_{17}NO_2$: 184.1337 (MH⁺); obs. 184.1335.

7-Methylene-nona-1,8-dien-3-one (2.67)[35]

2.66   **2.67**
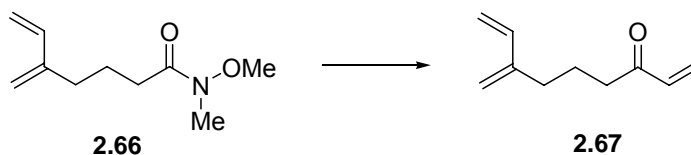
Vinylmagnesium bromide (28 mL of a 0.783 M solution in THF, 22 mmol) was added dropwise to a solution of **2.66** (2 g, 10.9 mmol) in THF (100 mL) at 0°C and allowed to stir at room temperature for 12 h. The mixture was quenched *via* the addition of saturated aqueous NH$_4$Cl solution (100 mL) and extracted with EtOAc (3 x 50 mL). The solvents were removed under reduced pressure to give a brown crude material that was pure upon inspection by ^{1}H NMR spectroscopy. Purification *via* flash chromatography on NEt$_3$-basified silica, with 5% EtOAc/petroleum ether with 1% NEt$_3$, gave the triene **2.67** (0.788 g, 47%).

FTIR (KBr, cm^{-1}): 2939, 2897, 1701, 1682, 1616, 1595, 1402, 1367, 1101, 991, 962, 897.

^{1}H NMR (500 MHz, CDCl$_3$): δ 1.84 (qn, 2H), 2.25 (t, *J* = 7.5 Hz, 2H), 2.62 (t, *J* = 7.3 Hz, 2H), 5.01 (d, *J* = 20.9 Hz, 1H,) 5.07 (d, *J* = 10.8 Hz, 1H), 5.25 (d, *J* = 17.3 Hz, 1H), 5.82 (dd, *J* = 1.1, 10.6 Hz, 1H), 6.22 (dd, *J* = 1.1, 17.3 Hz, 1H), 6.36 (dd, *J* = 10.6, 17.3 Hz, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 22.0, 30.5, 38.9, 113.4, 116.1, 127.8, 136.4, 138.4, 145.4, 200.5.

HRMS (EI): calc. for C$_{10}$H$_{14}$O: 150.1045; obs. 150.1045.

6.3   Experiments Described in Chapter Three

7-Methoxy-8-methylbicyclo[4.3.1]dec-7-en-2-one (3.55)
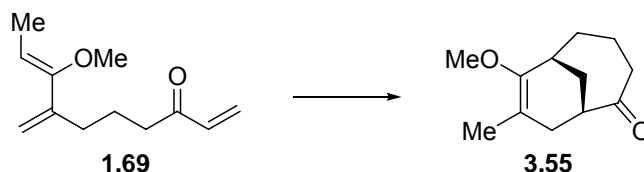
Thermal Conditions:

Methoxy-triene **1.69** (88.6 mg, 0.46 mmol) and a small crystal of BHT (~5 mg) were placed in a pressure tube and dissolved in benzene (5 mL). The sample was degassed with Ar for 5 min, sealed and heated at 170°C for 9 h. The tubes were opened and the solvent removed under reduced pressure. Purification *via* flash chromatography on silica, eluting with 10% EtOAc/petroleum, gave the $\Delta^{7,8}$-olefinic adduct **3.55** as a colourless oil (60.1 mg, 68%).

Lewis Acid Catalysed:

(a) BF$_3$.OEt$_2$: Freshly distilled BF$_3$.OEt$_2$ (782 µL, 6.2 mmol, 10 equiv) was added dropwise to a solution of triene **1.69** (122 mg, 0.62 mmol) in CH$_2$Cl$_2$ (10 mL) at -78°C and stirred for 2 h at -78°C. The reaction was quenched at -78°C *via* the addition of a saturated NaHCO$_3$ solution (10 mL), allowed to warm to room temperature and extracted with Et$_2$O (3 x 10 mL). The combined organic solvents were removed under reduced pressure and the residue purified *via* flash chromatography on silica, eluting with 4% EtOAc/petroleum ether to give the $\Delta^{7,8}$-olefinic adduct **3.55** as a colourless oil (56 mg, 46%).

(b) Et$_2$AlCl: Et$_2$AlCl (173 µL of a 1.5 M solution in heptane, 0.26 mmol) was added dropwise to a solution of triene **1.69** (51.2 mg, 0.26 mmol) in CH$_2$Cl$_2$ (10 mL) at -78°C. The resultant solution was stirred at -78°C for 10 min and allowed to warm to room temperature over 2 h. The reaction was quenched *via* the addition of a saturated NH$_4$Cl solution (10 mL), stirred vigorously for 1 h to solubilise the gelatinous precipitate and extracted with CH$_2$Cl$_2$ (3 x 10 mL).The solvents were removed under reduced pressure and the residue purified *via* flash chromatography on silica, eluting with 4% EtOAc/petroleum ether, to give the $\Delta^{7,8}$-olefinic adduct **3.55** as a colourless oil (41 mg, 79%).

FTIR (KBr, cm^{-1}): 2931, 1697, 1450, 1350, 1196, 1142, 1011.

¹H NMR (500 MHz, CDCl₃): δ 1.38 (qn, 1H), 1.46 (tt, J = 3.3, 13.0 Hz, 1H), 1.62 (s, 3H), 1.71-1.78 (m, 1H), 2.00-2.10 (m, 2H), 2.23 (m, 2H), 2.38-2.43 (m, 2H), 2.50 (d, J = 16.7 Hz, 1H), 2.68 (dt, J = 1.9, 12.7 Hz, 1H), 2.76 (broad s, 1H), 3.47 (s, 3H). See **Figure 3.15**.

¹³C NMR (75 MHz, CDCl₃): δ 16.1, 21.2, 29.8, 32.1, 32.5, 33.8, 43.5, 43.6, 57.4, 118.3, 148.5, 217.2.

HRMS (EI) calc. for $C_{12}H_{18}O_2$: 194.1307; obs. 194.1309.

7-Ethoxybicyclo[4.3.1]dec-7-en-2-one (3.65)

1.80   **3.65**
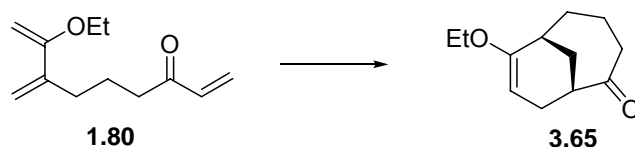
Ethoxy-triene **1.80** (55.3 mg, 0.28 mmol) and Proton-sponge® (18.3 mg, 0.09 mmol, 0.3 equiv) were placed in a pressure tube and dissolved in benzene (5 mL). The sample was degassed with Ar for 5 min, sealed and heated at 160°C for 24 h. The tubes were opened and the solvent removed under reduced pressure. Purification *via* flash chromatography on silica, eluting with 15% EtOAc/petroleum ether, gave the $\Delta^{7,8}$-olefinic adduct **3.65** as a colourless oil (34 mg, 62%).

FTIR (KBr, cm⁻¹): 2936, 2880, 1697, 1660, 1448, 1380, 1190.

¹H NMR (500 MHz, CDCl₃): δ 1.23 (t, J = 7.0 Hz, 3H), 1.32 (q, 1H), 1.46 (tt, J = 3.5, 13.4 Hz, 1H), 1.72 (m, 1H), 2.07 (dddd, J = 0.9, 3.9, 7.4, 14.3 Hz, 1H), 2.14-2.26 (m, 3H), 2.39-2.44 (m, 2H), 2.56 (d, J = 3.9 Hz, 1H), 2.63 (qt, J = 1.9, 5.8, 16.4 Hz, 1H), 2.68 (ddd, J = 2.0, 14.0, 17.3 Hz, 1H), 3.57 (qd, J = 7.0, 9.4 Hz, 1H), 3.70 (qd, J = 7.0, 9.4 Hz, 1H), 4.67 (d, J = 4.6 Hz, 1H). See **Figure 3.22**.

¹³C NMR (75 MHz, CDCl₃): δ 14.4, 20.8, 27.3, 29.3, 32.4, 35.1, 43.3, 43.7, 61.6, 95.2, 154.0, 217.3.

HRMS (EI): calc. for $C_{12}H_{18}O_2$: 194.1307; obs. 194.1308.

Bicyclo[4.3.1]dec-6-en-2-one (3.40)

2.67   **3.40**
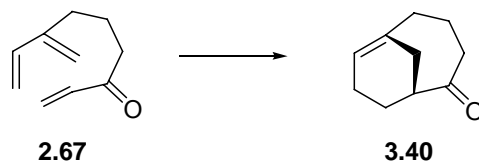
The triene **2.67** (37.4 mg, 0.25 mmol) and Proton-sponge® (16.0 mg , 0.07 mmol, 0.3 equiv) were placed in a Carius resealable pressure tube and subjected to a freeze/pump/thaw cycle (x 4).

The tube was sealed and heated at 160°C for 20 h. Upon cooling, the solvent was removed under reduced pressure and the residue purified by flash chromatography on silica gel, eluting with 5% Et_2O/petroleum ether, to give **3.40** as a colourless oil (21.3 mg, 56%).

The spectroscopic data obtained was in agreement with that previously reported by Shea *et al.*[35]

FTIR (KBr, cm^{-1}): 2943, 2864, 1699, 1447, 1317, 1171, 1038, 959, 854.

^{1}H NMR (500 MHz, CDCl$_3$): δ 1.44-1.53 (m, 1H), 1.79-1.87 (m, 2H), 1.99-2.11 (m, 4H), 2.19 (dt, *J* = 5.8, 11.5 Hz, 1H), 2.29 (ddd, *J* = 2.7, 5.9, 11.5 Hz, 1H), 2.36 (ddd, *J* = 1.6, 6.6, 12.0 Hz, 1H), 2.53 (tdd, *J* = 1.6, 3.4, 13.2 Hz, 1H), 2.60-2.63 (m, 1H), 2.88 (ddd, *J* = 3.0, 11.6, 13.3 Hz, 1H), 5.54 (d, *J* = 7.0 Hz, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 21.2, 24.2, 31.8, 32.4, 35.8, 41.8, 47.1, 123.7, 145.0, 216.7.

HRMS (EI): calc. for $C_{10}H_{14}O$: 150.1045; obs. 150.1046.

N-Methoxy-4-(6-methoxy-7-methyl-1,3-dioxo-2-phenyl-2,3,3a,4,7,7a-hexahydro-1H-isoindol-5-yl)-*N*-methylbutanamide (3.68)
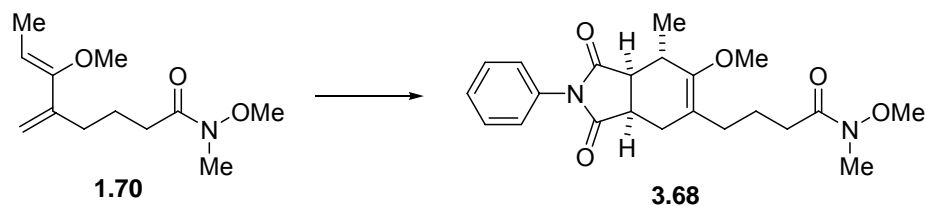
N-Phenylmaleimide (45.8 mg, 0.26 mmol) and **1.70** (20 mg, 0.088 mmol) in toluene (5 mL) were stirred at room temperature for 24 h. The solvent was removed under reduced pressure and the residue purified by flash chromatography on NEt$_3$-basified silica, eluting with 20% EtOAc/petroleum ether with 1% NEt$_3$, to give **3.68** as a cream solid (16.3 mg, 46%).

FTIR (KBr, cm^{-1}): 2939, 1713, 1659, 1501, 1458, 1385, 1192, 995, 918, 733.

^{1}H NMR (500 MHz, C$_6$D$_6$): δ 1.35 (d, *J* = 7.0 Hz, 3H), 1.87 (m, 1H), 2.00 (m, 1H), 2.22 (m, 2H), 2.37 (m, 2H), 2.61 (m, 4H), 2.70 (dd, *J* = 4.8, 15.6 Hz, 1H), 2.98 (s, 3H), 3.13 (s, 3H), 3.32 (s, 3H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.27 (m, 2H) 7.54 (d, *J* = 7.6 Hz, 2H). (500 MHz, CDCl$_3$): δ 1.22 (d, *J* = 7.2 Hz, 3H), 1.65-1.75 (m, 2H), 2.15-2.19 (m, 2H), 2.40 (t, *J* = 6.9 Hz, 2H), 2.45-2.49 (m, 1H), 2.59-2.64 (m, 1H), 2.96 (qn, 1H), 3.15 (s, 3H), 3.20-3.24 (m, 2H), 3.50 (s, 3H), 3.65 (s, 3H), 7.23 (d, *J* = 8.3 Hz, 2H), 7.37 (t, *J* = 7.7 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 1H).

^{13}C NMR (75 MHz, C$_6$D$_6$): δ 13.1, 23.0, 26.9, 29.5, 31.6, 32.1, 32.4, 39.7, 45.8, 58.5, 60.6, 118.5, 126.7, 128.2, 129.0, 133.0, 152.9, 174.1, 176.7, 178.3; (75 MHz, CDCl$_3$): δ 12.7, 22.3,

25.9, 28.8, 31.0, 31.3, 31.7, 38.9, 45.2, 58.1, 60.7, 117.5, 126.0, 128.1, 128.7, 131.5, 152.2, 173.8, 176.8, 178.6.

HRESIMS (E$^+$): calc. for $C_{22}H_{28}N_2O_5$: 401.2077 (MH$^+$); obs. 401.2075.

Silylation of Glassware

Glassware to be used for the IMDA cyclisation reaction, including the reaction flask, magnetic stirring bar and reflux condenser, were silylated utilising the following protocol: The glassware was soaked in an alcoholic sodium hydroxide solution for 30 min [12 mL of H_2O containing 12 g NaOH diluted into 100 mL of ethanol], washed with distilled water until neutral, with two small portions of EtOH (5 mL) and then placed in an electric oven for 1 h to dry. The glassware was cooled under argon and filled with a solution of 5% v/v Me_2SiCl_2 in CH_2Cl_2 and allowed to soak for 30 min. The silylation mixture was removed, the glassware washed with anhydrous CH_2Cl_2 (5 mL x3) and then filled with MeOH and allowed to soak for 1 h. The silylated glassware then was drained and dried overnight at 120°C.

Purification of Proton-Sponge®

The white crystalline solid was dissolved in a minimum of aqueous 1 M HCl solution and then triturated with a solution of saturated aqueous K_2CO_3 solution at 0°C causing a white suspension to form. After stirring for 1 h, the precipitate was collected and washed with distilled water until the washings were neutral. Distillation of this material *via* Kugelrohr (95°C / 0.1 mmHg) afforded a colourless liquid, which crystallised to a white solid upon cooling.

7-Methoxy-8-methyl-bicyclo[4.3.1]dec-6-en-2-one (1.68)
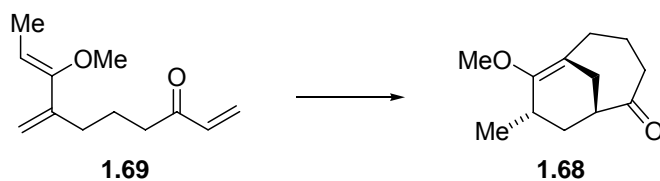
Triene **1.69** (400 mg, 2.06 mmol), Proton-sponge® (551 mg , 2.57 mmol, 1.25 equiv) and 5 mL of xylene were placed in a silylated round bottom flask with a reflux condenser and azeotropically dried *via* evacuation at 0.1 mmHg, until all the xylene had evaporated. Xylene (75 mL) was added and the reaction brought to reflux for 42 h. Upon cooling, the solvent was removed under reduced pressure (60°C / 24 mmHg / 23°C / 0.1 mmHg). The residue was

purified by flash chromatography on NEt₃-basified silica gel, eluting with 5% Et$_2$O/petroleum ether with 1% NEt₃, to give **1.68** as a colourless oil (320.6 mg, 80%).
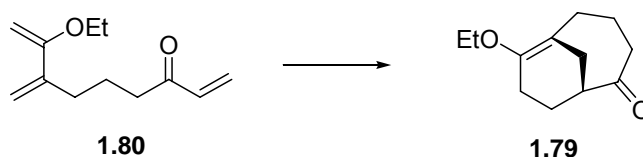
FTIR (KBr, cm^{-1}): 3381, 2936, 2870, 1699, 1657, 1456, 1256, 1157, 804.

^{1}H NMR (500 MHz, CDCl$_3$): δ 1.19 (d, J = 6.8 Hz, 3H), 1.67-1.76 (m, 4H), 1.85 (td, J = 8.1, 12.9 Hz, 1H), 2.12 (m, 3H), 2.30 (m, 2H), 2.52 (m, 1H), 2.77 (dd, J = 3.9, 7.8 Hz, 1H), 3.38 (s, 3H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 15.5, 30.2, 30.4, 30.6, 31.8, 35.4, 41.7, 47.1, 60.5, 122.2, 155.0, 213.6.

HRMS (EI): calc. for C$_{12}$H$_{18}$O$_2$: 194.1307; obs. 194.1308.

7-Ethoxy-bicyclo[4.3.1]dec-6-en-2-one (1.79)

Using the method described for the cyclisation of **1.69**, the triene **1.80** (34.0 mg, 0.18 mmol) and Proton-Sponge® (37 mg, 0.22 mmol, 1.25 equiv) were dissolved in xylene (10 mL) and heated to reflux for 42 h. Evaporation of the solvent and flash chromatography on NEt₃-basified silica gel, eluting with 2.5% Et$_2$O/petroleum ether with 1% NEt₃, gave **1.79** as a colourless oil (14.9 mg, 35%).

^{1}H NMR (500 MHz, CDCl$_3$): δ 1.14 (t, J = 7.0 Hz, 3H), 1.40-1.47 (m, 2H), 1.86-1.93 (m, 1H), 1.94-2.14 (m, 2H), 2.16 (br s, 1H), 2.19-2.22 (m, 2H), 2.31-2.36 (m, 2H), 2.47 (dt, J = 2.5, 11.1 Hz, 1H), 2.62-2.69 (m, 1H), 2.88 (t, J = 9.4 Hz, 1H), 3.54 (dq, J = 5.3, 7.0 Hz, 2H).

^{13}C NMR (75 MHz, C$_6$D$_6$): δ 15.6, 21.5, 22.4, 23.6, 27.3, 29.6, 37.3, 44.8, 62.6, 112.4, 148.9, 211.4.

HRMS (EI): calc. C$_{12}$H$_{18}$O$_2$: 194.1307; obs. 194.1310.

7-Methoxy-8-methyl-tricyclo[4.3.1.1^{7,8}]undecan-2-one (3.56)


3.55   **3.56**
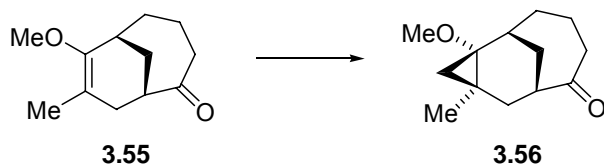
Et$_2$Zn (2.27 mL of a 1.236 M solution in toluene, 2.8 mmol, 5 equiv) was added dropwise to a solution of **3.55** (110.5 mg, 0.56 mmol) in DCE (20 mL) at -20°C and stirred for 30 min. CH$_2$I$_2$ (0.458 mL, 5.6 mmol, 10 equiv) was added dropwise and the solution allowed to warm to room temperature and stirred for 16 h resulting in the formation of a white precipitate. The mixture was quenched *via* the addition of a saturated solution of aqueous NH$_4$Cl (50 mL) and extracted with Et$_2$O (3 x 10 mL). The solvents were removed under reduced pressure and the residue purified *via* flash chromatography on silica, eluting with 10% EtOAc/petroleum ether, to give **3.56** as a colourless oil (78.3 mg, 67%).

FTIR (KBr, cm^{-1}): 2933, 2868, 2360, 1699, 1456, 1180, 1141, 1049.

^{1}H NMR (500 MHz, CDCl$_3$): δ 0.38 (d, *J* = 5.3 Hz, 1H), 0.45 (d, *J* = 5.3 Hz, 1H), 1.12 (s, 3H), 1.42 (m, 1H), 1.61 (m, 2H), 1.75 (m, 1H), 1.87 (m, 2H), 2.12 (d, *J* = 15.1 Hz, 1H), 2.25 (m, 2H), 2.56 (m, 2H), 2.70 (d, *J* = 3.1 Hz, 1H), 3.22 (s, 3H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 19.6, 20.9, 21.4, 22.8, 27.5, 30.7, 31.9, 34.5, 42.8, 43.2, 53.6, 65.7, 216.2.

HRMS (EI): calc. for C$_{13}$H$_{20}$O$_2$: 208.1463; obs. 208.1469.

7-Methoxy-8-methyl-tricyclo[4.3.1.1^{6,7}]undecan-2-one (3.74)

1.68   **3.74**
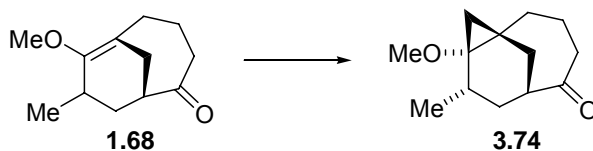
Et$_2$Zn (4.08 mL of a 1.236 M solution in toluene, 5.05 mmol, 5 equiv) was added dropwise to a solution of **1.68** (196 mg, 1 mmol) in DCE (10 mL) at -20°C. After stirring for 15 min at -20°C, CH$_2$I$_2$ (0.813 mL, 10.1 mmol, 10 equiv) was added dropwise and the solution allowed to stir at room temperature for 16 h resulting in the precipitation of a white material. The mixture was quenched with saturated Na/K-tartrate solution, stirred vigorously for 1 h and extracted with CH$_2$Cl$_2$ (30 mL x 3). The solvent was removed under reduced pressure and the residue purified by flash chromatography on silica, eluting with 20% EtOAc/petroleum ether, to give **3.74** as a

colourless oil (136 mg, 65%). No isomerisation of the $\Delta^{6,7}$-olefinic bond or cyclopropanation products arising from isomerisation were observed under these reaction conditions.

If a mixture of the $\Delta^{6,7}$ and the $\Delta^{7,8}$ alkenes **1.68** and **3.55** (76.5 mg, 0.39 mmol, ratio 62:38) was subjected to the stated cyclopropanation conditions, retention of the relative isomeric ratios was observed *via* ^{1}H NMR spectroscopy. The isolation of the desired adduct **3.74** could be facilitated by refluxing the crude cyclopropanation mixture in acidic EtOH for 6 h (50 mL; 10:1 EtOH / conc. aqueous HCl solution), under which conditions the selective hydrolysis of the $\Delta^{7,8}$ cyclopropane adduct **3.56** occurred. The solution was diluted with H_2O and extracted with Et_2O (20 mL x 3). Removal of the solvent under reduced pressure and purification of the residue by flash chromatography on silica, eluting with 10% EtOAc/petroleum ether, gave **3.74** as a colourless oil (43.2 mg, 65%, two steps).

FTIR (KBr, cm^{-1}): 2937, 2872, 1695, 1458, 1261, 1223, 1178, 1105, 1074.

^{1}H NMR (500 MHz, CDCl$_3$): δ 0.29 (d, J = 5.6 Hz, 1H), 0.77 (d, J = 5.6 Hz, 1H), 1.06 (ddd, J = 1.2, 5.6, 15.1 Hz, 1H), 1.13 (d, J = 6.8 Hz, 3H), 1.23 (m, 1H), 1.45-1.52 (m, 2H), 1.66-1.72 (m, 2H), 1.85 (ddd, J = 4.4, 11.7, 14.2 Hz, 1H), 1.92 (ddd, J = 5.9, 7.6, 13.5 Hz, 1H), 2.09 (dd, J = 1.1, 15.1 Hz, 1H), 2.49-2.64 (m, 2H), 3.30 (s, 3H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 16.3, 23.1, 24.3, 25.2, 30.1, 32.0, 33.3, 35.0, 41.6, 45.2, 57.7, 66.8, 217.8.

HRMS (EI): calc. for $C_{13}H_{20}O_2$: 208.1463; obs. 208.1461

7a-Hydroxy-7,7-dimethyl-octahydro-1,5-methano-inden-8-one (3.58)
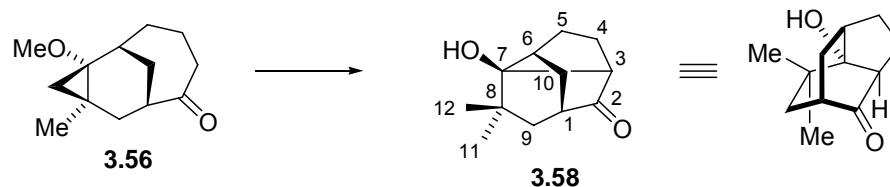
A solution of cyclopropane **3.56** (12 mg, 0.058 mmol) in EtOH (25 mL) and conc. aqueous HCl solution (5 mL) was heated to reflux for 12 h, whilst monitoring *via* TLC. Upon completion the mixture was quenched *via* addition to a saturated aqueous NaHCO$_3$ solution (50 mL) and extracted with Et_2O (20 mL x 3). The solvent was removed under reduced pressure and the residue purified by flash chromatography on silica, eluting with 20% EtOAc/petroleum ether, to give **3.58** as a colourless oil (11.2 mg, 98%).

FTIR (KBr, cm^{-1}): 3437, 2951, 2870, 1709, 1462, 1366, 1319, 1281, 1099, 1069.

^{1}H NMR (500 MHz, CDCl$_3$): δ 0.92 (s, 3H, H$_{11}$), 1.07 (s, 3H, H$_{12}$), 1.18-1.24 (m, 2H, H$_{10a}$, H$_{4a}$), 1.47-1.62 (m, 3H, H$_5$, H$_{9a}$, H$_{9b}$,), 1.96 (m, 1H, H$_{10}$), 2.10 (br s, 1H, H$_1$), 2.14-2.23 (m, 3H, H$_5$, H$_{4b}$, H$_6$), 2.44 (d, 1H, H$_3$); (500 MHz, C$_6$D$_6$): δ 0.98 (s, 3H), 0.97-1.03 (m, 1H), 1.09 (s, 3H), 1.10-1.16 (m, 1H), 1.40 (dd, J = 3.3, 13.6 Hz, 1H), 1.49 (td, J = 2.6, 13.6 Hz, 1H), 1.68 (dd, J = 10.5, 13.3 Hz, 1H), 1.75-1.81 (m, 1H), 2.09-2.13 (m, 1H), 2.15 (d, J = 2.1 Hz, 1H), 2.22-2.37 (m, 2H), 2.62 (d, J = 8.0 Hz, 1 H). See **Figure 3.17**.

^{13}C NMR (75 MHz, CDCl$_3$): δ 25.9 (C5), 27.1 (C11), 27.2 (C12), 31.5 (C4), 31.7 (C10), 32.9 (C8), 37.5 (C6), 41.6 (C9), 42.3 (C1), 55.1 (C3), 85.2 (7), 218.0 (C2); (75 MHz, C$_6$D$_6$): δ 26.8, 27.8, 27.9, 32.3, 32.4, 33.6, 38.3, 42.3, 43.2, 56.0, 85.6, 217.

HRMS (EI): calc. for C$_{12}$H$_{18}$O$_2$: 194.1307; obs. 194.1315.

7a-Hydroxy-3a,7-dimethyl-octahydro-1,5-methano-inden-8-one (3.83)

A solution of cyclopropane **3.74** (23.1 mg, 0.11 mmol) in EtOH (5 mL) and conc. aqueous HCl (5 mL) was heated to reflux of 12 h, whilst monitoring *via* TLC. The reaction was quenched *via* addition to a solution of saturated aqueous NaHCO$_3$ (40 mL) and extracted with Et$_2$O (30 mL x 3). The solvent was removed under reduced pressure and the residue purified by flash chromatography on silica, eluting with 20% EtOAc/petrole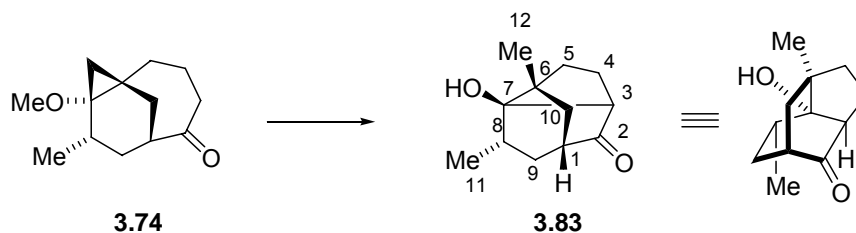um ether, to give **3.83** as a colourless oil (21 mg, 91%). Methyl-ether hydrolysis-cyclopropane fragmentation with concomitant aldol addition was similarly observed by exposure of **3.74** to TMSI (2 equiv) in CH$_2$Cl$_2$ at 0°C in quantitative yield.

FTIR (KBr, cm^{-1}): 3470, 2951, 2870, 1715, 1456, 1375, 1288, 1099, 679.

^{1}H NMR (500 MHz, CDCl$_3$): δ 1.00 (d, J = 5.1 Hz, 3H), 1.09 (s, 3H), 1.25 (d, J = 7.1 Hz, 1H), 1.35-1.40 (m, 1 H), 1.51-1.59 (m, 3H), 1.87 (dt, J = 5.2, 12.0 Hz, 1H), 2.00-2.05 (m, 2H), 2.11 (s, 1H), 2.12-2.17 (m, 1H), 2.56 (d, J = 8.6 Hz, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 18.1 (C11), 20.5 (C12), 24.9 (C5), 27.8 (C8), 34.9 (C9), 38.9 (C10), 40.0 (C5), 42.1 (C1), 43.0 (C6), 54.9 (C3), 83.3 (C7), 217.7 (C2).

HRMS (EI): calc. for $C_{12}H_{18}O_2$: 194.1307; obs. 194.1310.

7-Methoxy-8-methyl-tricyclo[4.3.1.1^{6,7}]undecan-2-ol

α-Alcohol

FTIR (KBr, cm^{-1}): 3371, 2931, 1458, 1227, 1065, 1034.

^{1}**H NMR** (500 MHz, CDCl$_3$): δ 0.14 (d, J = 5.4 Hz, 1H), 0.49 (d, J = 5.4 Hz, 1H), 0.89 (dd, J = 6.7, 14.8 Hz, 1H), 1.13 (s, 3H), 1.21 (ddd, J = 6.1, 10.7, 13.2 Hz, 1H), 1.31-1.48 (m, 5H), 1.59-1.73 (m, 5H), 2.28 (m, 1H), 3.29 (s, 3H), 3.63 (ddd, 1H, J = 3.2, 4.9, 11.0 Hz, 1H).

^{13}**C NMR** (75 MHz, CDCl$_3$): δ 16.8, 22.2, 22.8, 23.4, 27.3, 28.3, 28.6, 30.4, 35.8, 36.5, 57.6, 67.2, 78.9.

HRMS (EI): calc. for $C_{13}H_{22}O_2$: 210.1620; obs. 210.1627

β-Alcohol

FTIR (KBr, cm^{-1}): 3379, 2932, 1458, 1219, 1096, 1057, 1011, 671.

^{1}**H NMR** (500 MHz, CDCl$_3$): δ 0.19 (d, J = 5.4 Hz, 1H), 0.55 (d, J = 5.4 Hz, 1H), 0.75 (dd, J = 5.8, 14.7 Hz, 1H), 0.93 (dt, J = 6.0, 13.5 Hz, 1H), 1.10 (d, J = 6.6 Hz, 3H), 1.17-1.25 (m, 1H), 1.29-1.46 (m, 3H), 1.56-1.73 (m, 4H), 1.82-1.92 (m, 1H), 2.01-2.06 (m, 1H), 2.08 (d, J = 14.8 Hz, 1H), 3.30 (s, 3H), 3.66 (m, 1H).

^{13}**C NMR** (75 MHz, CDCl$_3$): δ 16.7, 17.3, 22.7, 24.3, 26.1, 28.0, 28.5, 32.0, 35.3, 38.7, 57.7, 67.1, 73.7.

HRMS (EI): calc. for $C_{13}H_{22}O_2$: 210.1620; obs. 210.1618

7-Methoxy-8-methyl-tricyclo[4.3.1.1^{6,7}]undecan-2-yl 3,5-dinitrobenzoate (3.84)
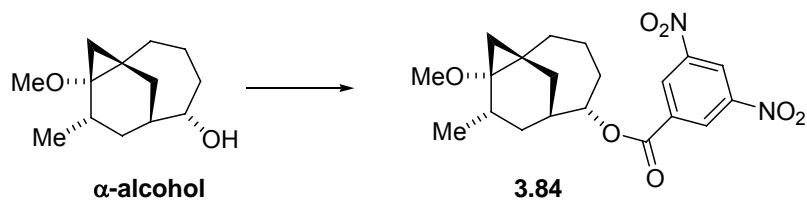
3,5-Dinitrobenzoyl chloride (250 mg, 1.08 mmol, 3 equiv) dissolved in CH_2Cl_2 (1 mL) was added *via* cannula to a solution of the above prepared **α-alcohol** (75.4 mg, 0.36 mmol), Et_3N (250 µL, 1.8 mmol, 5 equiv) and DMAP (8.8 mg, 0.07 mmol, 0.2 equiv) in CH_2Cl_2 (5 mL) at 0°C. The solution was allowed to warm to room temperature and stirred for 12 h. The solvent was removed under reduced pressure and the residue purified by flash chromatography on silica, eluting with 5% EtOAc/petroleum ether, to give **3.84** as a yellow solid (49.3 mg, 34%).

The solid was recrystallised from an Et_2O:petroleum ether solution and subjected to X-ray diffraction to obtain the crystallographic structure depicted in **Figure 3.33**. [P2$_1$/c, Z = 4, R = 3.6%].

mp: 162°C.

FTIR (KBr, cm^{-1}): 3101, 2939, 2870, 1724, 1628, 1547, 1462, 1346, 1281, 1169, 1072, 968, 910, 729.

^{1}H NMR (500 MHz, CDCl$_3$): δ 0.24 (d, *J* = 5.5 Hz, 1H), 0.60 (d, *J* = 5.5 Hz, 1H), 1.03 (dd, *J* = 6.6, 15.0 Hz, 1H), 1.19 (d, *J* = 6.4 Hz, 3H), 1.21-1.29 (m, 1H), 1.39-1.47 (m, 1H), 1.51-1.60 (m, 1H), 1.64 (dd, *J* = 5.3, 13.6 Hz, 1H), 1.67-1.73 (m, 1H), 1.78-1.86 (m, 1H), 1.95 (dd, *J* = 11.9, 24.5 Hz, 1H), 2.58 (dt, *J* = 5.4, 10.8 Hz, 1H), 3.36 (s, 1H), 5.07 (dt, *J* = 3.4, 11.8 Hz, 1H), 9.09 (m, 1H), 9.19 (dd, *J* = 1.6, 2.5 Hz, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 16.7, 21.9, 22.7, 23.2, 27.2, 27.7, 27.8, 28.3, 33.8, 35.8, 57.7, 67.0, 83.9, 122.0, 129.2, 134.6, 148.5, 161.6.

HRMS (EI): an accurate mass could not be obtained. A single ion with a *m/z* of 195 (C$_7$H$_3$N$_2$O$_5$) derived from cleavage of the 3,5-dinitrobenzoyl ester bond was observed.

2-*tert*-Butyldimethylsilyloxy-(7-methoxy-8-methylbicyclo[4.3.1]deca-1,7-diene (3.78)
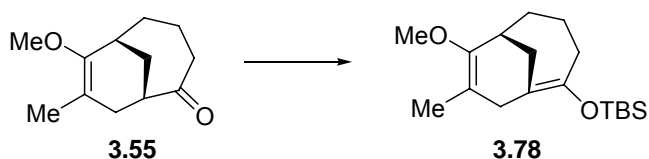
TBS-OTf (130 μL, 0.56 mmol) was added dropwise to a solution of **3.55** (50 mg, 0.26 mmol) and Et₃N (142 μL, 1.04 mmol) in Et₂O (5 mL) at 0°C. The solution was allowed to warm to room temperature and stirred for 5 h before being quenched *via* the addition to saturated aqueous NaHCO₃ solution (20 mL) and extracted with Et₂O (10 mL x 3). The solvent was removed under reduced pressure and the residue purified by flash chromatography on alumina, eluting with 2% and then 20% EtOAc/petroleum ether to give **3.77** as a colourless oil (68 mg, 87%).

FTIR (KBr, cm^{-1}): 2955, 2930, 2858, 1701, 1464, 1253, 1136, 839, 780.

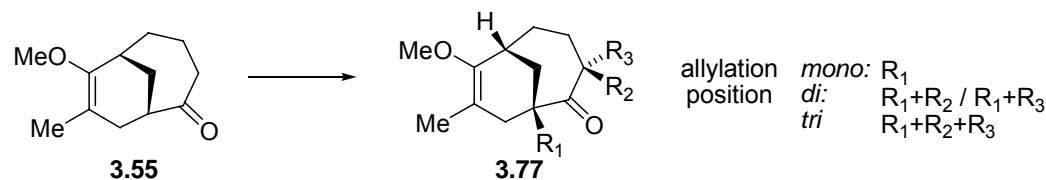**^{1}H NMR** (500 MHz, C₆D₆): δ 0.22 (s, 3H), 0.25 (s, 3H), 1.12 (s, 9H), 1.49-1.55 (m, H), 1.66-1.73 (m, 1H), 1.76-1.84 (m, 1H), 1.92 (s, 3H), 1.96 (ddd, *J* = 3.0, 5.7, 14.4 Hz, 1H), 2.06 (dd, *J* = 5.3, 12.4 Hz, 1H), 2.12-2.18 (m, 1H), 2.49-2.52 (m, 1H), 2.60 (dt, *J* = 1.7, 12.2 Hz, 2H), 2.87 (t, *J* = 12.7 Hz, 1H), 3.22 (d, *J* = 16.2 Hz, 1H), 3.38 (s, 3H).

^{13}C NMR (75 MHz, C₆D₆): δ -3.95, -3.89, 17.1, 18.8, 23.6, 26.3, 32.9, 33.4, 33.6, 35.1, 35.4, 57.7, 116.7, 121.7, 147.4, 153.4.

Allylation of 7-methoxy-8-methylbicyclo[4.3.1]dec-7-en-2-one (3.77)

KHMDS (0.927 μL of a 0.5 M solution in toluene, 0.44 mmol, 3 equiv) was added dropwise over 90 min to a solution of the ketone **3.55** (30 mg, 0.15 mmol) in THF (2 mL) and HMPA (0.4 mL, 20% v/v) at 0°C. The solution was stirred for 30 min at room temperature and then cooled to 0°C before the addition of allyl bromide (68 μL, 0.77 mmol, 5 equiv). The reaction was stirred for 12 h at room temperature before quenching with saturated aqueous NH₄Cl solution and extraction with EtOAc (10 mL x 3). The solvent was removed under reduced pressure and the residue purified by flash chromatography on silica, eluting with 3% EtOAc/pentane to give the tri-allylated adduct (8 mg, 19%), two di-allylated adducts (15.4 mg, 43%) and monoallylated adduct (4.9 mg, 14%) as colourless oils. The structures of the di- and tri-allylated adducts were confirmed by 2D NMR spectroscopy.

1,3,3'-Triallyl-7-methoxy-8-methylbicyclo[4.3.1]dec-7-en-2-one

^{1}H NMR (500 MHz, CDCl$_3$): δ 1.39-1.43 (m, 1H), 1.56 (s, 3H), 1.69 (m, 1H), 1.84 (ddd, *J* = 1.0, 6.7, 14.6 Hz, 1H), 1.90 (ddd, 1H, *J* = 3.1, 7.5, 11.2 Hz, 1H), 1.96 (d, *J* = 16.3 Hz, 1H), 2.09 (dd, *J* = 7.4, 13.8 Hz, 1H), 2.16 (dd, *J* = 7.0, 13.9 Hz, 1H), 2.23-2.36 (m, 5H), 2.43 (dd, *J* = 6.7, 14.5, Hz, 2H), 2.50 (dd, *J* = 7.5, 14.5 Hz, 1H), 2.80 (s, 1H), 3.46 (s, 3H), 4.93-5.12 (m, 6H), 5.67 (m, 3H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 15.8, 27.0, 30.1, 32.6, 35.4, 36.6, 41.9, 42.4, 45.7, 50.8, 55.1, 57.0, 117.0, 117.4, 118.2, 118.3, 133.1, 134.1, 135.7, 148.1, 216.8.

1,3,-Diallyl-7-methoxy-8-methylbicyclo[4.3.1]dec-7-en-2-one (as a 1:1 mixture of R$_1$+R$_2$ and R$_1$+R$_3$ diastereoisomers)

^{1}H NMR (500 MHz, CDCl$_3$): δ 1.13 (m, 2H), 1.24 (m, 1H), 1.44 (m, 2H), 1.53-1.66 (m, 3H), 1.58 (s, 3H), 1.60 (s, 3H), 1.73-1.84 (m, 4H), 1.84-1.98 (m, 2H), 2.00-2.09 (m, 2H), 2.13-2.43 (m, 7H), 2.51-2.69 (m, 4H), 2.70 (br s, 1H), 2.76 (br s, 1H), 3.43 (s, 3H), 3.48 (s, 3H), 4.93-5.07 (m, 8H), 5.60-5.72 (m, 4H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 15.6, 16.2, 27.0, 28.1, 28.9, 29.5, 31.6, 31.7, 33.3, 34.70, 34.74, 35.8, 38.1, 39.2, 42.4, 44.6, 45.5, 49.4, 49.5, 54.7, 56.9, 57.6, 116.3, 116.4, 117.8, 118.1, 118.4, 118.5, 132.9, 133.3, 135.2, 136.9, 148.5, 148.6, 216.8, 217.3.

1-allyl-7-methoxy-8-methylbicyclo[4.3.1]dec-7-en-2-one

^{1}H NMR (500 MHz, CDCl$_3$): δ 1.37 (q, *J* = 13.2 Hz, 1H), 1.41 (q, *J* = 13.2 Hz, 1H), 1.59 (s, 3H), 1.71-1.77 (m, 1H), 1.79-1.88 (m, 2H), 1.97 (dd, *J* = 7.8, 13.2 Hz, 1H), 2.06 (dd, *J* = 3.2, 13.2 Hz, 1H), 2.18 (dd, *J* = 1.6, 14.3 Hz, 1 H), 2.24 (dd, *J* = 7.5, 13.3 Hz, 1 H), 2.32 (dd, *J* = 7.3, 11.2 Hz, 1 H), 2.49 (dd, *J* = 1.6, 16.3 Hz, 1 H), 2.56 (t, *J* = 11.4 Hz, 1 H), 2.82 (s, 1 H), 3.46 (s, 1 H), 5.04 (dd, *J* = 13.5, 18.5 Hz, 1 H), 5.68 (m, 1H).

6.4   Experiments Described in Chapter Four

2-Iodoprop-2-en-1-ol (4.7a)[36]

4.7a

P = TBS **4.7b**
   = MOM **4.7c**
   = THP **4.7d**
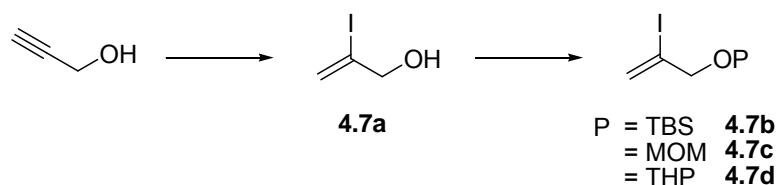
Chlorotrimethylsilane (15.2 mL, 0.12 mol) was added dropwise to a solution of NaI (17.9 g, 0.12 mol) dissolved in MeCN (100 mL) at room temperature. After stirring for 10 min, H_2O (1.08 mL, 0.06 mol) was added, followed after 5 min by propargyl alcohol (2.91 mL, 0.05 mol). The solution was stirred for 1 h and then quenched with the addition of H_2O (200 mL) and extracted with Et_2O (50 mL x 3). The combined organic phases were washed with saturated aqueous $Na_2S_2O_3$ solution (20 mL), H_2O (50 mL) and brine. The solvent was removed under reduced pressure and the residue purified by flash chromatography on alumina, eluting with 20% Et_2O/pentane, to give **4.7a** (4.7 g, 51%).

FTIR (KBr, cm^{-1}): 3325, 2916, 2857, 1629, 1443, 1400, 1231, 1146, 1034, 903, 648
^{1}H NMR (500 MHz, $CDCl_3$): δ 4.17 (t, J = 1.4 Hz, 3H), 5.86 (m, 1H), 6.38 (q, J = 1.7 Hz, 1H).
^{13}C NMR (75 MHz, $CDCl_3$): δ 70.6, 110.1, 124.4.
HRMS (EI): calc. for C_3H_5IO: 183.9385; obs. 183.9385.

Hydroxyl-protected derivatives of **4.7a** were prepared using standard protection methodology.[37]

tert-Butyl(2-iodoallyloxy)dimethylsilane (4.7b)[38]: prepared _via_ the reaction of **4.7a** (3 g, 16.3 mmol) with TBS-Cl (2.70 g, 17.9 mmol, 1.1 equiv) and imidazole (2.44 g, 35.9 mmol, 2.2 equiv) in sufficient DMF to effect dissolution (8 mL). After stirring for 2 h, aqueous work-up and extraction with Et_2O gave a quantitative return of the silylated adduct (4.9 g, 100%).

FTIR (KBr, cm^{-1}): 2955, 2932, 2858, 2361, 1628, 1470, 1258, 1134, 1084, 841, 780.
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.08 (s, 6H), 0.91 (s, 9H), 4.16 (t, J = 1.8 Hz, 2H), 5.80 (q, J = 1.6 Hz, 1H), 6.41 (dd, J = 1.8, 3.6 Hz, 1H).
^{13}C NMR (75 MHz, $CDCl_3$): δ -5.3, 18.3, 25.8, 71.0, 109.7, 122.8.
HRMS (EI): calc. for $C_9H_{19}IOSi$: 298.0250; obs. 240.9544 ($C_5H_{10}IOSi$, M^+ - ^tBu, calc: 240.9546).

2-Iodo-3-(methoxymethoxy)prop-1-ene (4.7c): MOM-Cl (0.42 mL, 5.44 mmol, 2 equiv) was added to a solution of **4.7a** (500 mg, 2.72 mmol) and Hünig's base (1.18 mL, 6.79 mmol, 2.5 equiv) in CH_2Cl_2 (5 mL) at 0°C. The solution was stirred at room temperature for 12 h, quenched with H_2O and extracted with Et_2O. The combined organics were washed with 1 M aqueous HCl solution followed by evaporation of the solvent under reduced pressure to give the title product as a colourless oil (0.546 g, 88%).

FTIR (KBr, cm^{-1}): 3452, 2889, 1628, 1447, 1400, 1215, 1153, 1103, 1045, 995, 907.

^{1}H NMR (500 MHz, CDCl$_3$): δ 3.39 (s, 3H), 4.13 (m, 2H), 4.66 (d, J = 0.8 Hz, 2H), 5.90 (m, 1H), 6.38 (m, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 55.5, 74.2, 95.0, 105.9, 126.3.

GCMS (EI): calc. for $C_5H_9IO_2$: 227.9647; obs. 228.

2-(2-Iodoallyloxy)-tetrahydro-2*H*-pyran (4.7d): DHP (496 μL, 5.44 mmol, 2 equiv) was added to a mixture of **4.7a** (508 mg, 2.76 mmol) and *p*-TsOH (52 mg, 0.27 mmol, 10 mol %) in CH_2Cl_2 (10 mL) at 0°C. The mixture was stirred for 1 h at 0°C and then at room temperature for 12 h. The solution was quenched with H_2O and extracted with Et_2O. The solvent was removed under reduced pressure and the residue purified by flash chromatography on silica, eluting with 10% EtOAc/petroleum ether, to give the THP protected adduct (551 mg, 74%).

FTIR (KBr, cm^{-1}): 2943, 2870, 1616, 1350, 1123, 1076, 1034, 980, 903, 872.

^{1}H NMR (500 MHz, CDCl$_3$): δ 1.50-1.69 (m, 4H), 1.71-1.77 (m, 1H), 1.80-1.90 (m, 1H), 3.50-3.54 (m, 1H) 3.86 (m, 1H), 4.24 (td, J = 1.3, 14.0 Hz, 1H), 4.10 (td, J = 1.3, 14.1 Hz, 1H), 4.68 (t, J = 3.4 Hz, 1H), 5.88 (d, J = 1.1 Hz, 1H), 6.38 (q, J = 1.5 Hz, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 18.9, 25.2, 30.2, 61.9, 73.7, 96.9, 106.7, 125.6.

HRMS (EI): calc. for $C_8H_{13}IO_2$: 267.9960: obs. 266.9893 ($C_8H_{12}IO_2$, M$^+$-H, calc: 266.9882), 166.9324 (C_3H_4I, M$^+$-OTHP, calc: 166.9358), 141.0910 ($C_8H_{13}O_2$, M$^+$-I, calc: 141.0916).

Hydrostannylation of Propargyl Alcohol Derivatives

	4.8a R = OH	4.8a-β
	4.8b R = OMOM	4.8b-β
	4.8c R = OTHP	4.8c-β
	4.8d R = OTBS	4.8d-β
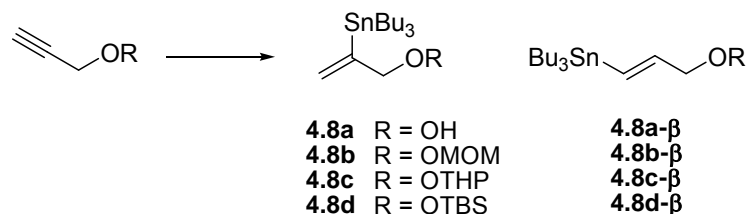
Hydrostannylation of propargyl alcohol and its protected derivatives was performed using the molybdenum catalyst Mo(*t*-BuNC)$_3$(CO)$_3$ and the method described in *Protocol B–b*. The protected propargyl alcohols were prepared *via* standard protection methodology.[37]

2-(Tributylstannyl)prop-2-en-1-ol (4.8a) and *(E)*-3-(Tributylstannyl)prop-2-en-1-ol (4.8a-β)

Stannylation of propargyl alcohol (56 mg, 1 mmol) in THF (1 mL) led to the isolation of **4.8a** (271 mg, 78%) and **4.8a-β** (3.8 mg, 1%) as colourless oils. The spectroscopic data acquired for these compounds were in agreement with reported literature values.[39]

2-(Tributylstannyl)prop-2-en-1-ol (4.8a)[39]

FTIR (KBr, cm^{-1}): 3314, 2959, 2938, 1462, 1377, 1022, 918, 667.

^{1}H NMR (500 MHz, CDCl$_3$): δ 0.86-0.94 (m, 15H), 1.31 (qd, *J* = 7.3, 14.4 Hz, 6H), 1.45-1.52 (m, 6H), 4.27 (tt, *J* = 5.9 Hz, $^3J_{\text{Sn-H}}$ = 30.0 Hz, 2H), 5.24 (dt, *J* = 1.7 Hz, $^3J_{\text{Sn-H}}$ = 61.5 Hz, 1H), 5.87 (dt, *J* = 1.8 Hz, $J_{\text{Sn-H}}$ =128.9 Hz, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 9.4, 13.6, 27.3, 29.1, 69.4, 122.7, 154.7.

(E)-3-(Tributylstannyl)prop-2-en-1-ol (4.8a-β)[39]

^{1}H NMR (500 MHz, CDCl$_3$): δ 0.86-0.90 (m, 15H), 1.30 (qd, *J* = 7.3, 14.5 Hz, 6H), 1.39-1.52 (m, 6H), 4.16 (dd, *J* = 3.5, 5.6 Hz, 2H), 6.13-6.21 (m, 2H).

Tributyl(3-(methoxymethoxy)prop-1-en-2-yl)stannane (4.8b)

Stannylation of 3-(methoxymethoxy)prop-1-yne (500 mg, 5 mmol) in THF (5 mL) led to the isolation of **4.8b** as a colourless oil (1.58 g, 81%).

FTIR (KBr, cm^{-1}): 2955, 2938, 2874, 1462, 1150, 1107, 1049, 922.

^{1}H NMR (500 MHz, CDCl$_3$): δ 0.85-0.92 (m, 15H), 1.30 (qd, *J* = 7.3, 14.4 Hz, 6H), 1.44-1.52 (m, 6H), 3.36 (s, 3H), 4.18 (td, *J* = 1.7 Hz, $^3J_{\text{Sn-H}}$ = 16.3 Hz, 2H), 4.62 (s, 2H) 5.26 (tdd, 1H, *J* = 1.6, 4.2 Hz, $^3J_{\text{Sn-H}}$ = 31.6 Hz, 1H), 5.88 (tdd, 1H, *J* = 1.8, 4.4 Hz, $^3J_{\text{Sn-H}}$ = 66.2 Hz, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 9.5, 13.7, 27.3, 29.1, 55.2, 74.2, 95.5, 125.7, 152.0.

HRMS (EI): calc. for C$_{13}$H$_{27}$O$_2$Sn: 392.1737; obs. 335.1045 (C$_{13}$H$_{27}$O$_2$Sn, M$^+$ - Bu, calc: 335.1033).

Tributyl(3-(tetrahydro-2*H*-pyran-2-yloxy)prop-1-en-2-yl)stannane 4.8c

Stannylation of 2-(prop-2-ynyloxy)-tetrahydro-2*H*-pyran (140.2 mg, 1 mmol) in THF (1 mL) led to the isolation of **4.8c** as a colourless oil (140 mg, 32%), (60% b.r.s.m.).

FTIR (KBr, cm^{-1}): 2955, 2938, 2870, 1462, 1119, 1080, 1030, 976.

^{1}H NMR (500 MHz, CDCl$_3$): δ 0.85-0.98 (m, 15H), 1.26-1.34 (m, 6H), 1.42-1.64 (m, 10H), 1.67-1.74 (m, 1H), 1.80-1.88 (m, 1H), 3.48-3.53 (m, 1H), 3.83-3.88 (m, 1H), 4.04 (dtt, *J* = 1.7, 12.8, Hz, $^3J_{Sn-H}$ = 16.5 Hz, 1H), 4.39 (dtt, *J* = 1.7, 12.8 Hz, $^3J_{Sn-H}$ = 16.5 Hz, 1H), 4.63 (t, *J* = 3.4 Hz, 1H), 5.24 (dtt, *J* = 1.8, 2.6 Hz, $^3J_{Sn-H}$ = 30.5 Hz, 1H), 5.89 (dtt, *J* = 1.8, 2.6 Hz, $^3J_{Sn-H}$ = 66.9 Hz, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 9.6, 13.7, 19.2, 25.5, 27.4, 29.1, 30.5, 61.7, 74.2, 97.9, 124.2, 152.4.

HRMS (EI): calc. for C$_{20}$H$_{40}$OSn: 432.205; obs. 375.1354 (C$_{16}$H$_{31}$O$_2$Sn, M$^+$ - Bu, calc: 375.1346).

tert-Butyldimethyl(2-(tributylstannyl)allyloxy)silane (4.8d)

Stannylation of *tert*-butyldimethyl(prop-2-ynyloxy)silane (500 mg, 2.9 mmol) in THF (5 mL) led to the isolation of **4.8d** (817 mg, 60%) and **4.8d-β** (59 mg, 4%) as colourless oils.

FTIR (KBr, cm^{-1}): 2955, 2928, 2855, 1462, 1254, 1076, 853, 775.

^{1}H NMR (500 MHz, CDCl$_3$): δ 0.05 (s, 6H), 0.86-0.91 (m, 15H), 0.90 (s, 9H), 1.30 (qd, *J* = 7.3, 14.5 Hz, 6H), 1.44-1.51 (m, 6H), 4.27 (tt, *J* = 1.9 Hz, $^3J_{Sn-H}$ = 12.7 Hz, 2H), 5.16 (tdd, 1 H, *J* = 1.9, 4.6 Hz, $^3J_{Sn-H}$ = 32.4 Hz, 1H), 5.85 (tdd, 1H, *J* = 2.0, 4.7 Hz, $^3J_{Sn-H}$ = 64.8 Hz, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ -5.3, 9.5, 13.7, 18.5, 26.0, 27.4, 29.2, 69.7, 121.9, 154.8.

HRMS (EI): calc. for C$_{21}$H$_{46}$OSiSn: 462.2340; obs. 405.1631 (C$_{17}$H$_{37}$OSiSn, M$^+$ - Bu, calc: 405.1636).

(But-2-ynyloxy)(*tert*-butyl)dimethylsilane (4.21a) and 2-(But-2-ynyloxy)-tetrahydro-2*H*-pyran (4.21b)

R = TBS **4.21a**
R = THP **4.21b**
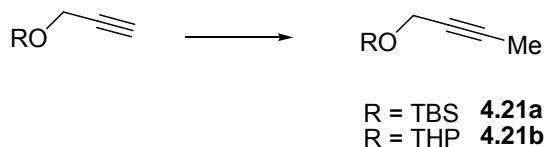
(But-2-ynyloxy)(*tert*-butyl)dimethylsilane (4.21a)[40]

n-BuLi (10.2 mL of a 1.6 M solution in hexanes, 16.3 mmol, 1.1 equiv) was added dropwise to *tert*-butyldimethyl(prop-2-ynyloxy)silane (2.54 g, 14.9 mmol) in THF (100 mL) at -50°C and stirred at -50°C for 2 h. Methyl iodide (0.93 mL, 45 mmol, 3 equiv) was added in one portion and the solution warmed to room temperature and stirred for 6 h. The mixture was quenched with the addition of saturated aqueous NH$_4$Cl solution (100 mL) and H$_2$O (300 mL) and extracted with CH$_2$Cl$_2$ (20 mL x 3). The solvents were removed under reduced pressure to give **4.21a** as light yellow liquid (2.57 g, 92%).

The spectroscopic data was in agreement with the reported literature values.[40]
FTIR (KBr, cm^{-1}): 2932, 2858, 1466, 1369, 1254, 1146, 1080, 1103, 837, 779.
^{1}H NMR (500 MHz, CDCl$_3$) δ 0.10 (s, 6H), 0.90 (s, 9H), 1.82 (t, *J* = 2.3 Hz, 3H), 4.26 (q, *J* = 2.3 Hz, 2H).
^{13}C NMR (75 MHz, CDCl$_3$): δ -5.3, 3.4, 18.3, 25.8, 51.8, 77.7, 80.8.

2-(But-2-ynyloxy)-tetrahydro-2*H*-pyran (4.21b) [41]

Prepared *via* the method described above: 2-(Prop-2-ynyloxy)-tetrahydro-2*H*-pyran (2.92 g, 20.8 mmol) was reacted with *n*-BuLi (15.6 mL of a 1.6M solution in hexanes, 25 mmol, 1.1 equiv) and the lithio species quenched with methyl iodide (6.5 mL, 104 mmol) to give the title compound upon work-up (3.14 g, 98%).

FTIR (KBr, cm^{-1}): 2943, 2870, 1443, 1346, 1265, 1119, 1026, 903.
^{1}H NMR (500 MHz, CDCl$_3$): δ 1.48-1.82 (m, 6H), 1.84 (t, *J* = 2.3 Hz, 1H), 3.51 (td, *J* = 4.8, 10.3 Hz, 1H), 3.77-3.86 (m, 1H), 4.14 (dq, *J* = 2.2, 15.2 Hz, 1H), 4.26 (dq, *J* = 2.2, 15.2 Hz, 1H), 4.78 (t, *J* = 3.3 Hz, 1H).
^{13}C NMR (75 MHz, CDCl$_3$): δ 3.1, 18.8, 25.1, 29.9, 54.1, 61.4, 74.7, 81.5, 96.2.

(E)-*tert*-Butyldimethyl(2-(tributylstannyl)but-2-enyloxy)silane   (4.10a)   and   (E)-*tert*-butyldimethyl(3-(tributylstannyl)but-2-enyloxy)silane (4.10a-β)
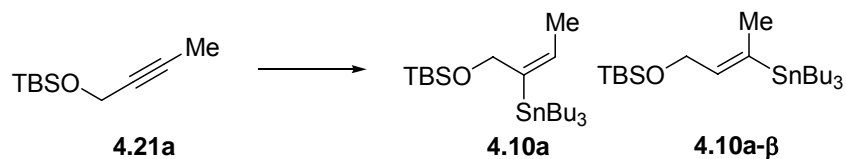
Prepared using *Protocol B-a* (23°C, 12 h); stannylation of **4.21a** (147 mg, 0.8 mmol) in THF (5 mL) led to the isolation of the products **4.10a** (137.5 mg, 36%) and **4.10a-β** (80.8 mg, 21%).

(E)-*tert*-Butyldimethyl(2-(tributylstannyl)but-2-enyloxy)silane (4.10a)

FTIR (KBr, cm^{-1}): 2955, 2928, 2856, 2365, 1464, 1258, 1082, 853, 835, 779.

^{1}H NMR (500 MHz, CDCl$_3$) δ 0.06 (s, 6H), 0.82-0.87 (m, 4H), 0.87 (t, $J = 7.5$ Hz, 9H), 0.91 (s, 9H), 1.29 (m, 6H), 1.34-1.52 (m, 18H), 1.63 (ddt, $J = 1.3, 6.8, 5.5$ Hz, 3H), 4.36 (tdd, $J = 1.2, 2.3$ Hz, $^3J_{\text{Sn-H}} = 35.0$ Hz, 2H), 5.54 (td, $J = 2.5, 6.5$ Hz, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ -5.3, 10.1, 13.7, 15.3, 18.6, 26.2, 27.5, 29.3, 64.7, 131.5, 148.0.

HRMS (EI): calc. for C$_{22}$H$_{48}$OSiSn: 476.2496; obs. 419.1773 (C$_{18}$H$_{39}$OSiSn, M$^+$- Bu, calc: 419.1792).

(E)-*tert*-butyldimethyl(3-(tributylstannyl)but-2-enyloxy)silane (4.10a-β)[42]

FTIR (KBr, cm^{-1}): 2928, 2959, 2855, 1462, 1377, 1254, 1088, 1042, 837, 775, 667.

^{1}H NMR (500 MHz, CDCl$_3$): δ 0.06 (s, 6H), 0.85-0.93 (m, 15H), 0.90 (s, 9H), 1.27-1.37 (m, 12H), (q, $J = 7.8$ Hz, 6H), 1.44-1.51 (m, 6H), 1.60-1.67 (m, 6H), 1.82 (t, $^3J_{\text{Sn-H}} = 45.0$ Hz, 3H), 5.51 (d, $J = 4.3$ Hz, 2H), 5.64 (t, $^3J_{\text{Sn-H}} = 68.0$ Hz, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ -5.1, 9.0, 13.6, 17.5, 25.9, 27.4, 27.8, 29.1, 60.0, 139.1, 140.7.

(E)-Tributyl(1-(tetrahydro-2*H*-pyran-2-yloxy)but-2-en-2-yl)stannane   (4.10b)   and   (E)-Tributyl(4-(tetrahydro-2*H*-pyran-2-yloxy)but-2-en-2-yl)stannane   (4.10b-β)
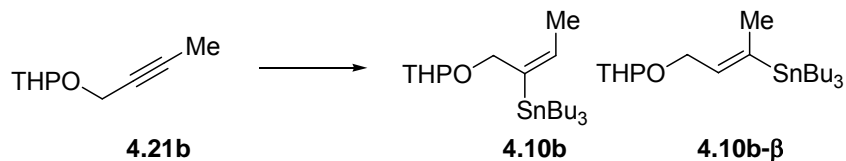
Prepared using *Protocol B-a* (23°C, 12 h); stannylation of **4.21b** (103 mg, 0.67 mmol) in THF (5 mL) led to the isolation of the products **4.10b** (85.1 mg, 29%) and **4.10b-β** (40.3 mg, 14%).

(*E*)-Tributyl(1-(tetrahydro-2*H*-pyran-2-yloxy)but-2-en-2-yl)stannane (4.10b)[43]

FTIR (KBr, cm^{-1}): 2955, 2924, 2361, 2341, 1026.

^{1}H NMR (500 MHz, CDCl$_3$): δ 0.87 (t, *J* = 7.5 Hz, 9H), 1.29 (m, 6H), 1.39-1.74 (m, 17H), 1.67 (dt *J* = 1.0, 6.5 Hz, 3H), 1.79-1.89 (m, 1H), 3.52 (ddt, *J* = 1.5, 4.0, 11.5 Hz, 1H), 3.84 (t, 1H), 4.04 (tddd, *J* = 1.5, 2.5, 13.0, 17.0 Hz, 1H), 4.54 (tddd, *J* = 1.3, 2.4, 13.0, 17.2 Hz, 1H), 4.65 (t, *J* = 3.5 Hz, 1H), 5.63 (tq, *J* = 2.3, 6.5 Hz, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 10.0, 13.7, 15.5, 19.1, 25.5, 27.4, 29.2, 30.5, 61.5, 69.3, 98.3, 133.4, 143.9.

HRMS (EI): calc. for C$_{17}$H$_{34}$O$_2$Sn: 446.2007; obs. 389.1505 (C$_{17}$H$_{33}$O$_2$Sn, M$^+$- Bu, calc: 389.1503).

Tributyl(4-(tetrahydro-2*H*-pyran-2-yloxy)but-2-en-2-yl)stannane (4.10b-β)[44]

FTIR (KBr, cm^{-1}): 2955, 2926, 2361, 2341, 1024.

^{1}H NMR (500 MHz, CDCl$_3$): δ 0.88 (t, *J* = 7.5 Hz, 9H), 1.30 (qd, *J* = 7.5, 14.5 Hz, 6H), 1.39-1.62 (m, 8H), 1.69-1.75 (m, 2H), 1.80-1.88 (m, 2H), 1.87 (t, *J* = 1.0 Hz, 3H), 3.50 (m, 1H), 3.89 (ddd, *J* = 3.0, 7.5, 11.0 Hz, 1H), 4.168 (dd, *J* = 6.5, 12.5 Hz, 1H), 4.28 (dd, *J* = 5.4, 12.6 Hz, 1H), 4.62 (dd, *J* = 3.5, 4.0 Hz, 1H), 5.67-5.71 (m, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 9.1, 13.7, 19.5, 19.6, 25.5, 27.4, 29.1, 30.7, 62.4, 63.1, 97.9, 136.5, 142.8.

HRMS (EI): calc. for C$_{17}$H$_{34}$O$_2$Sn: 446.2007; obs. 389.1501 (C$_{17}$H$_{33}$O$_2$Sn, M$^+$- Bu, calc: 389.1503).

(Z)-6-((*tert*-Butyldimethylsilyloxy)methyl)-*N*-methoxy-*N*-methyl-5-methyleneoct-6-enamide (4.22)
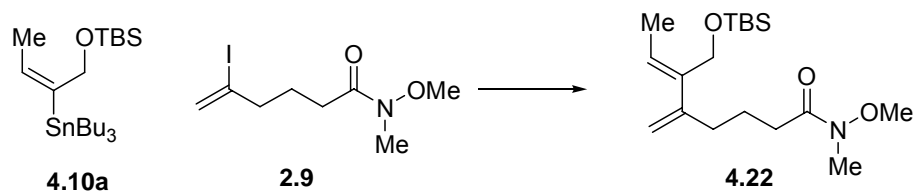
A solution of **2.9** (106 mg, 0.37 mmol) and **4.10a** (268 mg, 0.56 mmol) in NMP (5 mL) was degassed with Ar for 5 min at 0°C. Solid CuTC (142 mg, 0.75 mmol) was added in one portion and the reaction allowed to warm to room temperature with stirring over 12 h. The mixture was quenching *via* addition of saturated aqueous NH$_4$Cl solution (100 mL) and extracted with Et$_2$O (25 mL x 3). The combined organic layers were washed successively with 1 M aqueous HCl

solution (20 mL) and H_2O (20 mL x 5) to remove residual NMP. The solvent was removed under reduced pressure and the residue purified by flash chromatography on silica, eluting with 10% EtOAc/petroleum ether, to give the **4.22** as a colourless oil (30 mg, 24%) followed by unreacted **2.9** (60 mg, 56% recovery).

FTIR (KBr, cm^{-1}): 2955, 2932, 2856, 1665, 1462, 1414, 1387, 1254, 1178, 1080, 1003, 837, 775.

^{1}H NMR (500 MHz, CDCl$_3$): δ 0.05 (s, 6H), 0.09 (s, 9H), 1.76 (d, $J = 6.9$ Hz, 3H), 1.73-1.79 (m, 2H), 2.29 (t, $J = 7.5$ Hz, 2H), 2.40 (t, $J = 7.1$ Hz, 2H), 3.17 (s, 3H), 3.66 (s, 3H), 4.32 (s, 2H), 4.87 (s, 1H), 5.11 (s, 1H), 5.74 (q, $J = 6.9$ Hz, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ -5.3, 13.8, 18.3, 23.2, 25.9, 31.4, 32.2, 33.7, 58.8, 61.1, 111.4, 124.5, 126.0, 139.2, 147.6, 174.2.

HRESIMS (EI): calc. $C_{18}H_{35}NO_3Si$: 342.2465 (MH$^+$); obs. 342.2472.

Methyl 7-hdroxyhept-5-ynoate (4.42)
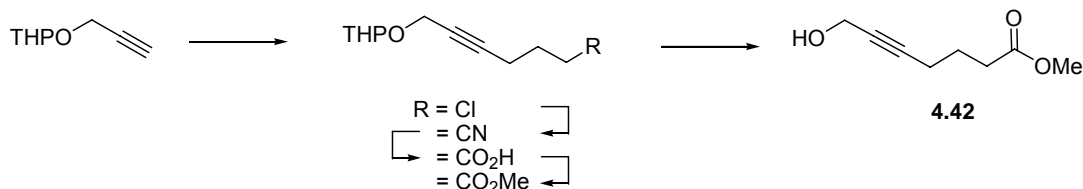
Prepared by the method initially reported by Corey and Sachdev[45] as detailed by Haynes *et al.*[46] and by Luo and Negishi.[47] Spectroscopic details of all intermediates were in agreement with those reported in the literature.

2-(6-Chlorohex-2-ynyloxy)-tetrahydro-2*H*-pyran[46]

n-BuLi (343 mL of a 1.6M solution in hexanes, 0.55 mol) was added dropwise to a solution of 2-(prop-2-ynyloxy)-tetrahydro-2*H*-pyran[48] (70 g, 0.5 mol) in THF (500 mL) at -30°C over 1 h. The solution was stirred at -15°C for 30 min, 0°C for 30 min and then treated with the dropwise addition of 1-bromo-3-chloropropane (74.2 mL, 0.75 mol) in THF (100 mL). The resultant mixture was stirred at -30°C for 30 min and then heated to reflux for 16 h. The reaction was quenched with the addition of H_2O (100 mL) and the solvents removed under reduced pressure to give a dark brown liquid which was diluted into H_2O (1.5 L) and extracted with Et$_2$O (200 mL x 4). Evaporation of the solvent and distillation under reduced pressure gave a pre-run of 1-

bromo-3-chloropropane (45-60°C / 0.1 mmHg) followed by the alkyl-chloride as a colourless liquid (88.5 g, 82%).

bp: 86-88°C / 0.1 mmHg, [lit. 112-114°C / 0.25 mmHg)[47]

FTIR (KBr, cm^{-1}): 2943, 2870, 1443, 1346, 1204, 1119, 1076, 1022, 903.

^{1}H NMR (500 MHz, CDCl$_3$): δ 1.47-1.64 (m, 4H), 1.72 (tt, J = 3.2, 10.1 Hz, 1H), 1.77-1.85 (m, 1H), 1.94 (qn, J = 6.6, 6.7 Hz, 2H), 2.40 (t, J = 6.8 Hz, 2H), 3.49-3.53 (m, 1H), 3.62 (t, J = 6.4 Hz, 2H), 3.79-3.84 (m, 1H), 4.17 (d, J = 15.3 Hz, 1H), 4.26 (d, J = 15.3 Hz, 1H), 4.77 (t, J = 3.3 Hz, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 16.0, 18.9, 25.2, 30.1, 31.1, 43.4, 54.2, 61.7, 76.7, 84.2, 96.5.

7-(Tetrahydro-2*H*-pyran-2-yloxy)hept-5-ynenitrile[46]

The above obtained alkyl chloride (83.1 g, 0.38 mol) was added dropwise to a solution of dry NaCN (20.8 g, 0.42 mol) in DMSO (300 mL) at 50°C such that the internal temperature did not exceed 65°C [Note: mild exotherm]. The solution was heated to 80°C for 48 h, cooled and quenched with the addition of H$_2$O (2 L). The aqueous layer was extracted with Et$_2$O (200 mL x 4) and the combined organic layers washed with H$_2$O (200 mL x 3) to remove residual DMSO. Evaporation of the solvents under reduced pressure gave a black oil which was distilled under reduced pressure to give the alkyl nitrile product as a colourless oil (65.5 g, 82%).

bp: 120°C / 0.1 mmHg, [lit. 105-108°C at / 0.015 mm Hg][46]

FTIR (KBr, cm^{-1}): 2943, 2870, 1442, 1346, 1119, 1022, 907, 733.

^{1}H NMR (500 MHz, CDCl$_3$): δ 1.48-1.64 (m, 4H), 1.69-1.76 (m, 1H), 1.77-1.89 (m, 4H), 2.40 (t, J = 6.7 Hz, 2H), 2.48 (t, J = 7.2 Hz, 2H), 3.49-3.54 (m, 1H), 3.82 (m, 1H), 4.19 (d, J = 15.4 Hz, 1H), 4.29 (d, J = 15.4 Hz, 1 H), 4.76 (t, J = 3.3 Hz, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 16.4, 18.3, 19.4, 24.8, 25.7, 30.6, 54.7, 62.3, 78.3, 83.9, 97.1, 119.5.

7-(Tetrahydro-2*H*-pyran-2-yloxy)hept-5-ynoic acid[47]

The above obtained alkyl cyanide (5 g, 24.1 mmol) was heated to reflux in a solution of EtOH (150 mL) and 10% aqueous NaOH (150 mL) until the evolution of ammonia ceased (*ca.* 36 h). The mixture was cooled, diluted with ice-cold H$_2$O (250 mL), acidified with conc. aqueous HCl solution and then extracted with Et$_2$O (100 mL x 3). Evaporation of the solvent gave the title compound as a colourless oil (5.1 g, 94%)

FTIR (KBr, cm^{-1}): 3105, 3047, 2943, 2870, 2361, 1709, 1439, 1204, 1118, 1022, 903.

^{1}H NMR (500 MHz, CDCl$_3$): δ 1.47-1.75 (m, 6H), 1.83 (qn, 2H), 2.30 (t, J = 6.9 Hz, 2H), 2.47 (t, J = 7.4 Hz, 2H), 3.47-3.54 (m, 1H), 3.80-3.85 (m, 1H), 4.18 (d, J = 15.3 Hz, 1H), 4.27 (d, J = 15.3 Hz, 1H), 4.79 (t, J = 3.3 Hz, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 18.0, 18.9, 23.3, 25.2, 30.1, 32.6, 54.4, 61.8, 76.7, 85.0, 96.5, 178.6.

Methyl 7-(tetrahydro-2*H*-pyran-2-yloxy)hept-5-ynoate[47]

A solution of crude 7-(tetrahydro-2*H*-pyran-2-yloxy)hept-5-ynoic acid (6.23 g, 27.6 mmol) in DMF (100 mL) was treated with anhydrous K$_2$CO$_3$ (5.7 g, 41.4 mmol) and methyl iodide (2.6 mL, 41.4 mmol). After stirring for 12 h at room temperature, the solution was quenched with H$_2$O (300 mL) and extracted with Et$_2$O (100 mL x 3). The solvent was removed under reduced pressure to give the title compound as a colourless oil (6.09 g, 92%).

FTIR (KBr, cm^{-1}): 2947, 2870, 1740, 1439, 1362, 1203, 1161, 1119, 1026.

^{1}H NMR (500 MHz, CDCl$_3$): δ 4.19-1.65 (m, 4H), 1.70-1.76 (m, 1H), 1.83 (qn, 2H), 2.29 (tt, J = 2.1, 7.0 Hz, 2H), 2.43 (t, J = 7.4 Hz, 2H), 3.48-3.54 (m, 1H), 3.67 (s, 3H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 18.0, 18.9, 23.5, 25.1, 30.0, 32.5, 51.3, 54.2, 61.7, 76.5, 84.9, 96.4, 173.2.

Methyl 7-hydroxyhept-5-ynoate (4.42)[46]

The above obtained ester (6 g, 25.0 mmol) in MeOH (100 mL) was treated with catalytic PPTS (150 mg, 2 mol %) and allowed to stir at room temperature for 12 h. The solution was quenched *via* the addition of saturated aqueous NaHCO$_3$ solution (100 mL) and extracted with Et$_2$O (100 mL x 3). The solvent was removed under reduced pressure and the product distilled to give **4.42** (3.51 g, 90%).

bp: 120°C / 0.1 mmHg, [lit. 105-108°C / 0.015 mm Hg].[47]

FTIR (KBr, cm^{-1}): 3425, 2951, 2924, 1736, 1439, 1669, 1127, 1161, 1015.

^{1}H NMR (500 MHz, CDCl$_3$): δ 1.81 (m, 2H), 2.27 (t, J = 6.9 Hz, 2H), 2.42 (t, J = 7.4 Hz, 2H), 3.65 (s, 3H), 4.21 (s, 2H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 17.8, 23.4, 32.4, 50.4, 51.3, 79.2, 84.1, 173.6

Methyl 7-(methoxymethoxy)hept-5-ynoate (4.43)


4.42   **4.43**
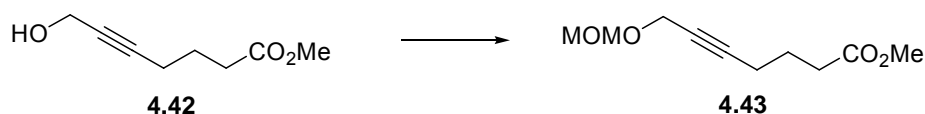
MOM-Cl (0.974 mL, 12.8 mmol) was added dropwise to a solution of **4.42** (1 g, 6.4 mmol) and Hünig's base (2.79 mL, 16.0 mmol) in CH_2Cl_2 (20 mL) at 0°C and stirred at room temperature for 12 h. The reaction mixture was quenched with the addition of saturated aqueous $NaHCO_3$ solution (50 mL) and extracted with Et_2O (50 mL x 3). The organic layer was washed with 1 M HCl solution (10 mL) and the solvent removed under reduced pressure. Purification of the residue by flash chromatography on silica gel, eluting with 20% EtOAc/petroleum ether, gave **4.43** as a colourless oil (1.28 g, 100%).

FTIR (KBr, cm^{-1}): 2951, 2893, 1740, 1439, 1373, 1215, 1153, 1045, 991, 921.

^{1}H NMR (500 MHz, CDCl$_3$): δ 1.83 (qn, J = 7.2 Hz, 2H), 2.29 (tt, J = 2.2, 6.9 Hz, 2H), 2.43 (t, J = 7.4 Hz, 2H), 3.36 (s, 3H), 3.66 (s, 3H), 4.18 (t, J = 2.2 Hz, 2H), 4.68 (s, 2H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 17.9, 23.5, 32.5, 51.3, 54.3, 55.2, 76.2, 85.3, 94.4, 173.2.

HRMS (EI): calc. for $C_{10}H_{16}O_4$: 200.1049; obs. 170.0935 ($C_9H_{14}O_3$, M$^+$ - OCH$_2$, calc: 170.0943), 155.0690 ($C_8H_{11}O_3$, M$^+$-CH$_2$OMe, calc: 155.0708).

Methyl 7-(*tert*-butyldimethylsilyloxy)hept-5-ynoate (4.44)

4.42   **4.44**
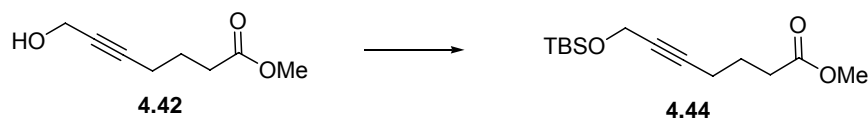
The alkynyl alcohol **4.42** (4.6 g, 29.5 mmol), TBDMS-Cl (4.9 g, 32.5 mmol, 1.1 equiv) and imidazole (4.4 g, 65.0 mmol, 2.2 equiv) were sequentially placed in a dry flask with a magnetic stirring bar and flushed with argon. Sufficient dry DMF (~14 mL) was then added to effect solution and the reaction stirred at room temperature for 12 h. The reaction was diluted into 200 mL of pentane and washed with H_2O (3 x 50 mL). The solvent was removed under reduced pressure and the residue purified by flash chromatography on silica gel, eluting with 10% EtOAc/petroleum ether, to give **4.44** as a colourless oil (7.3 g, 92%).

FTIR (KBr, cm^{-1}): 2932, 2859, 1744, 1439, 1370, 1254, 1138, 1080, 837, 779.

^{1}H NMR (500 MHz, CDCl$_3$): δ 0.10 (s, 6H), 0.90 (s, 9H), 1.82 (q, J = 7.1 Hz, 2H), 2.27 (tt, J = 2.2, 6.9 Hz, 2H), 2.43 (t, J = 7.5 Hz, 2H), 3.67 (s, 3H), 4.29 (dd, J = 2.0 Hz, 4.1 Hz, 2H).

^{13}C NMR (75 MHz, CDCl$_3$): δ -5.2, 18.1, 18.2, 23.6, 25.7, 32.6, 51.3, 51.7, 79.5, 83.8, 173.3.

HRMS (EI): calc. for C$_{14}$H$_{26}$O$_3$Si: 270.1651; obs. 239.1453 (C$_{13}$H$_{23}$O$_2$Si, M$^+$- OMe, calc: 239.1467), 213.0953 (C$_{10}$H$_{17}$O$_3$Si, M$^+$- t-Bu, calc: 213.0947).

Methyl 6-((methoxymethoxy)methyl)-5-methylenehept-6-enoate (4.46)
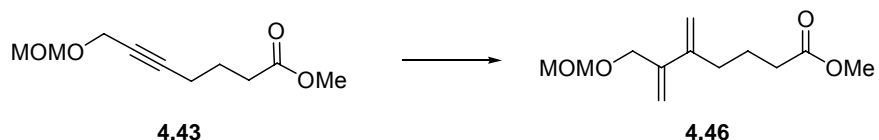
The alkyne **4.43** (400 mg, 2.04 mmol) was dissolved in toluene (40 mL) and sparged with ethylene for 5 min. Grubbs II catalyst **4.25** (34 mg, 0.04 mmol, 2 mol %) was added and the flask sealed under an ethylene atmosphere maintained by an attached balloon. The solution was heated at 80°C for 6 h with vigorous stirring resulting in complete consumption of the starting alkyne, as assessed by ^{1}H NMR spectroscopy. The reaction was quenched *via* the addition of ethyl vinyl ether (0.5 mL) and the solvent removed under reduced pressure and the residue purified by flash chromatography on silica, eluting with 10% EtOAc/petroleum ether, to give **4.46** as a colourless oil (440 mg, 96%).

FTIR (KBr, cm^{-1}): 2951, 2889, 1740, 1597, 1439, 1150, 1107, 1053, 914.

^{1}H NMR (500 MHz, CDCl$_3$): δ 1.80 (qn, J = 7.5 Hz, 2H), 2.32 (t, J = 7.5 Hz, 2H), 2.30 (t, J = 7.5 Hz, 2H), 3.37 (s, 3H), 3.66 (s, 3H), 4.22 (d, J = 1.8 Hz, 2H), 4.65 (s, 2H), 5.00 (s, 1H), 5.15 (s, 1H), 5.27 (s, 1H), 5.28 (s, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 23.3, 33.0, 33.1, 51.1, 55.0, 68.0, 94.2, 112.6, 113.9, 142.6, 144.3, 173.5.

HRMS (EI): calc. for C$_{10}$H$_{16}$O$_4$: 228.1361; obs. 198.1259 (C$_{11}$H$_{18}$O$_3$, M$^+$ - OCH$_2$, calc. 198.1256), 184.1101 (C$_{10}$H$_{16}$O$_3$, M$^+$ - CH$_2$OMe, calc. 184.1099)

Methyl 6-((*tert*-butyldimethylsilyloxy)methyl)-5-methylenehept-6-enoate (4.47)
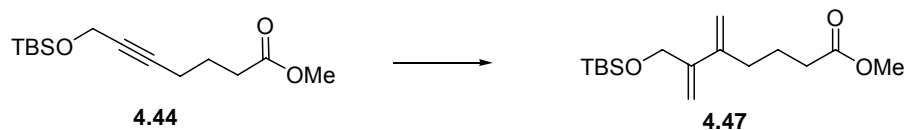
Atmospheric Ethylene Pressure:

The silyl-alkyne **4.44** (5 g, 18.5 mmol) was dissolved in toluene (100 mL) in a 250 mL flask equipped with a magnetic stirring bar and sparged with ethylene for 5 min. Grubbs II catalyst **4.25** (785 mg, 0.93 mmol, 5 mol %) was added and the flask sealed under a ethylene atmosphere maintained by an attached balloon. The solution was heated at 80°C for 12 h with vigorous stirring. The reaction was monitored *via* ^{1}H NMR spectroscopy of 100 μL sample aliquots. If necessary, additional catalyst (1 mol %) was added portion-wise to ensure complete conversion. Upon completion the reaction was cooled and quenched with the addition of ethyl vinyl ether (2 mL). Evaporation of the solvent yielded a black oil which was purified by flash chromatography on silica, eluting with 7.5% EtOAc/petroleum ether, to give **4.47** as a colourless oil (4.62 g, 84%).

High Pressure:

To a Parr stainless steel reaction vessel (with internal pressure and temperature control) was added **4.44** (1 g, 3.7 mmol), Grubbs II catalyst **4.25** (62 mg, 0.07 mmol, 2 mol %) and DCE (50 mL). The assembled reactor vessel was purged with ethylene (x 3), sealed and pressurised to 80 psi. The reactor was heated to 55°C, resulting in an increase in pressure to 109 psi, and stirred for 24 h. A sample aliquot indicated complete conversion after 24 h, as assessed by ^{1}H NMR spectroscopy. The solution was quenched with the addition of ethyl vinyl ether (2 mL) and the solvent evaporated under reduced pressure to yield a black oil. Purification of this material *via* flash chromatography on silica, eluting with 7.5% EtOAc/petroleum ether, gave **4.47** as a colourless oil (1.02 g, 92%).

FTIR (KBr, cm^{-1}): 2955, 2858, 1744, 1597, 1462, 1254, 1169, 1096, 903, 837, 775.

^{1}H NMR (500 MHz, CDCl$_3$): δ 0.07 (s, 6H), 0.91 (s, 9H), 1.79 (qn, 2H), 2.28 (t, *J* = 7.8 Hz, 2H), 2.31 (t, *J* = 7.7 Hz, 2H), 3.66 (s, 3H), 4.29 (s, 2H), 4.91 (s, 1H), 4.99 (s, 1H), 5.19 (s, 1H), 5.33 (s, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ -5.3, 23.5, 33.2, 33.4, 51.4, 55.3, 68.3, 95.5, 112.9, 114.2, 142.8, 144.5, 173.8.

HRMS (EI): calc. for C$_{16}$H$_{30}$O$_3$Si: 298.19642; obs. 283.1719 (C$_{15}$H$_{27}$O$_3$Si, M$^+$ - Me, calc: 283.1730), 241.1257 (C$_{12}$H$_{21}$O$_3$Si, M$^+$ - ^{t}Bu, calc: 241.1260).

N-Methoxy-6-((methoxymethoxy)methyl)-N-methyl-5-methylenehept-6-enamide (4.17)

**4.46**   **4.17**
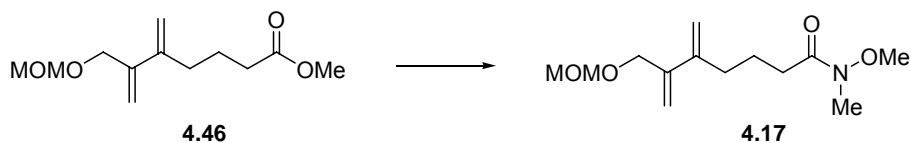
Me$_3$Al (16.4 mL of a 2 M solution in toluene, 32.9 mmol) was added dropwise to a stirred suspension of *N,O*-dimethylhydroxylamine hydrochloride (3.34 g, 34.2 mmol) in CH$_2$Cl$_2$ (150 mL) at -40°C and allowed to warm to room temperature over 1 h. A solution of MOM-ester **4.46** (3.00 g, 13.2 mmol) in CH$_2$Cl$_2$ (20 mL) was added *via* cannula and the solution refluxed for 16 h. The cooled reaction mixture was quenched with a saturated aqueous solution of Na/K-tartrate (100 mL) and stirred vigorously for 1 h resulting in separation of the mixture into two clear layers. The aqueous layer was extracted with CH$_2$Cl$_2$ (50mL x 3) and the combined organic layers evaporated under reduced pressure to give a yellow oil. The crude material was purified by flash chromatography on silica, eluting with 40% EtOAc/petroleum ether, to give **4.17** as a colourless oil (2.49g, 73%) and returned starting material **4.46** (0.255 g, 8.5%).

FTIR (KBr, cm^{-1}): 3503, 2939, 2889, 1666, 1443, 1416, 1385, 1150, 1107, 1053, 995, 918.

^{1}H NMR (500 MHz, CDCl$_3$): δ 1.81 (q, 2H), 2.32 (t, *J* = 7.3 Hz, 2H), 2.43 (t, *J* = 7.2 Hz, 2H), 3.16 (s, 3H), 3.37 (s, 3H), 3.66 (s, 3H), 4.22 (s, 2H), 4.65 (s, 2H), 5.01 (s, 1H), 5.14 (s, 1H), 5.27 (s, 1H), 5.31 (s, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 23.0, 31.1, 31.9, 33.3, 55.1, 60.9, 68.2, 96.3, 112.5, 114.0, 142.7, 144.7. 174.1.

HRESIMS (EI): calc. for C$_{13}$H$_{23}$NO$_4$ (MH$^+$): 258.1705; obs. 257.0740 (C$_{13}$H$_{23}$NO$_4$, MH$^+$ -H, calc: 257.1627).

6-((*tert*-Butyldimethylsilyloxy)methyl)-N-methoxy-N-methyl-5-methylenehept-6-enamide (4.18)

4.47   **4.18**
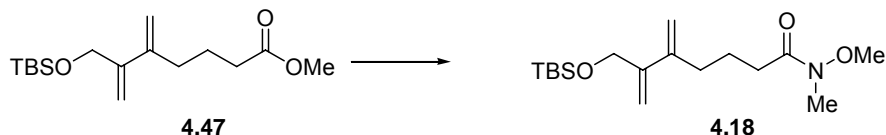
Prepared using the procedure detailed for the preparation of **4.17**. The amino-aluminate species, prepared from Me$_3$Al (10.06 mL of a 2 M solution in toluene, 20.1 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (2.06 g, 21.1 mmol) in CH$_2$Cl$_2$ (100 mL), was reacted with the silyl ester **4.47** (3.00 g, 10.1 mmol) at reflux for 16 h. Upon work-up, the crude yellow

oil was passed through a 5 cm silica plug, eluting with 50% Et$_2$O/petroleum ether, to give **4.18** as a colourless oil (2.62 g, 80%).

FTIR (KBr, cm^{-1}): 2955, 2932, 2858, 1670, 1462, 1412, 1385, 1254, 1096, 1003, 899, 837, 780.

^{1}H NMR (500 MHz, CDCl$_3$): δ 0.07 (s, 6H), 0.91 (s, 9H), 1.81 (qn, 2H), 2.31 (td, *J* = 7.4, 0.7, 2H), 2.42 (t, *J* = 7.3 Hz, 2H), 3.17 (s, 3H), 3.66 (s, 3H), 4.30 (t, *J* = 1.5 Hz, 2H), 4.93 (s, 1H), 4.99 (s, 1H), 5.23 (m, 1H), 5.33 (t, *J* = 1.3 Hz, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ -5.5, 18.2, 23.2, 25.8, 31.2, 32.0, 33.8, 61.0, 63.6, 110.9, 111.2, 144.9, 145.3, 174.4.

HRESIMS (EI): calc. for C$_{17}$H$_{34}$NO$_3$Si: (MH$^+$) 328.2308; obs. 328.2182.

**8-((Methoxymethoxy)methyl)-7-methylenenona-1,8-dien-3-one (4.48)**
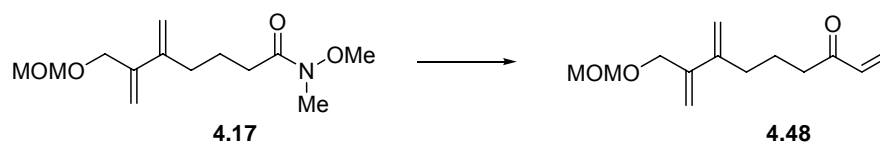
Vinyl magnesium bromide (0.39 mL of a 1 M solution in THF, 0.389 mmol) was added dropwise to a solution of **4.17** (50 mg, 0.19 mmol) in THF (10 mL) at 0°C. The solution was warmed to room temperature and then refluxed for 1 h. The mixture was cooled to 0°C and quenched with saturated aqueous NH$_4$Cl solution (20 mL) and extracted with Et$_2$O (20 mL x 3). The combined organic extracts were evaporated under reduced pressure to give **4.48** as a brown oil which was analytically clean as assessed by ^{1}H NMR spectroscopy. The brown discolouration was removed upon purified by flash chromatography on silica, eluting with 10% EtOAc/petroleum ether, to give **4.48** as a colourless oil (45.7 mg, 94%).

FTIR (KBr, cm^{-1}): 2939, 2885, 1682, 1597, 1404, 1150, 1103, 1049, 918.

^{1}H NMR (500 MHz, CDCl$_3$): δ 1.81 (qn, *J* = 7.4 Hz, 2H), 2.30 (t, *J* = 7.5 Hz, 2H), 2.60 (t, *J* = 7.3 Hz, 2H), 3.37 (s, 3H), 4.22 (d, *J* = 0.8 Hz, 1H), 4.65 (s, 2H), 5.00 (s, 1H), 5.15 (s, 1H), 5.28 (s, 1H), 5.30 (s, 1H), 5.80 (dd, *J* = 1.1, 10.6 Hz, 1H), 6.20 (dd, *J* = 1.1, 17.7 Hz, 1H), 6.34 (dd, *J* = 10.6, 17.7 Hz, 1H). See **Figure 4.14**-*A*

^{13}C NMR (75 MHz, CDCl$_3$): δ 22.3, 33.2, 38.7, 55.2, 68.3, 95.4, 112.7, 114.2, 127.7, 136.4, 142.7, 144.7, 200.4.

8-((*tert*-Butyldimethylsilyloxy)methyl)-7-methylenenona-1,8-dien-3-one (4.49)
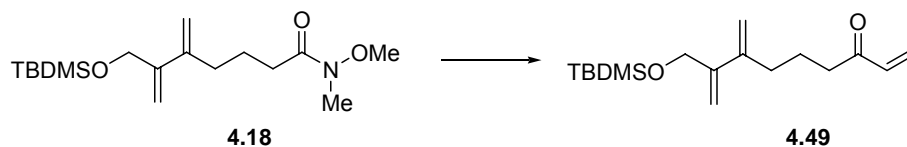
Vinyl magnesium bromide (5.85 mL of a 0.783 M solution in THF, 4.584 mmol) was added dropwise to **4.18** (500 mg, 1.53 mmol) in THF (50 mL) at 0°C. The solution was warmed to room temperature and stirred for 16 h. The mixture was quenched with saturated aqueous NH_4Cl solution (100 mL) and extracted with Et_2O (50 mL x 3). The solvents were removed under reduced pressure and the crude material purified by flash chromatography on silica, eluting with 10% EtOAc/petroleum ether, to give **4.49** as a colourless oil (440 mg, 98%).

FTIR (KBr, cm^{-1}): 2932, 2855, 1682, 1597, 1466, 1404, 1258, 1096, 903, 841, 779.
^{1}H NMR (500 MHz, CDCl$_3$): δ 0.07 (s, 6H), 0.91 (s, 9H), 1.80 (qn, J = 7.4 Hz, 2H), 2.29 (t, J = 7.5 Hz, 2H), 2.58 (t, J = 7.3 Hz, 2H), 4.30 (t, J = 1.4 Hz, 2H), 4.91 (s, 1H), 4.99 (d, J = 5.0 Hz, 1H), 5.21 (d, J = 1.2 Hz, 1H), 5.32 (s, 1H), 5.80 (dd, J = 1.1, 10.6 Hz, 1H), 6.20 (dd, J = 1.1, 17.7 Hz, 1H), 6.34 (dd, J = 10.6, 17.7 Hz, 1H).
^{13}C NMR (75 MHz, CDCl$_3$): δ -5.4, 18.3, 22.5, 25.86, 25.94, 33.7, 39.9, 63.7, 111.1, 111.5, 127.9, 136.5, 144.8, 145.3, 200.5.

Methyl 7-(allyldimethylsilyloxy)hept-5-ynoate (4.64)
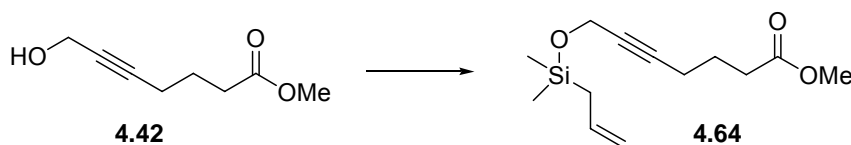
Allylchlorodimethylsilane (470 μL, 3.84 mmol) was added dropwise to a solution of **4.42** (500 mg, 3.20 mmol) and NEt$_3$ (1.35 ml, 9.61 mmol) in CH$_2$Cl$_2$ (25 mL) at 0°C and stirred for 12 h. The reaction mixture was quenched *via* addition to a saturated solution of aqueous NaHCO$_3$ (100 mL) and extracted with Et$_2$O (50 mL x 3). The solvents were removed under reduced pressure and the crude material purified by flash chromatography on silica, eluting with 5% EtOAc/petroleum ether, to give **4.64** as a colourless oil (765 mg, 94%).

FTIR (KBr, cm^{-1}): 2955, 2872, 1742, 1631, 1437, 1371, 1254, 1161, 1078, 839.

¹H NMR (500 MHz, CDCl₃): δ 0.16 (s, 6 H), 1.67 (d, J = 8.0 Hz, 2 H), 1.79-1.86 (qn, 2H), 2.28 (t, J = 6.7 Hz, 2H), 2.43 (t, J = 7.4 Hz, 2H), 3.67 (s, 3 H), 4.28 (s, 2 H), 4.85-4.93 (m, 2H), 5.77-5.85 (m, 1H).

¹³C NMR (75 MHz, CDCl₃): δ -2.5, 18.2, 23.6, 24.3, 32.7, 46.1, 51.4, 79.0, 84.3, 113.8, 133.7, 173.4.

**Methyl 5-(2,2-dimethyl-3,6-dihydro-2H-1,2-oxasilin-5-yl)hex-5-enoate (4.65)**
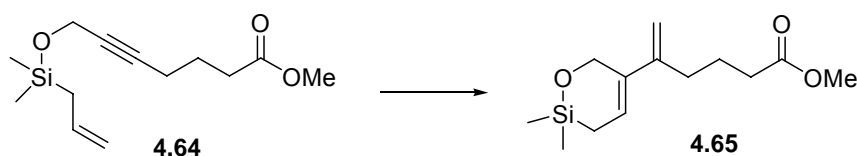
Grubbs II catalyst **4.25** (6.6 mg, 7.8 µmol, 2 mol %) was added to a solution of allylsilyl-alkyne **4.64** (100 mg, 3.93 mmol) dissolved in CH₂Cl₂ (25 mL) and the reaction mixture heated to reflux, whilst being monitored *via* ¹H NMR spectroscopy. Upon completion (*ca.* 3 h), the reaction was cooled to room temperature and concentrated under reduced pressure. The black oil was purified by flash chromatography on silica, eluting with 5% EtOAc/petroleum ether, to give **4.65** as a colourless oil (93 mg, 93%).

Whilst this material was stable in CDCl₃, the use of deuteriopyridine-doped CDCl₃ resulted in instantaneous decomposition to an unknown compound and the formation of a pink solution.

¹H NMR (500 MHz, CDCl₃): δ 0.16 (s, 6H), 1.35-1.38 (m, 2H), 1.71-1.78 (qn, 2H), 2.23 (t, J = 7. 6 Hz, 2H), 2.28 (t, J = 7.5 Hz, 2H), 3.65 (s, 3H), 4.50-4.52 (m, 2H), 4.78 (s, 1H), 4.79 (s, 1H), 6.00-6.05 (m, 1H).

¹³C NMR (75 MHz, CDCl₃): δ -1.1, 12.3, 23.3, 33.0, 33.5, 51.0, 63.4, 109.7, 122.1, 137.0, 145.4, 173.4.

7-((Methoxymethoxy)methyl)bicyclo[4.3.1]dec-6-en-2-one (4.69)
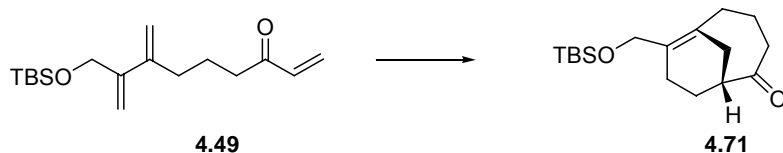

4.48   **4.69**
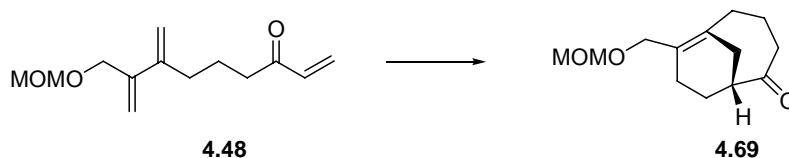
MOM-triene **4.48** (264 mg, 1.03 mmol), Proton-sponge® (66 mg, 0.31 mmol, 0.3 equiv) and benzene (20 mL) were placed in a resealable Carius tube and sparged with argon for 10 min. The tube was sealed and heated at 160°C for 40 h. Upon cooling, the solvent was removed under reduced pressure and the crude material taken up in Et$_2$O (20 mL) and washed with 1 M aqueous HCl solution (5 mL) and water (20 mL). The residue was purified by flash chromatography on silica, eluting with 15% EtOAc/petroleum ether, to give **4.69** as a colourless oil (135.5 mg, 51%).

FTIR (KBr, cm^{-1}): 2943, 2874, 1701, 1442, 1146, 1099, 1045, 941, 918.

^{1}H NMR (500 MHz, CDCl$_3$): δ 1.38-1.48 (m, 1H), 1.80-1.95 (dddd, J = 2.7, 6.1, 11.6, 13.2 Hz, 2H), 1.99-2.15 (m, 4H), 2.19 (dd, J = 8.1, 14.2 Hz, 1H), 2.30 (ddd, J = 2.8, 5.5, 11.6 Hz, 1H), 2.56 (ddd, J = 1.4, 3.5, 13.2 Hz, 1H), 2.62 (td, J = 2.7, 8.5 Hz, 1H), 2.77 (dd, J = 5.8, 12.6 Hz, 1H), 2.89 (ddd, J = 3.1, 11.6, 13.5 Hz, 1H), 3.34 (s, 3H), 3.83 (d, J = 11.2 Hz, 1H), 4.11 (d, J = 11.2 Hz, 1H), 4.53 (d, J = 6.6 Hz, 1H), 4.57 (d, J = 6.6 Hz, 1H); See **Figure 4.14**-*B*.

^{13}C NMR (75 MHz, CDCl$_3$): δ 23.98, 24.00, 30.9, 32.5, 33.0, 41.9, 46.6, 55.2, 65.5, 95.3, 130.8, 141.7, 216.2.

HRMS (EI): calc. for C$_{13}$H$_{20}$O$_3$: 224.1412; obs. 223.1334 (C$_{13}$H$_{19}$O$_3$, M$^+$ - H, calc: 223.1339).

7-((*tert*-Butyldimethylsilyloxy)methyl)bicyclo[4.3.1]dec-6-en-2-one (4.71)

4.49   **4.71**

Small scale - Pressure Tube:

TBS-triene **4.49** (100.8 mg, 0.34 mmol), Proton-sponge® (21.8 mg, 0.10 mmol, 0.3 equiv) and benzene (10 mL) were placed in a resealable Carius tube and sparged with argon for 5 min. The tube was sealed and heated at 160°C for 40 h. The solvent was removed under reduced pressure and the crude material taken up in Et$_2$O (10 mL) and washed with 0.5 M aqueous solution HCl (2 mL) and water (5 mL). The residue was purified by flash chromatography on silica, eluting with 10% EtOAc/petroleum ether, to give **4.71** as a colourless oil (73.5 mg, 73%).

Large scale:

A solution of TBS-triene **4.49** (2.5 g, 8.5 mmol) in xylene (50 mL) was added over 8 h, *via* syringe pump, to a refluxing solution of Proton-sponge® (0.43 g, 2.0 mmol) in xylene (1.5 L). The mixture was refluxed for 40 h at which time complete consumption of the triene material was observed to have occurred as assessed by ^{1}H NMR spectroscopy of sample aliquots. The solvent was removed under reduced pressure, the residue dissolved in Et_2O (100 mL) and washed with 0.5 M aqueous HCl solution (20 mL) and water(20 mL x 2). The residue was purified by flash chromatography on silica, eluting with 5% EtOAc/petroleum ether, to give **4.71** as a colourless oil (1.85 g, 80%).

FTIR (KBr, cm^{-1}): 2932, 2858, 1701, 1462, 1254, 1146, 1069, 837, 775.

^{1}**H NMR** (500 MHz, CDCl$_3$): δ 0.03 (s, 3H), 0.03 (s, 3H), 0.87 (s, 9H), 1.35-1.45 (m, 1H), 1.80-1.90 (m, 2H), 1.96-2.11 (m, 4H), 2.16-2.22 (m, 1H), 2.30 (ddd, J = 2.7, 5.7, 11.6 Hz, 1H), 2.50 (ddd, J = 1.5, 3.4, 13.3 Hz, 1H), 2.60 (m, 1H), 2.75 (ddd, J = 1.6, 6.0, 12.5 Hz, 1H), 2.86 (ddd, J = 3.0, 11.6, 13.4 Hz, 1H), 3.91 (d, J = 11.7 Hz, 1H), 4.19 (d, J = 11.7 Hz, 1H).

^{13}**C NMR** (75 MHz, CDCl$_3$): δ -5.42, -5.37, 18.2, 23.4, 24.2, 25.8, 30.6, 32.3, 32.7, 41.8, 46.7, 61.5, 133.9, 138.2, 216.1.

HRMS (EI): calc. for $C_{17}H_{30}O_2Si$: 294.2015; obs. 279.1749 ($C_{16}H_{27}O_2Si$, M$^+$-Me, calc. 279.1780), 237.1306 ($C_{13}H_{21}O_2Si$, M$^+$-^{t}Bu, calc. 237.1311).

7-((Methoxymethoxy)methyl)-tricyclo[4.3.1.1^{6,7}]undecan-2-one (4.77) and

7-((Methoxymethoxy)methyl)-2-methylene-tricyclo[4.3.1.1^{6,7}]undecane (4.78)
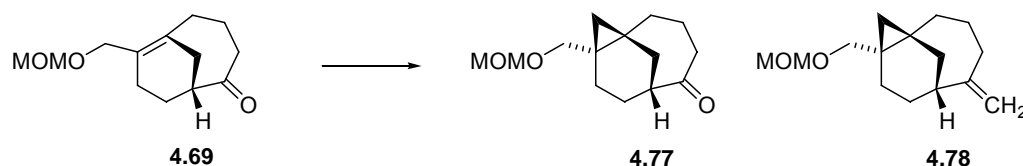
Et$_2$Zn (803 µL, 0.99 mmol) was added dropwise to a solution of **4.69** (74.1 mg, 0.33 mmol) in toluene (10 mL) at 0°C causing gas evolution. After 30 min CH$_2$I$_2$ was added dropwise and O$_2$ slowly bubbled through the solution for 2 h causing a milky white suspension to form. The solution was stirred for 12 h, quenched *via* the addition of saturated aqueous NH$_4$Cl solution (50 mL) and extracted with Et$_2$O (20 mL x 3). The solvent was removed under reduced pressure and the residue purified by flash chromatography on silica, eluting with 10% EtOAc/petroleum ether, to give **4.77** as a viscous oil (29.1 mg, 37%) and **4.78** as a colourless oil (36.6 mg, 47%).

7-((Methoxymethoxy)methyl)-tricyclo[4.3.1.1^{6,7}]undecan-2-one (4.77)

FTIR (KBr, cm^{-1}): 3433, 2939, 1697, 1458, 1150, 1103, 1049, 918.

^{1}H NMR (500 MHz, CDCl$_3$): δ 0.43 (d, J = 4.5 Hz, 1H), 0.59 (d, J = 4.6 Hz, 1H), 1.02-1.10 (m, 1H), 1.27 (ddd, J = 0.9, 4.4, 15.0, 1H), 1.42 (td, J = 3.4, 14.3, 1H), 1.50 (tdd, J = 1.4, 4.2, 12.8, 1H), 1.79-1.86 (m, 1H), 1.93-2.08 (m, 4H), 2.27 (dd, J = 2.3, 15.0 Hz, 1H), 2.48-2.54 (m, 2H), 2.83 (dt, J = 2.3, 12.8 Hz, 1H), 3.27 (d, J = 9.9 Hz, 1H), 3.34 (s, 3H), 3.50 (d, J = 9.9 Hz, 1H), 4.60 (dd, J = 6.5, 15.2 Hz, 2H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 23.6, 24.1, 24.8, 25.5, 27.4, 32.3, 35.2, 42.6, 43.5, 53.6, 55.0, 71.2, 96.2, 218.0.

HRMS (EI): calc. for C$_{14}$H$_{22}$O$_3$: 238.1569; obs. 223.1339 (C$_{13}$H$_{19}$O$_3$, M$^+$ - Me, calc. 223.1334).


7-((Methoxymethoxy)methyl)-2-methylene-tricyclo[4.3.1.1^{6,7}]undecane (4.78)

FTIR (KBr, cm^{-1}): 2939, 2878, 1466, 1373, 1211, 1150, 1088, 1049, 988, 918.

^{1}H NMR (500 MHz, CDCl$_3$): δ 0.28 (d, J = 4.5 Hz, 1H), 0.32 (d, J = 4.5 Hz, 1H), 0.97 (dd, J = 6.1, 15.2 Hz, 1H), 1.04 (dt, J = 4.8, 14.4 Hz, 1H), 1.23 (m, 1H) 1.57-1.64 (m, 1H), 1.65-1.84 (m, 4H), 1.87 (dd, J = 7.5, 14.3 Hz, 1H), 2.00 (dd, J = 1.0, 15.1 Hz, 1H), 2.04 (ddd, J = 2.0, 4.9, 14.2 Hz, 1H), 2.23 (ttd, J = 1.6, 6.0, 11.1 Hz, 1H), 2.32 (t, J = 13.5 Hz, 1H), 3.36 (s, 3H), 3.47 (d, J = 10.1 Hz, 1H), 3.55 (d, J = 10.1 Hz, 1H), 4.64 (q, J = 6.6 Hz, 1H), 5.05 (s, 1H), 5.14 (s, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 20.1, 20.2, 22.2, 24.7, 24.9, 27.1, 28.6, 29.6, 30.6, 37.7, 55.1, 71.7, 93.7, 96.5, 114.2.

HRMS (EI): calc. for C$_{15}$H$_{24}$O$_2$: 236.1776; obs. 236.1406.

7-(*tert*-Butyldimethylsilyloxymethyl)-tricyclo[4.3.1.1^{6,7}]undecan-2-one (4.89)
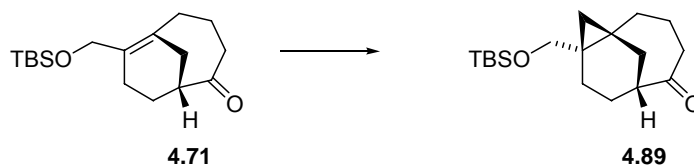
Activated zinc powder (1.86 g, 28.4 mmol, 20 equiv) and CuCl (56 mg, 0.57 mmol, 2 mol % based on Zn) were placed in a reflux set-up and evacuated for 30 min. Et$_2$O (50 mL) and a single crystal of iodine were added and the solution subjected to ultrasound irradiation, causing reflux, for 30 min. Sonication was continued as olefin **4.71** (418 mg, 1.42 mmol) was added in one portion, followed by the dropwise addition of CH$_2$I$_2$ (1.14 mL, 14.2 mmol, 10 equiv in 5 mL of Et$_2$O) over 8 h. Upon completion (*ca.* 24 h of sonication) the organic layer was separated from the solid *via* decantation. The solid residues were placed on a Celite pad and exhaustively

extracted with Et_2O, EtOAc and CH_2Cl_2. The combined organic solvents was removed under reduced pressure and the residue purified by flash chromatography on silica, eluting with 5% EtOAc/petroleum ether, to give **4.89** as a colourless oil (141.4 mg, 32%).

FTIR (KBr, cm^{-1}): 2858, 2361, 2341, 1697, 1466, 1254, 1072, 837, 775, 667.

^{1}H NMR (500 MHz, CDCl$_3$): δ 0.03 (s, 3H), 0.04 (s, 3H), 0.29 (d, *J* = 4.5 Hz, 1H), 0.45 (d, *J* = 4.5 Hz, 1H), 0.89 (s, 9H), 1.05 (m, 1H), 1.25 (dd, *J* = 5.0, 15.0 Hz, 2H), 1.47 (td, *J* = 4.0, 14.0 Hz, 1H), 1.69 (m, 1H), 1.79 (m, 1H), 1.90-2.07 (m, 4H), 2.26 (dd, *J* = 2.0, 15.0 Hz, 1H), 2.50 (m, 1H), 2.59 (dd, *J* = 7.5, 12.0 Hz, 1H), 2.80 (dt, *J* = 2.5, 13.0 Hz, 1H), 3.44 (d, *J* = 10.5 Hz, 1H), 3.61 (d, *J* = 10.5 Hz, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ -5.6, -5.5, 18.2, 24.2, 24.5, 24.9, 25.6, 25.87, 25.92, 26.6, 32.6, 34.8, 42.7, 43.8, 66.6, 218.1.

HRMS (EI): calc. for $C_{18}H_{32}O_2Si$: 308.2172; obs. 251.1472 ($C_{14}H_{23}O_2Si$, M$^+$ - ^{t}Bu, calc: 251.1467).

### 7-(Hydroxymethyl)bicyclo[4.3.1]dec-6-en-2-one (4.73)
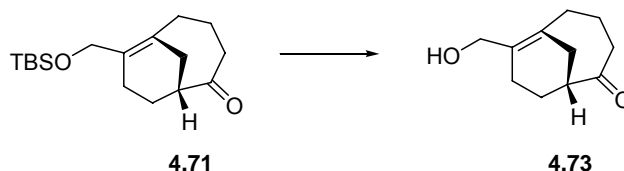
TBAF (1.5 mL of a 1 M solution in THF, 1.5 mmol) was added to **4.71** (405 mg, 1.37 mmol) in THF (25 mL) at 0°C resulting in a peach colouration. The solution was stirred for 12 h at room temperature. The reaction mixture was quenched *via* addition to a solution of saturated aqueous NaHCO$_3$ solution and water (1:1, 100 mL) and extracted with CH$_2$Cl$_2$ (20 mL x 3). The solvent was removed under reduced pressure and the residue purified by flash chromatography on silica, eluting with 40% EtOAc/petroleum ether, to give **4.73** as a colourless oil (197 mg, 80%).

FTIR (KBr, cm^{-1}): 3412, 2939, 2870, 1695, 1443, 1142, 1034, 1011.

^{1}H NMR (500 MHz, CDCl$_3$): δ 1.37-1.46 (m, 1H), 1.79-1.86 (m, 1H), 1.88-1.96 (m, 1H), 2.02-2.13 (m, 4H), 2.23 (dd, *J* = 8.2, 14.7 Hz, 1H), 2.29 (ddd, *J* = 3.1, 5.2, 11.6 Hz, 1H), 2.54 (ddd, *J* = 1.6, 3.6, 13.3 Hz, 1H), 2.61-2.64 (m, 1H), 2.76 (dd, *J* = 6.1, 11.8 Hz, 1H), 2.91 (ddd, *J* = 3.0, 11.1, 21.8 Hz, 1H), 3.96 (d, *J* = 11.7 Hz, 1H), 4.10 (d, *J* = 11.7 Hz, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 23.2, 23.8, 31.2, 32.2, 32.8, 41.7, 46.6, 60.9, 133.6, 139.9, 216.7.

HRMS (EI): calc for $C_{11}H_{16}O_2$: 180.1150; obs. 162.1051 ($C_{11}H_{14}O$, M$^+$-H$_2$O, calc: 162.1045).

7-Hydroxymethyl-tricyclo[4.3.1.1^{6,7}]undecan-2-one (4.92) and

7-Methoxymethyl-tricyclo[4.3.1.1^{6,7}]undecan-2-one (4.93)
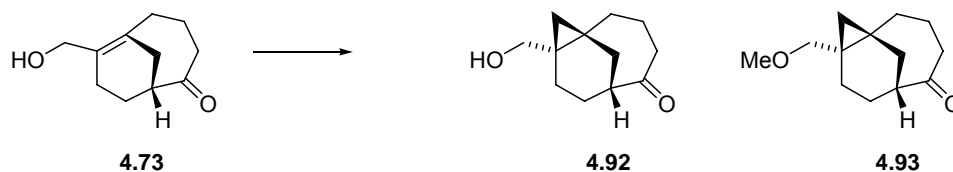
Et$_2$Zn (1.519 mL of a 1.236 M solution in toluene, 1.88 mmol) was added dropwise to a solution of DME (195 μL, 1.88 mmol) in CH$_2$Cl$_2$ (40 mL) at -15°C (internal temperature) at such a rate that the temperature remained constant. After 5 min, CH$_2$I$_2$ (303 μL, 3.76 mmol) was added dropwise so that no exotherm occurred. After 15 min at -15°C, **4.73** (169.1 mg, 0.94 mmol) was added *via* cannula in one portion with 2 x 1 mL CH$_2$Cl$_2$ washes and stirred at -15°C for 10 min and then at room temperature for 4 h. The mixture was quenched *via* the addition of saturated aqueous NH$_4$Cl solution (100 mL) and extracted with CH$_2$Cl$_2$ (20 mL x 3). The solvents were removed under reduced pressure and the residue purified by flash chromatography on silica, eluting with 40% EtOAc/petroleum ether, to give the methyl ether **4.93** as a colourless oil (25.4 mg, 13%) and **4.92** as a colourless oil (133.2 mg, 73%).

7-Hydroxymethyl-tricyclo[4.3.1.1^{6,7}]undecan-2-one (4.92)

FTIR (KBr, cm^{-1}): 3437, 2941, 1698, 1448, 1319, 1170, 959.

^{1}H NMR (500 MHz, CDCl$_3$): δ 0.36 (d, J = 4.3 Hz, 1H), 0.54 (d, J = 4.3 Hz, 1H), 1.05 (ddd, J = 7.2, 14.6, 17.1 Hz, 1H), 1.26 (dd, J = 4.5, 15.0 Hz, 2H), 1.42 (dd, J = 5.5, 15.5 Hz, 2H), 1.82-1.92 (m, 2H), 2.02-2.09 (m, 3H), 2.29 (d, J = 14.9 Hz, 1H), 2.48 (dd, J = 7.0, 11.0 Hz, 1H), 2.86 (t, J = 12.5 Hz, 1H), 3.33 (d, J = 11.0 Hz, 1H), 3.56 (d, J = 11.0 Hz, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 23.9, 24.6, 24.8, 25.2, 25.8, 27.2, 32.3, 35.3, 42.5, 43.7, 65.5, 218.5.

**HRMS** (EI): calc C$_{12}$H$_{18}$O$_2$: 194.1307; obs. 194.1312.

7-Methoxymethyl-tricyclo[4.3.1.1^{6,7}]undecan-2-one (4.93)

FTIR (KBr, cm^{-1}): 2960, 2874, 1693, 1458, 1196, 1168, 1103, 918.

^{1}H NMR (500 MHz, CDCl$_3$): δ 0.41 (d, J = 4.4 Hz, 1H), 0.59 (d, J = 4.5 Hz, 1H), 1.02 (m, 1H), 1.25 (m, 2H), 1.44 (m, 1H), 1.83 (m, 1H), 1.89-2.06 (m, 4H), 2.26 (d, J = 15.0 Hz, 1H), 2.49 (m, 2H), 2.83 (t, J = 12.8 Hz, 1H), 3.07 (d, J = 9.6 Hz, 1H), 3.30 (s, 3H), 3.37 (d, J = 9.6 Hz, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 23.8, 24.0, 24.1, 24.9, 25.3, 27.6, 32.4, 35.3, 42.7, 42.6, 58.6, 76.0, 218.0.

HRMS (EI): calc for C$_{13}$H$_{20}$O$_2$: 208.1463; obs. 208.1467.

S-Methyl-O-(2-oxobicyclo[4.3.1.1⁶,⁷]undecan-7-yl)-methyl dithiocarbonate (4.99)
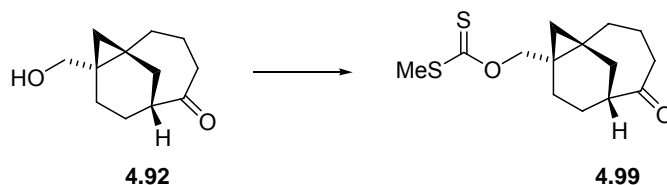

Alcohol **4.92** (27.6 mg, 0.154 mmol) in THF (1 mL) was added to a solution of NaH (18.5 mg of a 60% dispersion in oil, 0.46 mmol) in THF (5 mL) and stirred for 30 min. Imidazole (0.5 mg, 0.007 mmol, 5 mol %) and carbon disulfide (55.8 μL, 0.93 mmol) were added and the solution refluxed for 1 h. The reaction was cooled to room temperature and methyl iodide (115.5 μL, 1.85 mmol) added in one portion. The solution was refluxed for 1 h. The mixture was cooled, quenched *via* the addition to saturated aqueous NH$_4$Cl solution (50 mL) and extracted with CH$_2$Cl$_2$ (10 mL x 3). The solvents were removed under reduced pressure and the residue purified by flash chromatography on silica, eluting with 10% EtOAc/petroleum ether, to give **4.99** as a yellow oil (29.7 mg, 74%).

FTIR (KBr, cm^{-1}): 2939, 2870, 1697, 1643, 1458, 1319, 1221, 1065, 918, 872.

^{1}H NMR (500 MHz, CDCl$_3$): δ 0.50 (d, *J* = 4.8 Hz, 1H), 0.69 (d, *J* = 4.8 Hz, 1H), 1.11-1.18 (m, 1H), 1.30 (dd, *J* = 4.3, 15.0 Hz, 1H), 1.38-1.45 (m, 1H), 1.83-1.90 (m, 1H), 1.90-2.00 (m, 2H), 2.05-2.15 (m, 2H), 2.35 (d, *J* = 15.2 Hz, 1H), 2.47-2.53 (m, 2H), 2.55 (s, 3H), 2.90 (dt, *J* = 2.5, 12.8 Hz, 1H), 4.38 (d, *J* = 11.4 Hz, 1H), 4.56 (d, *J* = 11.4 Hz, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 19.0, 22.8, 24.2, 25.0, 25.3, 25.9, 27.9, 32.5, 35.3, 42.7, 43.4, 78.6, 216.4, 217.4.

HRMS (EI): calc for C$_{14}$H$_{20}$O$_2$S$_{20}$: 284.09047; obs. 284.0911

6-Methyl-7-methylenebicyclo[4.3.1]decan-2-one (4.102) and

8-Methylenebicyclo[4.4.1]undecan-2-one (4.104)
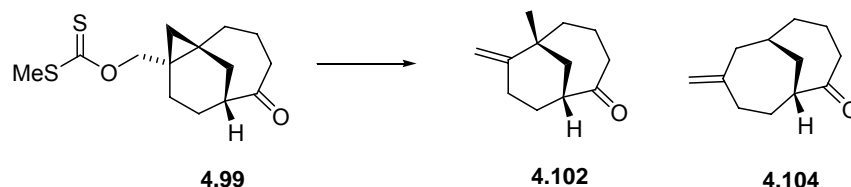
The xanthate ester **4.99** (11.6 mg, 0.04 mmol), Bu$_3$SnH (41 μL, 1.5 mmol) and AIBN (0.8 mg, 0.004 mmol) were dissolved in benzene (25 mL) and degassed with a flow of argon for 5 min before being heated to reflux for 2 h. The solution was cooled to room temperature and the

solvent removed under reduced pressure. The crude material contained a mixture of **4.104** [δ_H 4.66 (d, J = 2.2 Hz, 1H), 4.76 (s, 1H)] and **4.102** [δ_H 4.62 (qn, J = 1.85 Hz, 2H)] in a ratio of 5:1 based on ^{1}H NMR integration values. The residue was purified by flash chromatography on silica, eluting with 5% EtOAc/petroleum ether to give **4.104** (8 mg, 74%), contaminated with a small amount of tin residues.

FTIR (KBr, cm^{-1}): 2932, 2862, 1705, 1458, 1265, 1072, 1026, 802.

^{1}H NMR (500 MHz, CDCl$_3$): δ 1.21-1.27 (m, 1H), 1.61-1.75 (m, 5H), 1.99 (dd, J = 7.0, 15.3 Hz, 1H), 2.13-2.22 (m, 3H), 2.26-2.38 (m, 4H), 2.65-2.73 (m, 2H), 4.66 (d, J = 2.4 Hz, 1H), 4.76 (d, J = 1.2 Hz, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 20.9, 29.4, 32.3, 34.8, 35.0, 35.5, 37.0, 42.7, 48.5, 111.4, 148.6, 214.9.

HRMS (EI): calc for C$_{12}$H$_{18}$O: 178.1358; obs. 178.1360

6-Methyl-7-methylenebicyclo[4.3.1]decan-2-ol (4.105) and

(±)-(2S)-8-Methylenebicyclo[4.4.1]undecan-2-ol (4.106) and

(±)-(2R)-8-Methylenebicyclo[4.4.1]undecan-2-ol (4.107)
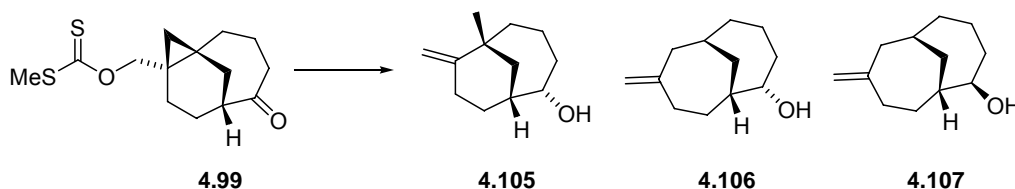
The xanthate ester **4.99** (89.8 mg, 0.126 mmol), Bu$_3$SnH (255 μL, 0.378 mmol) and AIBN (15.5 mg, 0.04 mmol) were dissolved in toluene (10 mL) and heated to reflux for 30 min. The solution was then cooled to -78°C and DIBAL-H (3.6 mL of 0.35 M solution in hexanes, 0.50 mmol) added dropwise. The mixture was stirred for 30 min at -78°C and then for 90 min at 0°C before quenching with the addition of saturated aqueous Na/K-tartrate solution (30 mL). The solution was vigorously stirred for 1h and then extracted with EtOAc (25 mL x 3). The solvents were removed under reduced pressure and the residue purified by flash chromatography on silica, eluting with 10% EtOAc/petroleum ether to give the two alcohol diastereoisomers of **4.106** (36 mg, 63%) and **4.107** (7.5 mg, 13%) as yellow oils. The desired bicyclo[4.3.1]decane **4.105** eluted subsequently, but was unable to be separated from co-eluting contaminants.

(±)-(2*S*)-8-Methylenebicyclo[4.4.1]undecan-2-ol (4.106)

FTIR (KBr, cm^{-1}): 3341, 2870, 1643 (w), 1450, 1358, 1296, 1026, 887.

^{1}H NMR (500 MHz, CDCl$_3$): δ 1.27-1.36 (m, 1H), 1.43-1.80 (m, 8H), 1.97-2.10 (m, 3H), 2.15-2.33 (m, 4H), 3.82 (dt, *J* = 2.8, 5.9 Hz, 1H), 4.62 (dd, *J* = 1.2, 2.5 Hz, 1H), 4.74 (d, *J* = 2.2 Hz, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 20.8, 29.9, 31.6, 33.1, 34.7, 34.8, 36.0, 43.2, 43.8, 73.0, 112.1, 150.2.

HRMS (EI): calc for C$_{12}$H$_{20}$O: 180.1514; obs. 180.1512.

(±)-(2*R*)-8-Methylenebicyclo[4.4.1]undecan-2-ol (4.107)

**FTIR** (KBr, cm^{-1}): 3356, 2324, 2862, 1643 (w), 1458, 1026, 887.

^{1}H NMR (500 MHz, CDCl$_3$): δ 1.17-1.34 (m, 3H), 1.47-1.67 (m, 3H), 1.80 (ddd, *J* = 8.2, 15.5, 22.9 Hz, 1H), 1.85-1.92 (m, 1H), 1.94-2.05 (m, 2H), 2.22 (m, 2H), 2.21-2.29 (m, 1H), 2.39 (dd, *J* = 7.4, 13.4 Hz, 1H), 3.72 (td, *J* = 4.8, 10.1 Hz, 1H), 4.60 (s, 1H), 4.76 (d, *J* = 2.6 Hz, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 21.6, 25.9, 30.96, 31.01, 33.9, 34.1, 35.2, 41.9, 45.9, 77.7, 112.5, 150.8.

HRMS (EI): calc for C$_{12}$H$_{20}$O: 180.1514; obs. 180.1507.

6-Methyl-7-methylenebicyclo[4.3.1]decan-2-ol (4.105)

Characteristic data: **^{1}H NMR** (500 MHz, CDCl$_3$): δ 4.60 (s, 1H), 4.75 (s, 1H).

(±)-(2*S*)-8-Methylenebicyclo[4.4.1]undecan-2-yl 3,5-dinitrobenzoate (4.108)
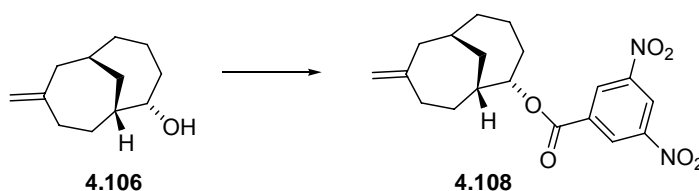
3,5-Dinitrobenzoyl chloride (69.1 mg, 0.3 mmol) in 2 mL of CH$_2$Cl$_2$ was added *via* cannula to a solution of the alcohol **4.106** (36 mg, 0.2 mmol), Et$_3$N (104 μL, 0.75 mmol) and DMAP (5 mg, 0.04 mmol) in CH$_2$Cl$_2$ (5 mL) at 0°C. The addition resulted in the formation of a deep red solution which was stirred at room temperature for 16 h. The solution was quenched *via* the addition of saturated aqueous NH$_4$Cl solution (20 mL) and extracted with EtOAc (10 mL x 3). The solvents were removed under reduced pressure and the residue purified by flash chromatography on silica, eluting with 10% EtOAc/petroleum ether to give **4.108** as a yellow

solid (31 mg, 54%). The solid was crystallized from an Et$_2$O:pentane solution to give yellow needles, which were subjected to X-ray diffraction to obtain the crystallographic structure depicted in **Figure 4.21**. [P-1, Z = 2, R = 3.4%].

mp: 108-109°C.

FTIR (KBr, cm^{-1}): 3101, 2928, 2874, 2361, 2341, 1724, 1628, 1547, 1462, 1346, 1281, 1173, 1076, 961, 910, 729.

^{1}H NMR (500 MHz, CDCl$_3$): δ 1.31 (t, J = 12.5 Hz, 1H), 1.42 (q, J = 12.7 Hz, 1H), 1.54(q, J = 12.8 Hz, 1H), 1.69-1.78 (m, 2H), 1.82 (q, J = 12.9 Hz, 1H), 1.94 (t, J = 8.3 Hz, 1 H), 1.97-2.16 (m, 4H), 2.27 (m, 2H), 2.43 (dd, J = 7.5, 13.2 Hz, 1H), 2.51 (m, 1H), 4.66 (s, 1H), 4.82 (s, 1H), 5.18 (dt, J = 4.8, 11.5 Hz, 1H), 9.09 (s, 2H), 9.20 (s, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 21.3, 26.8, 30.6, 30.8, 31.5, 33.7, 33.8, 39.1, 45.7, 82.5, 113.1, 122.1, 129.2, 134.6, 148.5, 150.1, 161.6.

HRMS (EI): an accurate mass could not be obtained. A single ion with a m/z of 195, (C$_7$H$_3$N$_2$O$_5$) derived from cleavage of the 3,5-dinitrobenzoyl ester bond was observed.

7-(*tert*-Butyldimethylsilyloxymethyl)-12,12'-dichlorotricyclo[4.3.1.1^{6,7}]undecan-2-one (4.143)

4.71   **4.143**
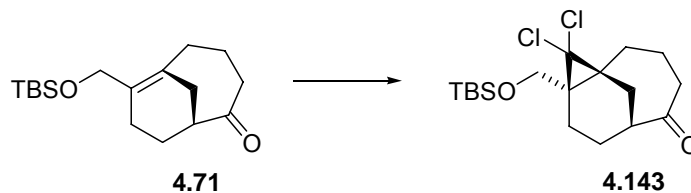
50% Aqueous NaOH solution (10 mL) was added to a solution of the olefin **4.71** (200 mg, 0.68 mmol) and tetraethylammonium chloride (12 mg, 0.068 mmol) in CHCl$_3$ (20 mL) at 0°C and stirred vigorously for 12 h at room temperature forming a white emulsion. The reaction was quenched *via* dilution with water (50 mL) and extracted with CH$_2$Cl$_2$ (20 mL x 3). The solvents were removed under reduced pressure and the residue purified by flash chromatography on silica, eluting with 5% EtOAc/petroleum ether to give **4.143** as a colourless oil (215 mg, 84%).

FTIR (KBr, cm^{-1}): 2955, 2930, 2858, 1701, 1472, 1464, 1256, 1097, 854, 837, 777.

^{1}H NMR (500 MHz, CDCl$_3$): δ 0.93 (s, 3H), 0.95 (s, 3H), 1.78 (s, 9H), 2.39-2.52 (m, 2H), 2.69-2.98 (m, 8H), 3.11 (d, J = 15.1 Hz, 1H), 3.39-3.46 (m, 2H), 3.74 (t, J = 21.7 Hz, 1H), 4.54 (m, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ -5.7,-5.6, 18.1, 20.0., 22.7, 23.9, 25.7, 28.0, 31.6, 34.1, 34.2, 42.0, 42.1, 63.7, 75.9, 215.6.

HRMS (EI): calc. for C$_{18}$H$_{30}$^{35}Cl$_2$O$_2$Si: 376.1392, obs. 319.0688 (C$_{14}$H$_{21}$^{35}Cl$_2$O$_2$Si, M$^+$ - ^{t}Bu, calc: 319.0688), 340.1610 (C$_{18}$H$_{29}$^{35}Cl$_1$O$_2$Si, M$^+$ - HCl, calc. 340.1625).

12,12'-Dichloro-7-hydroxymethyl-tricyclo[4.3.1.1^{6,7}]undecan-2-one (4.144)

TBAF (0.64 mL of a 1.0 M solution in THF, 0.64 mmol) was added to a solution of **4.143** (200 mg, 0.53 mmol) in THF (20 mL) at 0°C and stirred at room temperature 12 h. The reaction was quenched *via* the addition of H$_2$O (100 mL) and extracted with EtOAc (20 mL x 3). The solvents were removed under reduced pressure and the residue purified by flash chromatography on silica, eluting with 40% E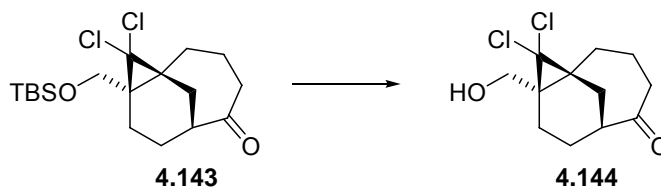tOAc/petroleum ether to give **4.144** as a colourless oil which readily solidified to an amorphous mass upon standing (131 mg, 94%). The solid was recrystallised from Et$_2$O:hexane to yield large crystalline plates which were subjected to X-ray diffraction to obtain the crystallographic structure depicted in **Figure 4.30**, [P-1, Z = 2, R = 2.6%].

mp: 106-108°C.

FTIR (KBr, cm^{-1}): 3422, 2955, 2870, 1695, 1456, 1034, 851.

^{1}H NMR (500 MHz, CDCl$_3$): δ 1.32-1.40 (m, 1H), 1.58-1.64 (m, 1H), 1.72-1.79 (m, 1H), 1.91 (ddd, *J* = 1.6, 4.4, 15.2 Hz, 1H), 1.95-2.13 (m, 5H), 2.25 (d, *J* = 14.5 Hz, 1H), 2.45-2.49 (m, 1H), 2.53-2.58 (m, 1H), 2.91 (dt, *J* = 2.4, 12.8 Hz, 1H), 3.66 (q, *J* = 11.6 Hz, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 19.1, 22.2, 24.7, 28.4, 31.9, 34.9, 35.2, 41.9, 42.2, 63.6, 76.0, 216.0.

S-Methyl-*O*-(12,12'dichloro-2-oxobicyclo[4.3.1.1^{6,7}]undecan-7-yl)-methyl   dithiocarbonate (4.145)



4.144   **4.145**
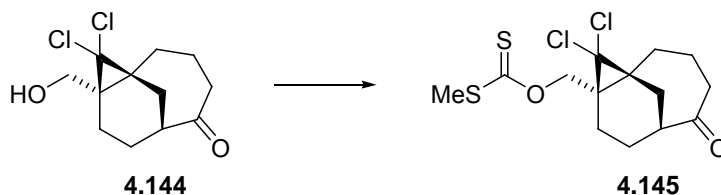
The dichloro-xanthate ester was prepared *via* a method analogous to that used for the preparation of cyclopropyl-xanthate ester **4.99.** Using these conditions **4.144** (37.5 mg, 0.143 mmol) was converted to the xanthate ester **4.145** (32 mg, 64%), which was isolated as a yellow oil following flash chromatography on silica, eluting with 10% EtOAc/petroleum ether.

FTIR (KBr, cm^{-1}): 2934, 1701, 1460, 1448, 1290, 1070, 955, 854, 733.

^{1}H NMR (500 MHz, CDCl$_3$): δ 1.37-1.47 (m, 1H), 1.71 (td, *J* = 8.7, 16.0 Hz, 1H), 1.76-1.81 (m, 1H), 1.91-1.98 (m, 2H), 2.01-2.12 (m, 4H), 2.33 (d, *J* = 15.2 Hz, 1H), 2.48-2.53 (m, 1H), 2.56-2.60 (m, 1H), 2.57 (s, 3H), 2.94 (dt, *J* = 2.4, 13.1 Hz, 1H), 4.52 (d, *J* = 11.4 Hz, 1H), 4.61 (d, *J* = 11.4 Hz, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 19.0, 20.0, 22.2, 24.8, 28.4, 32.1, 32.2, 35.6, 42.9, 74.9, 75.0, 214.9, 215.6.

HRMS (EI): calc. for C$_{14}$H$_{18}$^{35}Cl$_2$O$_2$S$_2$: 352.0125; obs. 244.0416 (C$_{12}$H$_{14}$Cl$_2$O, M$^+$ - MeSC(S)OH, calc. 244.0422).

7-Bromomethy-12,12'-dichloro-tricyclo[4.3.1.1^{6,7}]undecan-2-one (4.146)

4.144   **4.146**
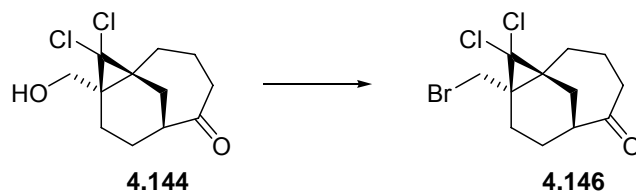
Bromine (122 mg, 0.77 mmol) in CH$_2$Cl$_2$ (1 mL) was added dropwise to a solution of triphenylphosphine (210 mg, 0.8 mmol) in CH$_2$Cl$_2$ (5 mL) at 0°C resulting in immediate decolouration. The solution was stirred at 0°C for 30 min before **4.144** (100 mg, 0.382 mmol) was added *via* cannula in 1 mL of CH$_2$Cl$_2$ (10 mL x 4). The reaction mixture was stirred for 12 h at room temperature and then quenched with the addition of a saturated aqueous solution of NaHCO$_3$ (20 mL) and extracted with CH$_2$Cl$_2$. The solvent was removed under reduced pressure

and the residue purified by flash chromatography on silica, eluting with 5% EtOAc/petroleum ether, to give **4.146** as a colourless oil (89 mg, 72%).

FTIR (KBr, cm^{-1}): 2951, 2866, 2361, 2341, 1701, 1655, 1458, 1231, 1180, 1061, 1026, 903, 849, 733, 617.

^{1}H NMR (500 MHz, CDCl$_3$): δ 1.31-1.41 (m, 1H), 1.69-1.75 (m, 2H), 1.94 (ddd, J = 1.1, 4.3, 15.2 Hz, 1H), 1.97-2.10 (m, 5H), 2.30 (dd, J = 1.7, 15.1 Hz, 1H), 2.43-4.48 (m, 1H), 2.58-2.60 (m, 1H), 2.92 (dt, J = 2.5, 13.1 Hz, 1H), 3.37 (d, J = 10.2 Hz, 1H), 3.50 (d, J = 10.2 Hz, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 21.2, 22.4, 25.2, 29.0, 32.3, 33.9, 37.3, 37.9, 41.8, 42.4, 76.6, 215.0.

HRMS (EI): calc. for C$_{12}$H$_{15}$^{79}Br^{35}Cl$_2$O: 323.9683; obs. 288.9995 (M$^+$ - Cl, C$_{12}$H$_{15}$^{79}Br^{35}ClO, calc: 288.9995), 245.0494 (M$^+$ - Br, C$_{12}$H$_{15}$^{35}Cl$_2$O, calc: 245.0500).

7,7-dichloro-8-methylenebicyclo[4.4.1]undecan-2-one (4.148)

Bromo adduct **4.146** (62 mg, 0.19 mmol) was added to a solution of activated Zn dust (125 mg, 10 equiv) and two drops of glacial acetic acid in EtOH (25 mL) and heated to reflux for 6 h. The solution was cooled and passed through a Celite® plug, eluting with EtOAc to remove solid materials. The combined organic solvent was removed under reduced pressure and the residue purified by flash chromatography on silica, eluting with 5% EtOAc/petroleum ether to give **4.148** as a colourless oil (39 mg, 83%).
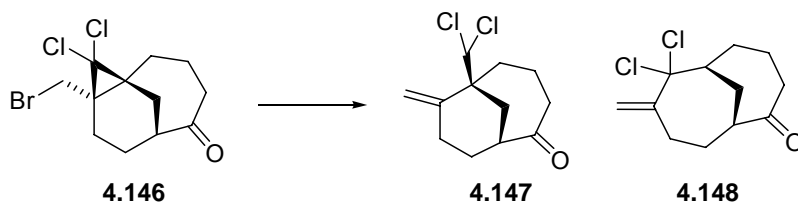
FTIR (KBr, cm^{-1}): 2937, 2866, 1685, 1448, 1346, 1136, 1094, 912, 733, 648.

^{1}H NMR (500 MHz, CDCl$_3$): δ 1.72-1.85 (m, 2H), 1.98-2.04 (m, 1H), 2.05-2.11 (m, 1H), 2.17-2.24 (m, 1H), 2.26-2.31 (m, 1H), 2.35-2.39 (m, 1H), 2.41-2.47 (m, 2H), 2.54-2.59 (m, 2H), 2.74-2.84 (m, 2H), 3.03 (td, J = 3.8, 12.2 Hz, 1H), 5.23 (t, J = 1.3 Hz, 1H), 5.26 (s, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 26.5, 29.2, 29.6, 30.0, 32.7, 35.5, 36.1, 42.1, 42.3, 45.3, 117.8, 147.7, 213.8.

HRMS (EI): calc. for C$_{12}$H$_{16}$^{35}Cl$_2$O: 246.0578; obs. 210.0810 (M$^+$ - HCl, C$_{12}$H$_{15}$^{35}ClO, calc: 210.08114).

6.5   X-Ray Crystallographic Data

Table 6.1 lists the crystallographic data and X-ray experimental details for the three crystal structures described in this thesis. Complete crystallographic data and structure refinement tables including atomic coordinates, anisotropic displacement parameters and hydrogen atom coordinates are available from the Chemistry Department of the University of Canterbury.

All measurements were made with a Seimens P4 four circle diffractometer, using a Siemens SMART 1K CCD area detector and irradiating the sample with graphite monochromated $Mo_{K\alpha}$ (λ 0.71073 Å) radiation. The crystals were mounted 5.5 cm from the detector. The data was collected by the *SMART* program[49] and data reduction was performed using *SAINT*.[50] Intensities were corrected for Lorentz and polarization effects and for adsorption using *SADABS*.[51] The structures were solved by direct and vector methods and refined using the *SHELXTL*[52] program. All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were placed at calculated ideal positions and refined using a riding model.

Table 6.1 Crystal data and X-ray experimental details for **3.83**, **4.108** and **4.144**.

Compound	3.84	4.108	4.144
Empirical Formula	$C_{20}H_{24}N_2O_7$	$C_{19}H_{22}N_2O_6$	$C_{12}H_{16}Cl_2O_2$
Formula Weight	404.41	374.39	263.15
Temperature (K)	90(2)	273(2)	273(2)
Crystal system	Monoclinic	Triclinic	Triclinic
Space group	$P2_1/c$	P-1	P-1
Unit cell dimensions: a (Å)	13.7761(9)	7.6788(5)	6.5166(3)
b (Å)	6.5610(3)	11.7696(8)	7.8814(4)
c (Å)	21.5742(4)	11.8737(8)	12.3504(7)
α (°)	90.00	112.9560(10)	80.6830(10)
β (°)	91.6100(10)	105.8940(10)	89.5060(10)
γ (°)	90.00	100.8480(10)	66.1070(10)
Volume ($Å^3$)	1949.2(2)	896.06(10)	571.51(5)
Z	4	2	2
Density (calculated) Mg/m^3	1.378	1.388	1.529
Adsorption coefficient (mm^{-1})	0.105	0.104	0.549
F (000)	856	396	276
Crystal size	0.59x0.41x0.12	0.47x0.25x0.09	0.80x0.37x0.10
Theta range for data collection (°)	1.89 to 26.39	1.99 to 26.43	1.67 to 28.85
Reflections collected	16453	11619	5906
Independent reflections [R(int)]	3955	3632	2639
Data / restraints / parameters	3955 / 0 / 263	3632 / 0 / 244	2639 / 0 / 146
Goodness-of-fit on F^2	1.034	1.031	0.942
R [$I > 2\sigma(I)$]	0.0364	0.0336	0.0245
Rw [$I > 2\sigma(I)$]	0.0480	0.0387	0.0256

6.6   References for Experimental

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