Studies towards the total synthesis of a natural product: Ophiobolin M

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Studies Towards the Total Synthesis of a Natural Product: Ophiobolin M

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To the memory of my mother
and my darling niece, Sharan

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I would like to take this opportunity to thank everyone who has in some manner contributed towards this thesis and everyone who has made my stay in Bath an enjoyable experience.

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support and encouragement, Anj for being there, Gill Christie for shelter and support and my family without whom this PhD would not have been possible.

And lastly, the EPSRC and Zeneca Agrochemicals for funding this PhD project.

ABSTRACT

Studies towards the total synthesis of ophiobolin M, a natural product possessing a 5-8-5 fused tricyclic skeleton have been conducted based on a convergent approach.

A route to the left hand, 5-membered ring A has been explored. The synthesis commenced with lactone **3.1**, which is readily obtained in three synthetic steps from simple starting materials - isoprene and diethylketomalonate. The lactone was then reacted sequentially with 2-methylallylmagnesium chloride and sodium borohydride to give homoallylic, allylic diol **3.8**. This was subjected to epoxidation making use of the allylic alcohol moiety. The primary alcohol was then protected, the secondary alcohol oxidised and the resulting keto-epoxide **3.11** was treated with a range of bases and Lewis acids to induce cyclisation. Although cyclisation did not take place, D_2O studies show the formation of the desired anion. An alternative route based on dihydroxylation has been suggested.

The core 8-5 B/C sub-unit has been assembled in four steps, starting from commercially available 1,3-cyclopentanedione which transforms into the right hand 5-membered ring C. 1,3-Cyclopentanedione was allylated at position 2 using palladium catalysed allylic substitution. Its enol form was trapped as a methyl enol ether and reacted with pentenylmagnesium bromide affording cyclopentenone with allyl and pentenyl susbstituents in the α- and β-positions respectively (triene **4.4**). This was then subjected to a ring-closing metathesis reaction using Grubbs catalyst to form the central 8-membered ring B, yielding the 8-5 core in up to 45% yield from the monocyclic precursor.

The core 8-5 bicycle (**4.5**) was then furnished with two substituents in three synthetic steps. A 1,4-conjugate addition on the core bicyclic enone gave a quaternary methyl substituent at the B/C ring junction. A kinetic enolate on ring C was trapped as the triflate and coupled, in a model reaction, with a methylmagnesium bromide in the presence of palladium catalyst to give an exocyclic methyl substituent on ring C.

The stereochemical aspects of the synthesis have also been investigated.

ABBREVIATIONS

Ac	Acetyl
acac	Acetylacetonate
aq	Aqueous
Ar	Aryl
BINAP	(2*R*, 3*S*)-2,2-Bis(diphenylphosphino)-1,1'-binapthyl
Bn	Benzyl
BSA	N,O-Bis(trimethylsilyl)acetamide
Bu	Butyl
CAN	Ceric ammonium nitrate
con	Conversion
Cy	Cyclohexyl
d	Day, days
DABCO	1,4-Diazobicyclo[2.2.2]octane
de	Diastereomeric excess
DEAD	Diethylazadicarboxylate
DET	Diethyl tartrate
DIEA	Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	N,N'-Dimethylformamide
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
dppe	1,2-Bis(diphenylphosphino)ethane
dppf	Bis(diphenylphosphino)ferrocene
ee	Enantiomeric excess
Et	Ethyl

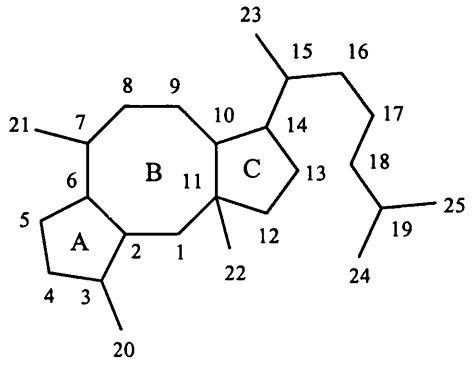
GC	Gas chromatography
eq	Equivalent
h	Hour, hours
HMPA	Hexamethylphosphoramide
i-Pr	Isopropyl
LDA	Lithium diisopropylamide
LHMDS	Lithium hexamethyldisilazide
[M]	[Metal]
Me	Methyl
MEM	Methoxyethoxymethyl
min	Minute, minutes
mol sieves	Molecular sieves
Ms	Methanesulfonyl
MTPA	(+)-α-Methoxy-α-(trifluoromethyl)phenylacetyl
PCC	Pyridinium chlorochromate
Ph	Phenyl
PMA	Phosphomolybdic acid
Pv	Pivaloyl, $(CH_3)_3CCO$
RHS/rhs	Right hand side
rt	Room temperature
TBDMS	*t*-Butyldimethylsilyl
TBHP	*t*-Butylhydroperoxide
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
Th	Thienyl

THF	Tetrahydrofuran
THP	Tetrahydropyran
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl

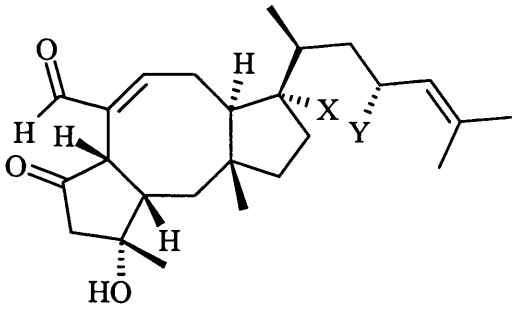
CONTENTS

1. INTRODUCTION

One of the more recently isolated group of naturally occurring terpenoids (compounds originating from the 5-carbon isoprene unit) is that of the C25 sesterterpenes.[1-3] Based on structure type, a 5-8-5 ring system shown below, the largest group of sesterterpenes is of the ophiobolanes. There are two major subclasses of ophiobolane sesterterpenes - ophiobolins and ceroplastins, the former being more prevalent.



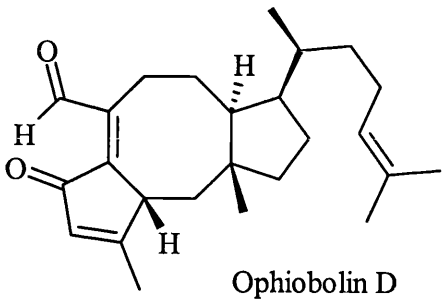
Ophiobolins[1-14] have been isolated from broths of phytopathogenic fungi. Ophiobolin A, the first of the ophiobolins, was originally isolated as a metabolite of the fungus *helminthosporium oryzoe* which causes leaf spot disease in rice seedlings. Its structure and complete stereochemistry were established by Nozoe *et al.*[4] and Canonica *et al.*[5] in the late 1960's. Several ophiobolins have since been isolated from fungal broths and their chemistry is discussed in several reveiws.[1-3] Ophiobolin M, isolated from the extracts of the fungus *cochliobolous heterostrophus* is the most recent of the series.[12] Structures of ophiobolin M and some of the other ophiobolins are shown overleaf.



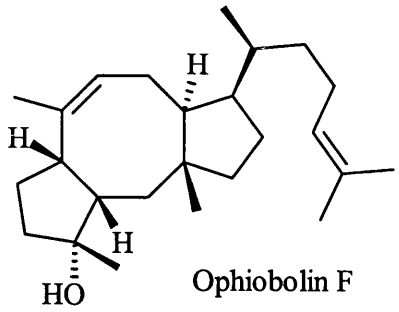
Ophiobolin A X=Y= O

Ophiobolin B X= OH, Y= H

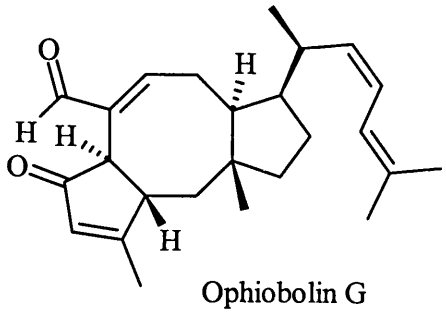
Ophiobolin C X=Y= H



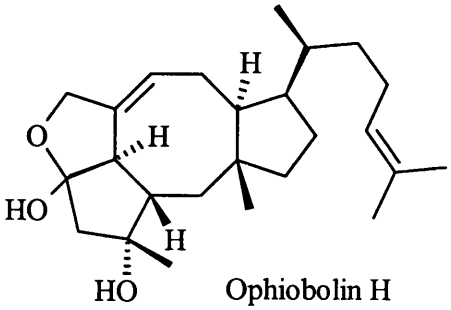
Ophiobolin D



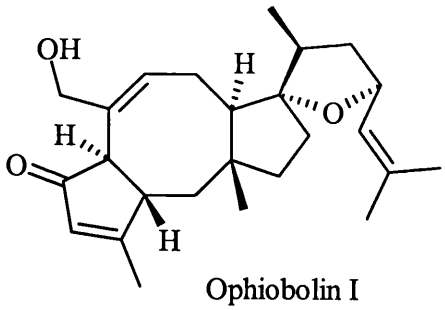
Ophiobolin F



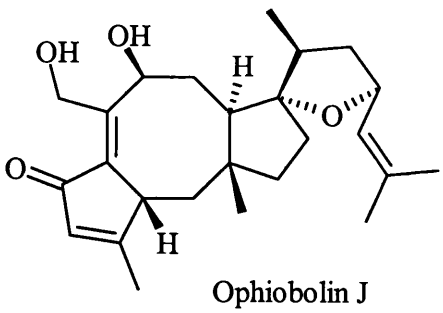
Ophiobolin G



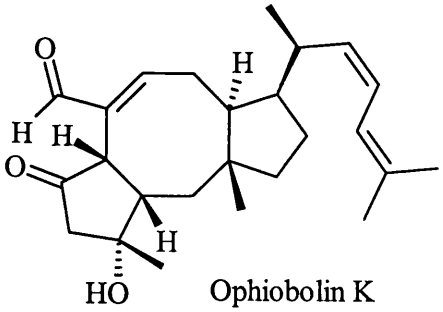
Ophiobolin H



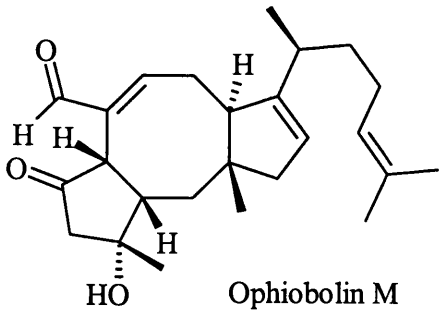
Ophiobolin I



Ophiobolin J

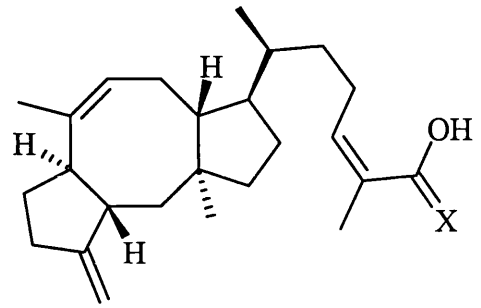


Ophiobolin K



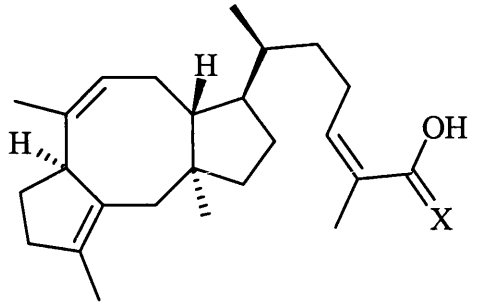
Ophiobolin M

The ceroplastins, typified by the structures shown below, are isolated from the protective wax secreted by a species of scale insects.[1,2,15-17]



Ceroplastol I X= H,H

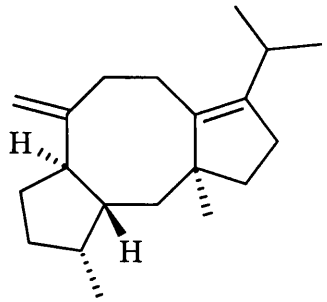
Ceroplasteric Acid X= O



Ceroplastol II X= H,H

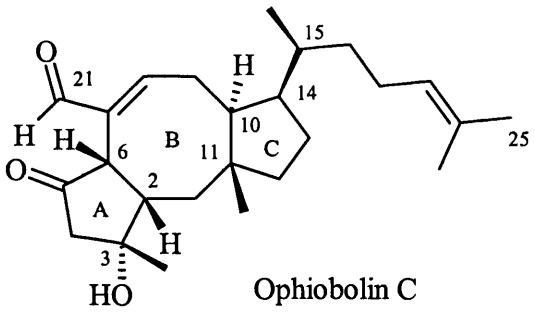
Albolic Acid X= O

Fusicoccosin diterpenes (C20 compounds) such as cycloaraneosene shown below, also possess the same fused ring system with a shorter 3-carbon side-chain.[1]

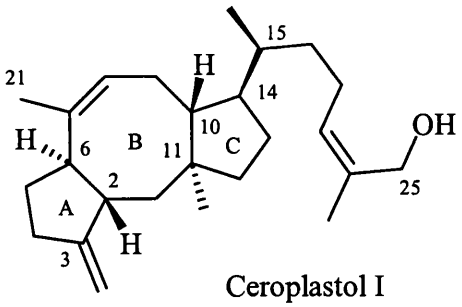


Cycloaraneosene

The sesterterpenes show a variety of biological activity. For instance, ophiobolins K[11] and M[12] show potent nematocidal activity against the free-living nematode *Caenorhabditis elagans*. They show potential as a cure for parasitic diseases caused by arthropods and nematodes in both humans and animals. More interesting however, is the molecular structure.



Ophiobolin C



Ceroplastol I

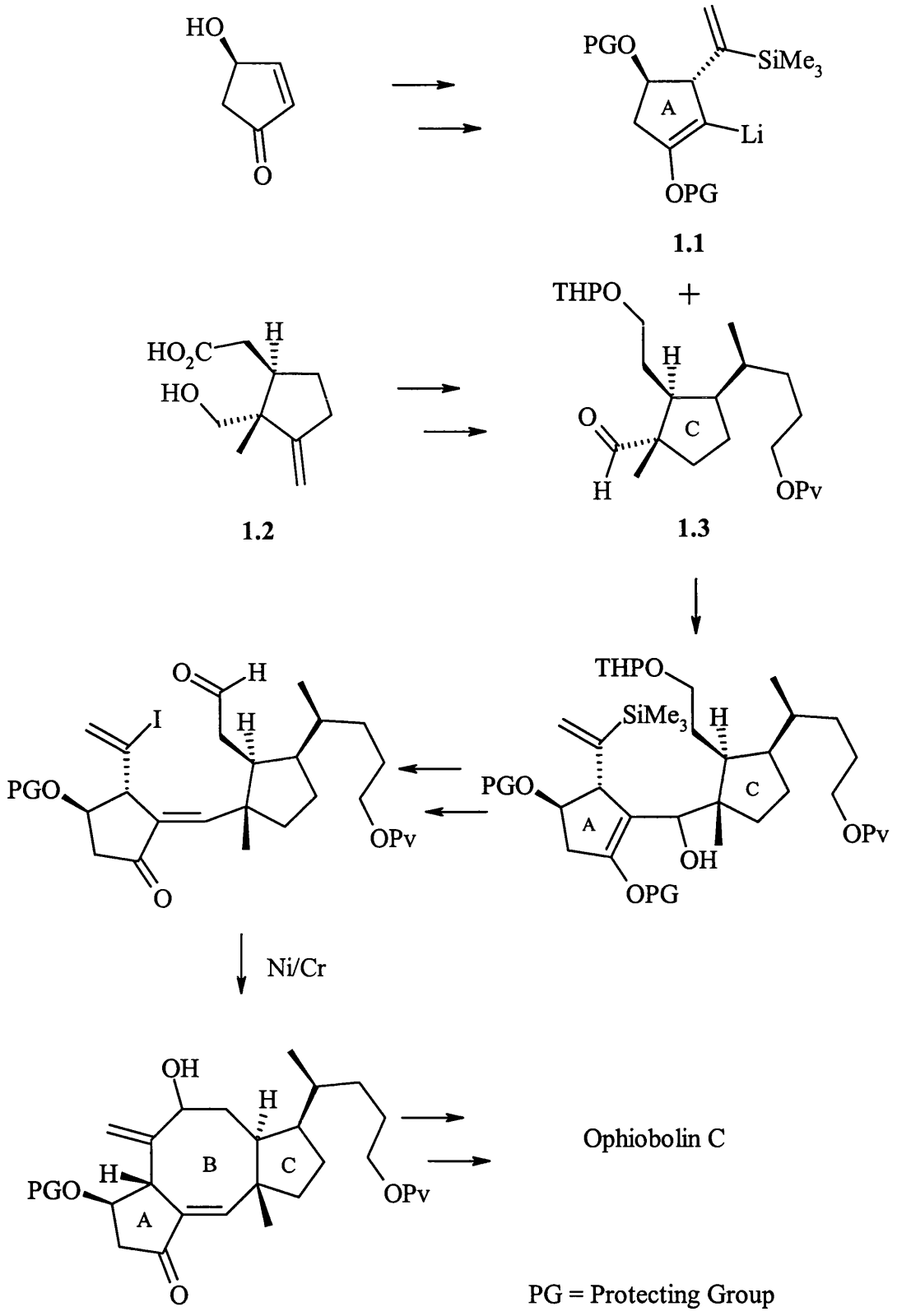
Using ophiobolin C as a typical example of the ophiobolin molecular structure, it is observed that there are 6 stereocentres on the ring system, the A/B and B/C ring junctions are *cis* and *trans* respectively, the side chain is *trans* to the C-10 hydrogen and the C-2 hydrogen is *cis* to the C-11 methyl. There is a tertiary alcohol at C-3 and quaternary centre at C-11. The exocyclic heptenyl chain also shows stereochemistry at C-15. Ophiobolin M is the first example of an ophiobolin with a double bond in ring C.

Ceroplastol I, a typical ceroplastin also possesses a similar framework except that the ring junctions are both *trans* and the absolute configurations at C-6, C-10 and C-11 are opposite to those of the ophiobolins. The oxidation states at C-3, C-21 and C-25 also differ in the two series.

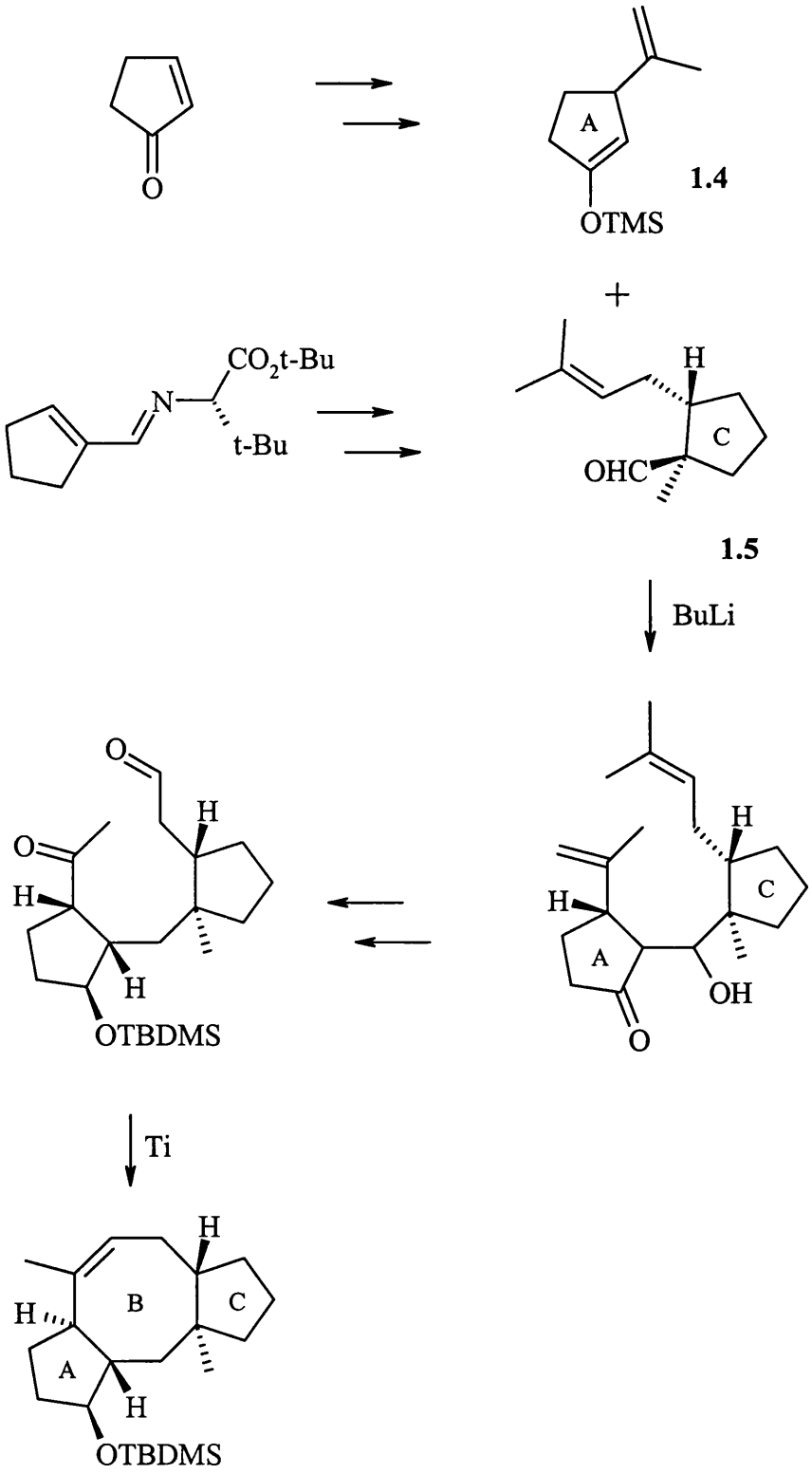
The construction of this unusual 5-8-5 tricyclic fused system with its 6 chiral centres on the ring poses an interesting synthetic challenge and has inspired considerable synthetic effort.[18-34] Approaches to the core ring system have been reported including accomplishments in total synthesis of some of these compounds such as ophiobolin C (the only total synthesis of an ophiobolin),[18] ceroplastol I[24] and II,[27] albolic acid[27,35] have been reported.

The central 8-membered ring has been mainly generated by one of four strategies: ring-closure of a dicyclopentane system, ring-expansion, fragmentation of a polycycle or cycloaddition. The stereochemical aspects have been addressed in part by making use of the stereochemical features of the starting materials, and in part by steric interactions in the molecule during reaction. The most efficient method for attaching the exocyclic side-chain has been by a 1,4-conjugate addition of an appropriate cuprate to a modified C-ring cyclopentenone. Following is a brief overview of some of the key steps in achieving the synthesis of ophiobolane sesterterpenes.

A convergent approach has been used by several groups where a dicyclopentane system has been ring-closed by a metal mediated coupling reaction. Kishi *et al.* achieved the total synthesis of ophiobolin C by this strategy.[18] *R*-4-Hydroxycyclopent-2-enone derived from D-tartaric acid was modified to the vinyl lithium **1.1** which would form ring A. Hydroxy acid **1.2** from 3-*endo*-bromocamphor was transformed by a multi-step protocol to **1.3**, ring C of the molecule with a pentanyl pivalate ester to be converted into the heptenyl side-chain at a later stage in the synthesis. The key reaction in the synthesis was the intramolecular Ni/Cr mediated coupling between the vinyl iodide and aldehyde on the connected A/C dicyclopentane ring system to form the central ring.


HO
O
PGO
SiMe3
A
Li
OPG
1.1
HO2C
H
HO
1.2
THPO
+
H
O
C
H
OPv
1.3
O
H
I
H
PGO
OPv
O
THPO
SiMe3
H
PGO
C
A
OH
OPv
OPG
Ni/Cr
OH
H
B
C
H
PGO
OPv
A
O
Ophiobolin C
PG = Protecting Group

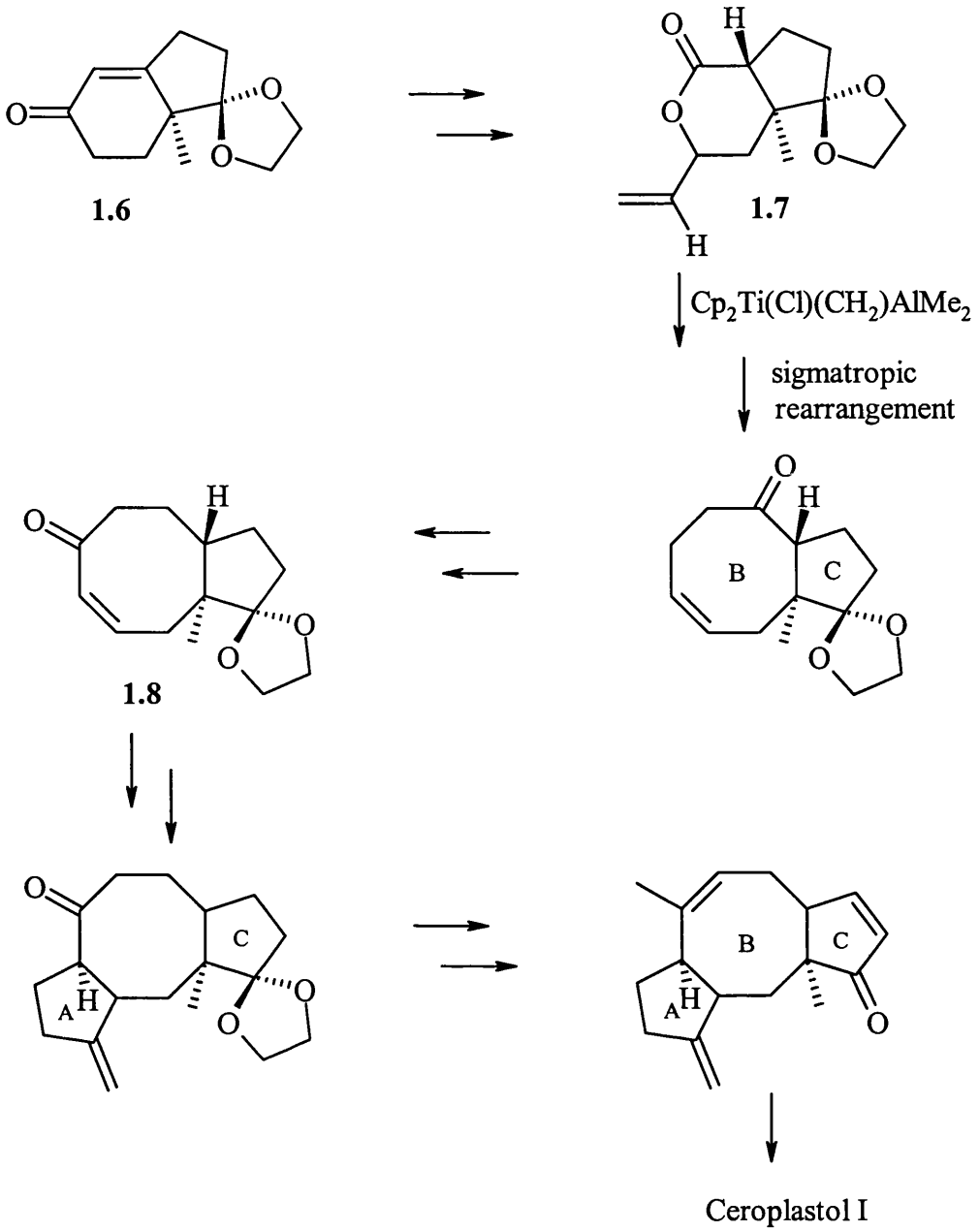
Snider's approach to the synthesis of the ceroplastin nucleus involved connection of precursor rings A and C, **1.4** and **1.5** respectively, via an aldol reaction. The central 8-membered ring was formed via a McMurry coupling reaction.[28]



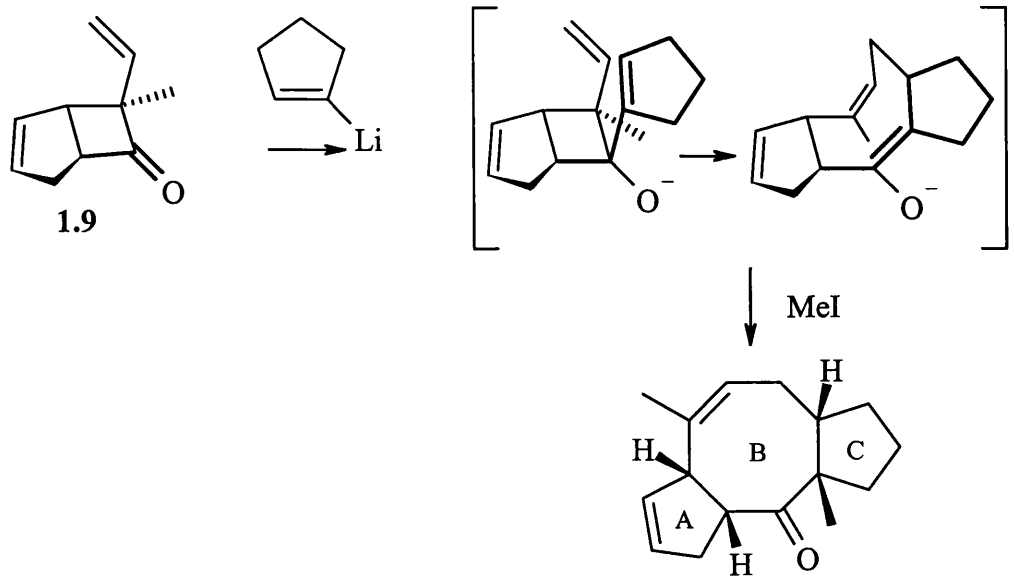
Dauben and Warshawsky also used a similar approach where McMurry coupling of a dicyclopentane system gave the tricyclic ceroplastin framework.[29] Making use of steric factors in precursor olefin systems, hydrogenation reactions were used to set the stereochemistry on the A/B and B/C ring junctions.

Kato accomplished the total syntheses of ceroplastol II and albolic acid via a convergent synthesis, again utilising Ti-mediated coupling to generate the central 8-membered carbocycle.[27,35]

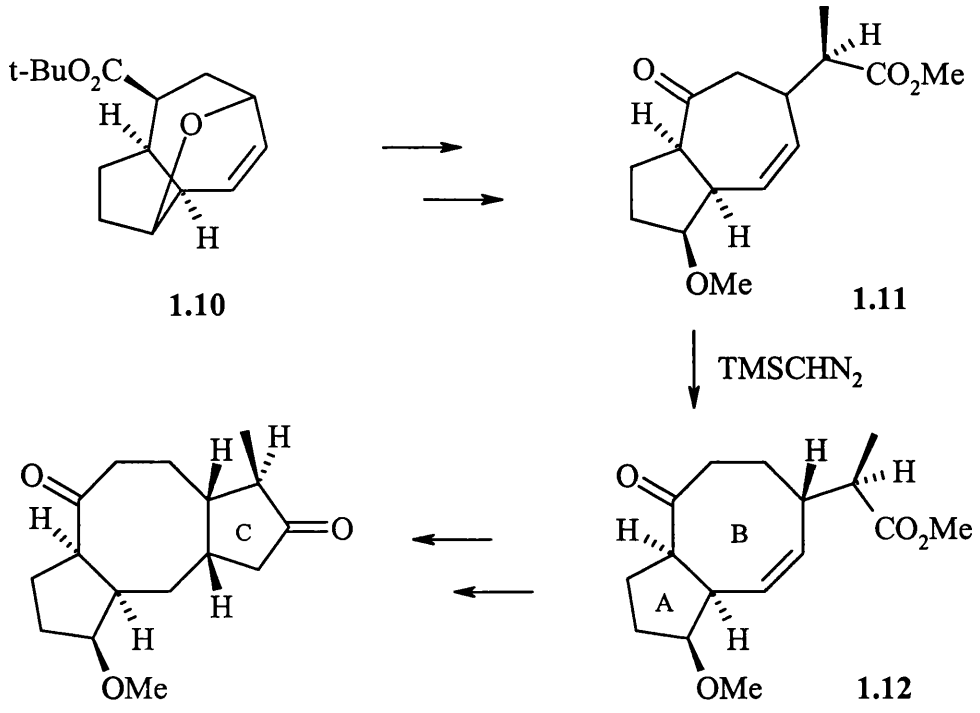
A second popular theme in the synthesis of the ophiobolane nucleus has been that of ring expansion. Outlined in the scheme overleaf are the key stages in Paquette's synthesis of ceroplastol I.[24] Lactone **1.7** from optically pure **1.6**, was treated with Tebbe's reagent and the resulting vinyl ether subjected to a [3,3]-sigmatropic rearrangement to afford the 8-5 B/C sub-unit. This was transformed into enone **1.8** which was subjected to 1,4-conjugate addition of $(Cl_2CH_2CH_2C{=}CH_2)_2CuLi$. An intramolecular cyclisation of the resulting addition product on exposure to potassium hydride formed the 5-carbon ring A. Ring C was modified into a cyclopentenone moiety on which a Grignard precursor of the exocyclic chain underwent a 1,4-conjugate addition reaction.



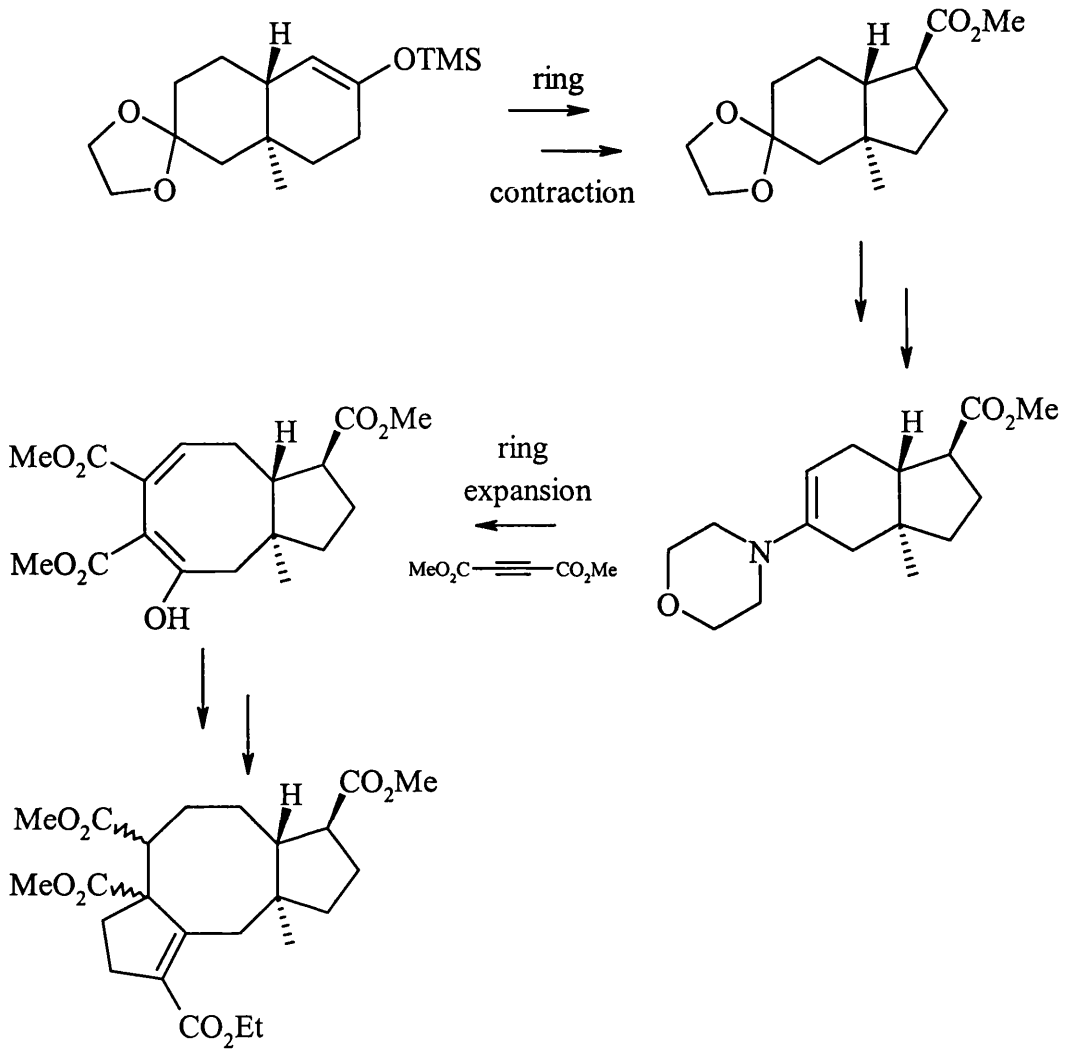
A similar strategy was used earlier by Paquette to synthesise the tricyclic ophiobolane core.[21,22] An oxy-Cope rearrangement on the anion generated from the reaction between ketone **1.9** and cyclopentenyllithium, followed by C-trapping of the enolate anion by treatment with methyl iodide furnishes the 5-8-5 nucleus along with the quaternary methyl at the B/C ring junction.



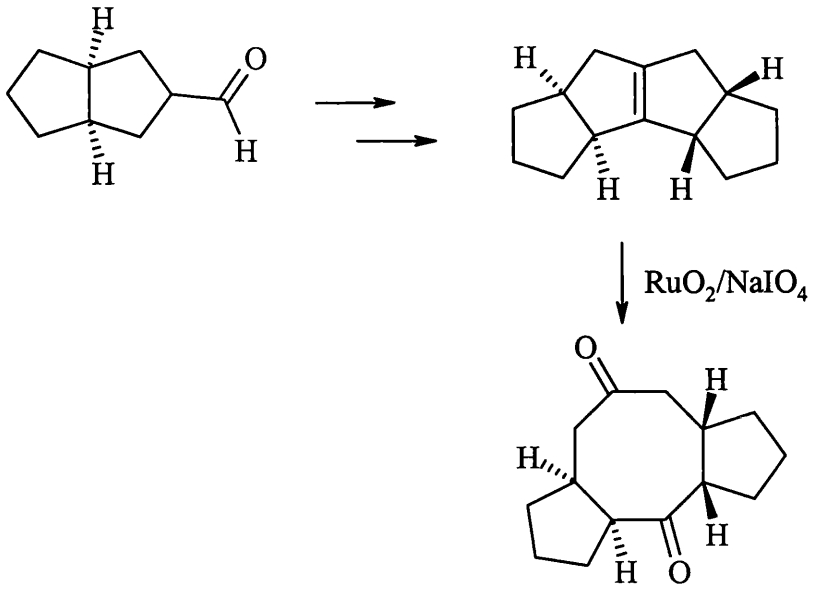
Rigby and Senanayake modified the 5-7 ether-bridged bicycle **1.10** into the ketone **1.11** and then using diazomethane homologation of ketones caused a 1-carbon ring expansion to yield the 5-8 bicyclic system **1.12**.[19] The ester side-chain on the cyclooctenone was modified to graft ring C of the molecule by a multi-step protocol to give an ophiobolane core.



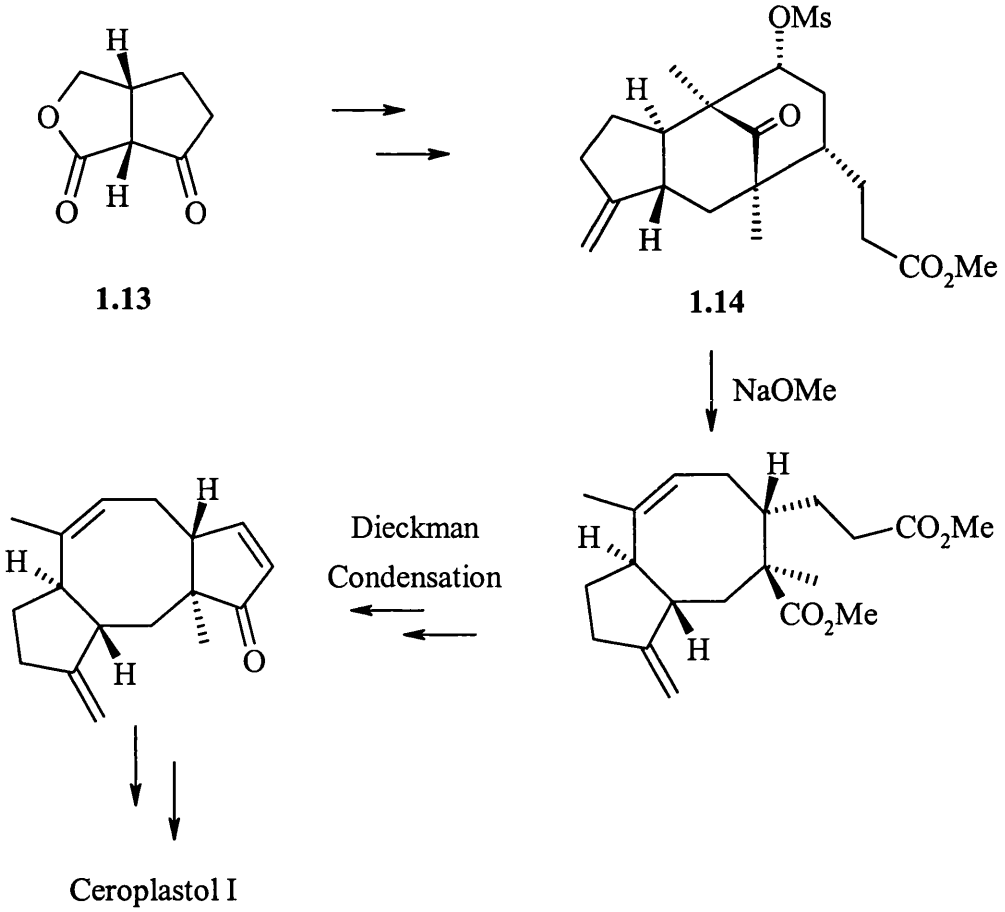
A ring-contraction, ring-expansion protocol and then an annellation reaction allowed Dauben and Hart, an entry into the 5-8-5 ophiobolane nucleus.[20]



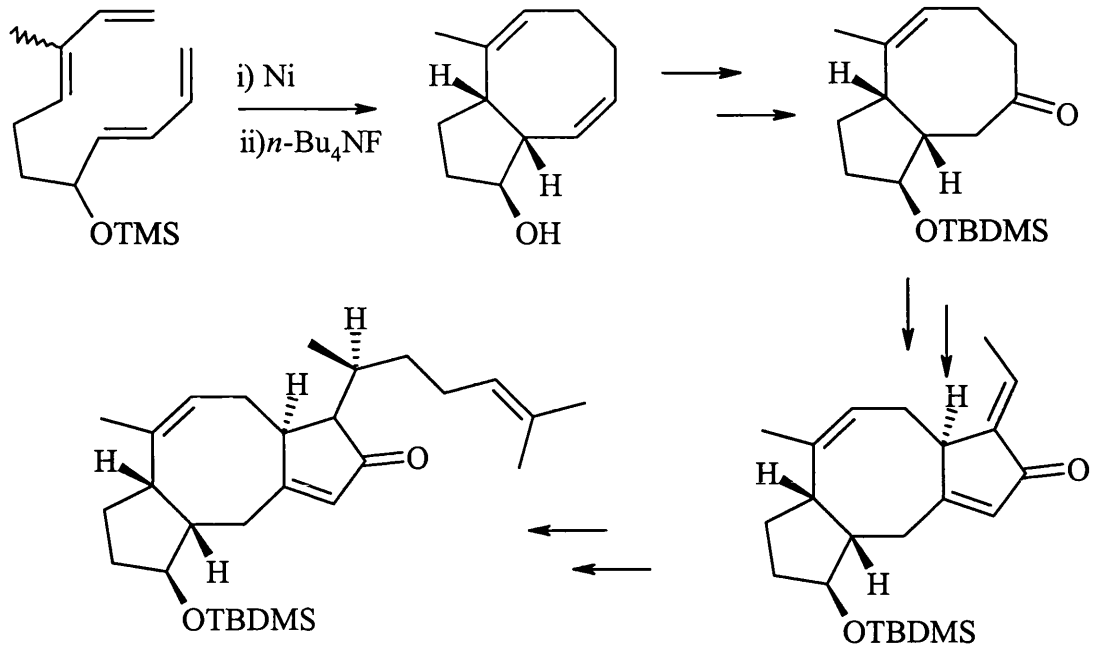
A third protocol for synthesis of the fused tricyclic ophiobolane core is that of ring fragmentation in a polycyclic system. Metha *et al.* ring-fragmented a 5-5-5-5 to a 5-8-5 ring system.[25] The stereochemical pattern of the tetraquinane was used to transcribe stereochemistry into the 5-8-5 system.



Boeckman transformed bicyclic keto-lactone **1.13** into a tricyclic ketone (**1.14**), which on exposure to sodium methoxide, led to ring-cleavage yielding the 8-5 sub-unit of a ceroplastin.[30,31] A Dieckman condensation completed the ring system. Further modification of this ring to cyclopentenone allowed the enone to be manipulated for the introduction of the exocyclic side-chain and leading to a total synthesis of ceroplastol I.



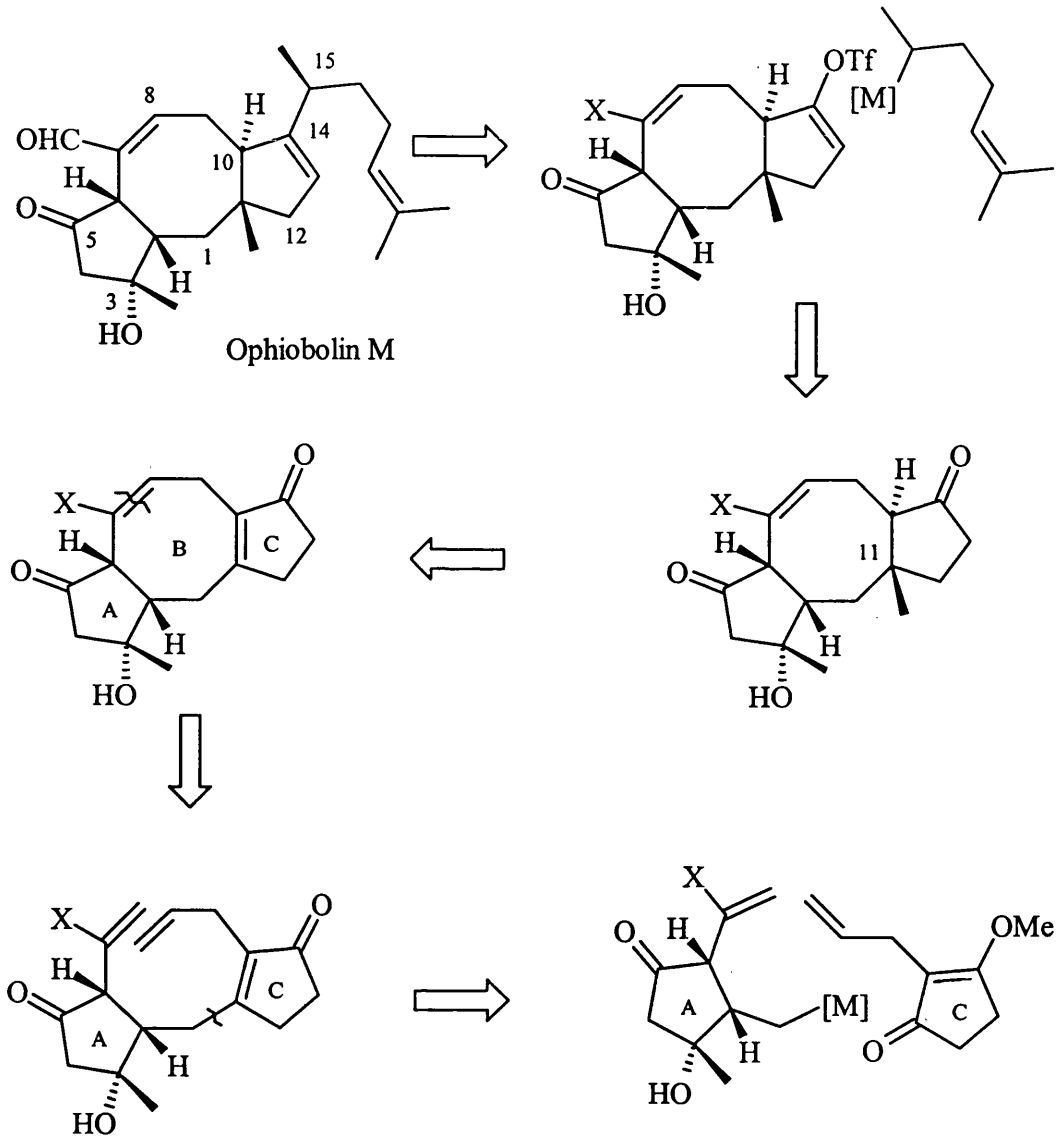
More recently Wender *et al.* have reported a fourth route into the 5-8-5 tricyclic framework.[34] The 5-8 sub-unit was formed by a cycloaddition reaction and then the 5-carbon ring C was assembled and transformed into a cyclopentenone system which was used to introduce the exocyclic side-chain via a 1,4-conjugate addition reaction.



This report describes the synthetic strategy and some model studies towards the total synthesis of one of the ophiobolins - ophiobolin M. As the preceding overview shows, only one total synthesis of this subclass of sesterterpenes has been attempted, that of ophiobolin C, by Kishi *et al.* in 1989 which involved a long multi-step protocol devised for the 5-8-5 ring skeleton.[18]

2. SYNTHETIC STRATEGY

It was envisaged that the strategy followed towards the synthesis of ophiobolins - targeted at ophiobolin M, would be that of a convergent synthesis.



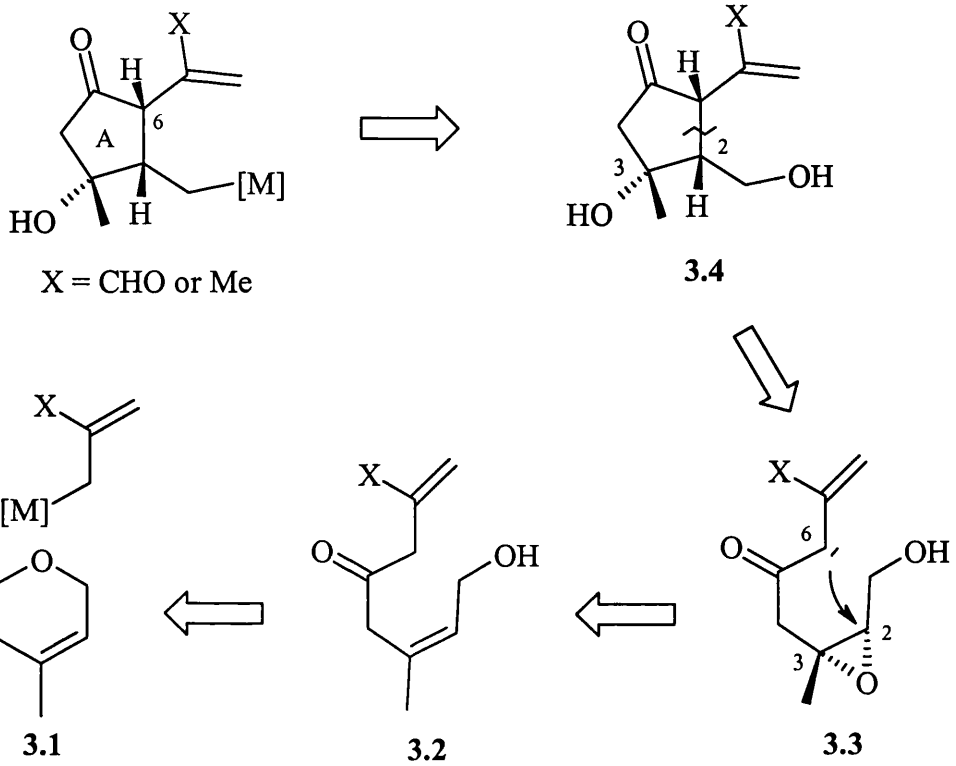
Pre-formed ring A would be attached to the cyclopentenone system of ring C via a metal mediated reaction. A ring-closing metathesis reaction would generate the central 8-membered ring, thus furnishing the 5-8-5 tricyclic backbone. 1,4-Conjugate

addition would introduce the quaternary methyl group at C-11 and the exocyclic heptenyl chain would be attached by reaction between a precursor generated by trapping a kinetic enolate on ring C and an appropriate heptenyl organometallic. Stereochemical aspects are discussed in the individual chapters on the synthetic studies towards assembling rings A and C.

3. SYNTHESIS OF RING A

3.1 Retrosynthetic Analysis

Synthesis of ring A was based on the retrosynthetic analysis of this part of the molecule as outlined below.



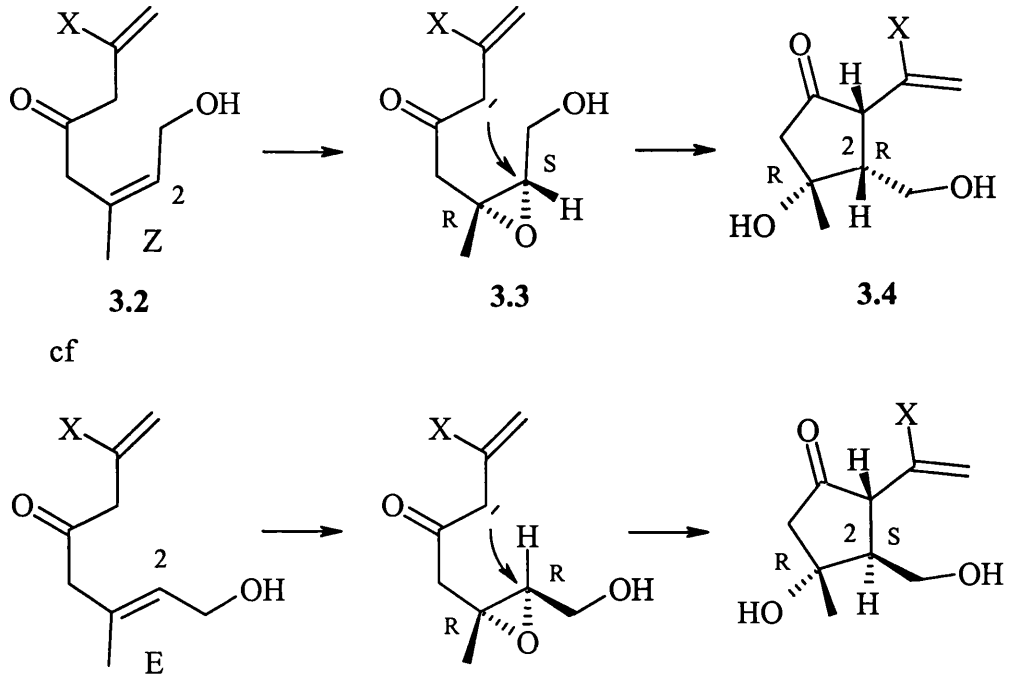
It was envisaged that ring A could be attached to ring C via an appropriate organometallic precursor of ring A. This organometallic could be derived from the alcohol **3.4** which itself could be obtained from the key keto-epoxide intermediate **3.3**. In the forward synthesis, subjecting the keto-epoxide **3.3** to a base such as lithium diispropylamide would yield an anion at C-6 which would be favoured and stabilised by enolate formation at that position. The epoxide can then, with the aid of

a Lewis acid, be opened by the anion to the cyclised ring A precursor generating the hydroxyl at C-3 and some stereochemistry at positions C-2 and C-6.

The asymmetric keto-epoxide can be derived from intermediate **3.2**. In a forward sense, site-selective asymmetric epoxidation on the allylic alcohol gives an asymmetric functional group that can be manipulated to give a cyclised product, a tertiary alcohol and hopefully, two stereocentres in one step.

The allylic alcohol **3.2** can be generated from the non-conjugated lactone **3.1**. Reaction of the lactone with an allylic nucleophile should open it to the intermediate **3.2**. This intermediate contains two essential features: allylic alcohol from the lactone for transformation into an epoxy alcohol and a terminal alkene from the allylic nucleophile which participates in the ring-closing metathesis reaction.

Use of lactone **3.1** sets the geometry for alkene epoxidation by ensuring that the Z-alkene is produced. As illustrated overleaf, Z-geometry of the tri-substituted alkene leads to the generation of the correct stereochemistry at position C-2 in the cyclised product **3.4**. The lactone **3.1** can be synthesised according to literature procedures.[36,37]



3.2 **3.3** **3.4**

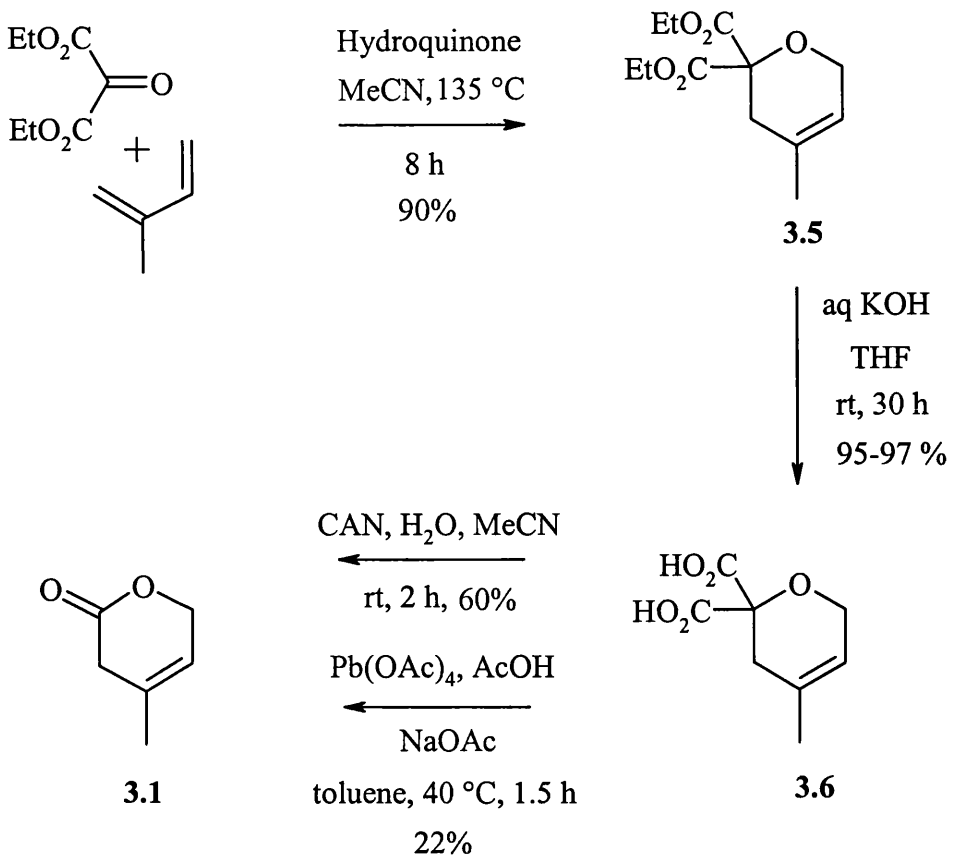
cf

The substituent X which will appear at C-7 of the ophiobolin can either be a methyl as in ophiobolin F or in the case of ophiobolin M, a formyl group obtainable by hydroformylation of an acetylene pecursor.[38]

All of the carbonyl groups and the relevant alcohols would be protected during synthesis.

3.2 Synthesis of starting lactone 3.1

Model studies towards the synthesis of ophiobolin M commenced with the synthesis of lactone **3.1** which is accessible via literature procedures.



Based on the method of Ruben *et al.*,[36] a Diels-Alder reaction between isoprene and diethylketomalonate, followed by aqueous KOH hydrolysis on the resulting adduct **3.5** furnished di-acid **3.6** in good overall yield. ^{1}H NMR analysis of the adduct **3.5** showed the ratio of 4-Me:5-Me regio-isomers is 12:1. The literature ratio was reported as 11:1.[36] These regio-isomers could not be separated by simple chromatography and were carried through the synthesis as a mixture.

At this point the literature procedure was deviated from. The literature is a multi-step protocol involving a bis-Curtius rearrangement via a di-acyl azide or alternatively, uses lead tetraacetate to transform the di-acid to the carbonyl giving yields of 60% and 40% respectively. Attempts to mimic these conditions with diphenylphosphorazide[39] to generate an *in situ* bis-acyl azide did not work. Use of

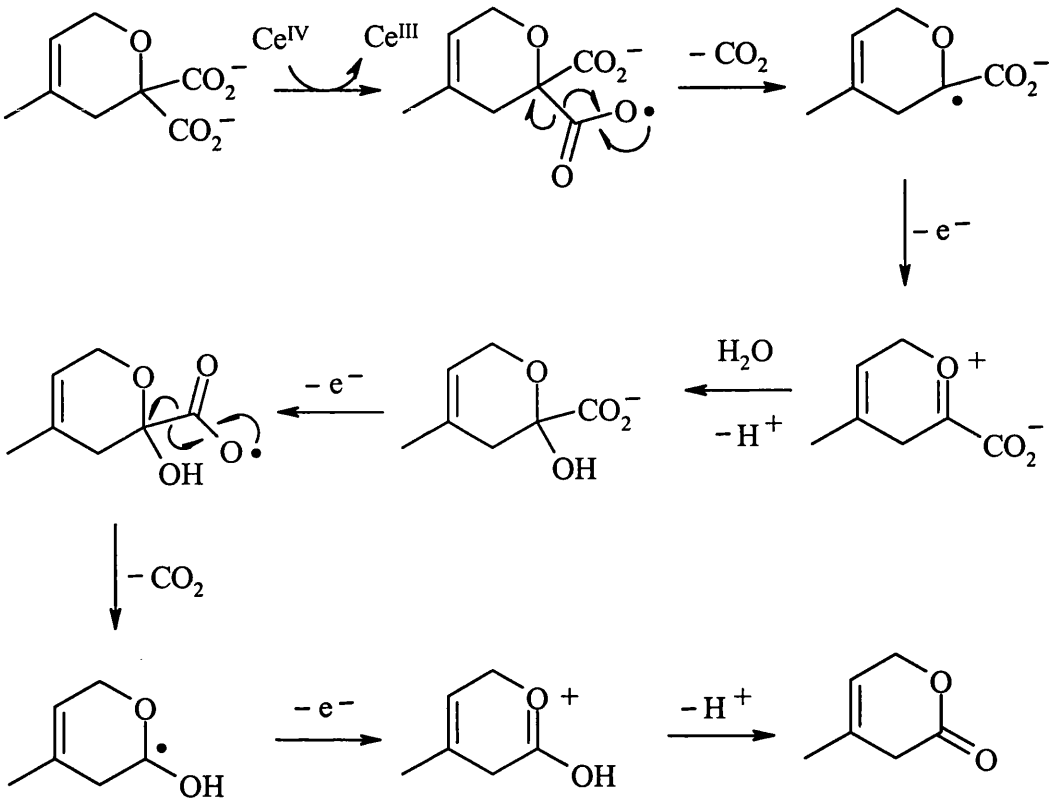
lead tetraacetate gave a 22% yield which could not be improved on. The milder, one-step procedure used by Salomon *et al.* to achieve oxidative bis-decarboxylation of α-alkoxymalonic acids using ceric ammonium nitrate (CAN)[40] proved more successful.

Initial reactions using a one-pot procedure with aqueous/acetonitrile solutions of the di-acid and CAN at room temperature for 1 h gave moderate yields of up to 40%. A large amount of gelatinous precipitate was formed during reaction and work-up, making it difficult to separate the aqueous and organic phases. This probably contributed to loss of product.

Reaction carried out in the absence of water gave only a very small amount of product. Allowing water into the reaction mixture gave some product, implying that water was necessary for reaction. However, variation in the amount of water or CAN, or use of a base such as triethylamine to assist ionisation of the di-acid, did not improve the yield.

A change in the reaction and work-up technique improved the yield up to 60%, comparable to the value obtained by Ruben *et al.* for the same di-acid to carbonyl transformation in the literature synthesis of the lactone **3.1**. Water was added dropwise over 1 h and the mixture stirred for a further hour. The reaction mixture was not subjected to the usual aqueous/organic work-up; instead acetonitrile was removed, the concentrate diluted with dichloromethane and a drying agent such as magnesium sulfate added. This seemed to pre-adsorb all of the precipitate in the reaction mixture and filtration of the resultant solid gave a clear organic phase from which the product could be easily isolated.

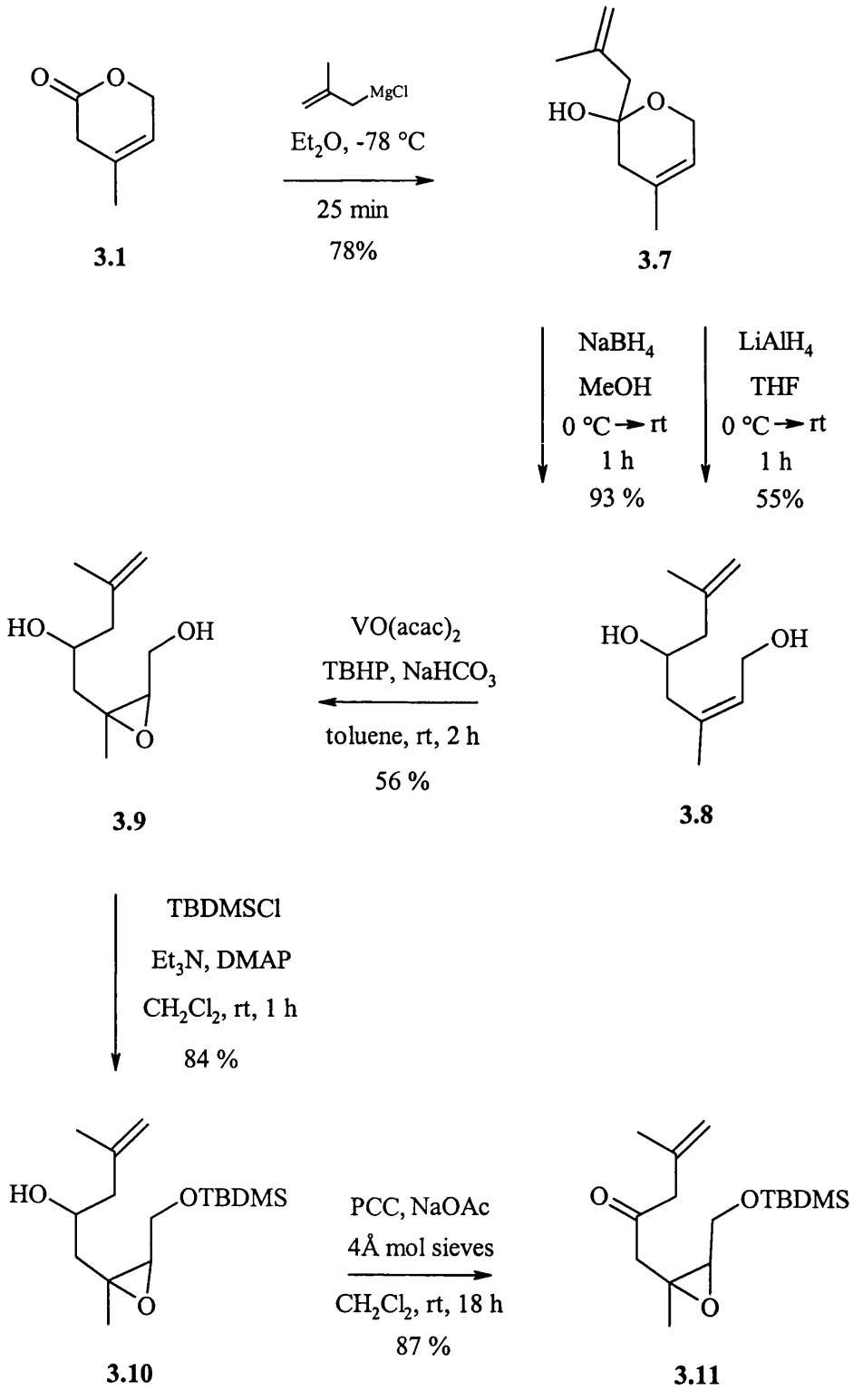
A proposed mechanism for the reaction of the di-acid with CAN is outlined in the scheme below.



In a brief attempt at decarboxylation via electrolysis only over-oxidised products were observed.

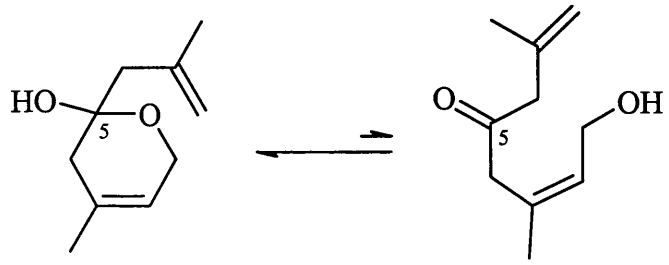
3.3 Synthesis of TBDMS-protected key keto-epoxide intermediate 3.11

The synthetic route to access the keto-epoxide is illustrated overleaf. The epoxide was synthesised as a racemate in the first instance in order to test the cyclisation reaction.



2-Methylallylmagnesium chloride was used as model reagent to open lactone **3.1** in an attempt to yield the keto-alcohol **3.2**. However, at -78 °C the reaction afforded, perhaps unsurprisingly, the product in a lactol form (**3.7**) in up to 78% yield. A

carbonyl peak was not observed in the IR spectrum. The ^{13}C NMR spectrum showed three quaternary carbons at 95.2, 129.4 and 142.3 ppm due to the quaternary hemi-ketal and two alkene carbons of the lactol. The carbon resonances do not indicate the presence of a carbonyl carbon which would be further downfield at a higher shift value.



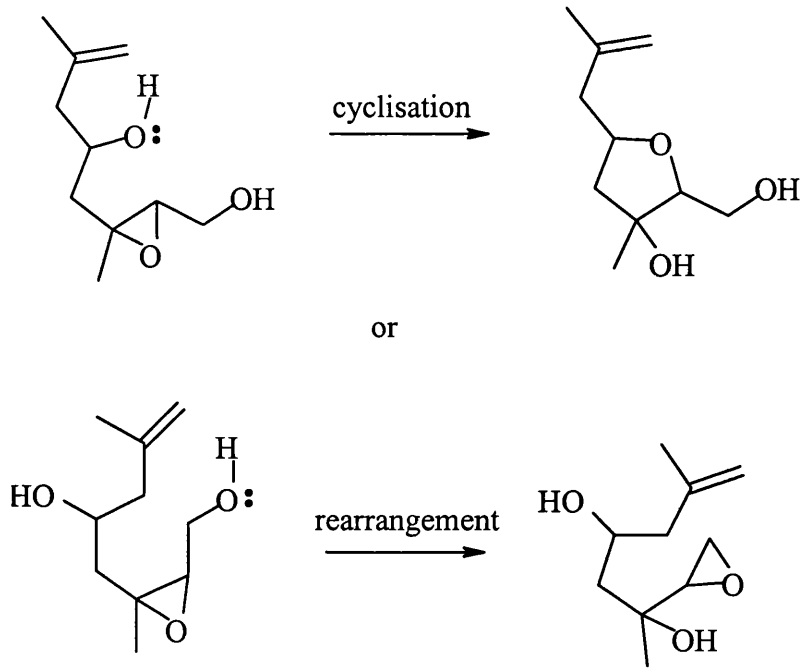
3.7 **3.2**

Assuming that the lactol **3.7** is in some degree of equilibrium with the hydroxy-carbonyl **3.2**, an attempt was made to open the lactol by reaction with ethylene glycol, thus providing the carbonyl at C-5 of the ophiobolin protected as a ketal. This proved unsuccessful, as did reaction with 1,2-ethanedithiol. Reductive opening of the lactol with sodium borohydride proved to be more successful in yielding the diol **3.8**. A similar reaction with lithium aluminium hydride gave a comparatively lower yield.

It was hoped to open the lactol as a ketal or a thioketal in anticipation of possible problems with stereochemistry during asymmetric epoxidation with an allylic, homoallylic system such as that generated by reaction with sodium borohydride.

The synthesis was taken forward by the formation of a racemic epoxide by the method of Clive and Zhang.[41] Reaction of the allylic alcohol **3.8** with *t*-

butylhydroperoxide and vanadyl acetylacetone under slightly basic conditions, gave the epoxy-alcohol **3.9** in 50-62% yield as an 88:12 ratio of diastereomers. A significant amount (~20-25%) of a side-product which had a slightly higher R_f value than that of the epoxide was isolated each time the reaction was done. From ^1H and ^{13}C NMR spectrum analysis, possible structures of the side-product are shown below.† These could result from either cyclisation or rearrangement of the formed epoxide.



The achiral epoxidation appears to have an unusually high de. In theory the de should be zero as the homoallylic centre was generated in a racemic reaction in the first instance. The de has been derived from ^1H NMR spectrum - the terminal alkene protons appear as a major set of signals at 4.78 and 4.87, and a minor set at 4.83 and 4.91 ppm. Most of the other signals overlap. In view of the high selectivity and a significantly high amount of side-product (20-25%), it could be inferred that one

† See experimental chapter **7**, section **7.1** for data.

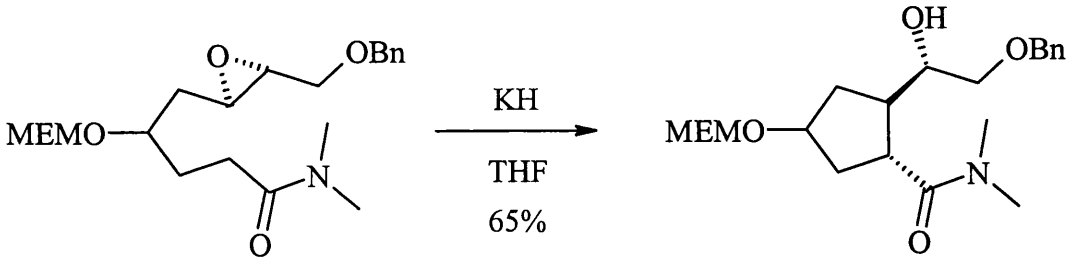
configuration of the homoallylic alcohol may allow one pair of isomers to cyclise or rearrange in preference to the other pair.

The primary alcohol in **3.9** was then selectively protected with *t*-butyldimethylsilyl chloride in the presence of triethylamine and DMAP[42] to give **3.10**. Oxidation[41] of the secondary alcohol in **3.10** proceeded smoothly with PCC to give the key keto-epoxide intermediate **3.11** (TBDMS-protected form of the keto-alcohol **3.3** discussed in the retrosynthetic analysis) in good yield.

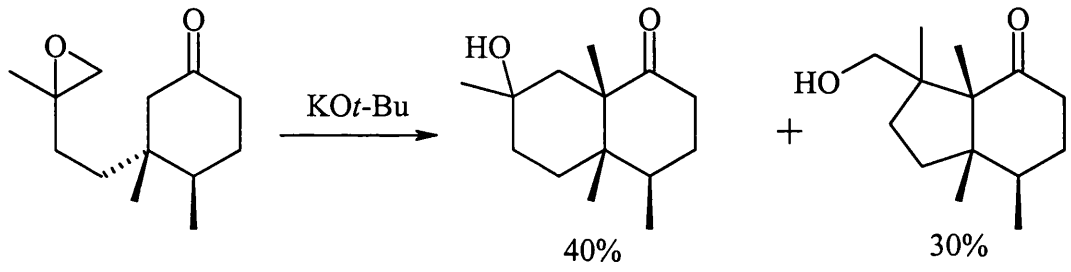
3.4 Attempts to cyclise keto-epoxide 3.11

Cyclisation of bifunctional molecules is widely used in organic synthesis to form carbocyclic systems of all sizes. A bifunctional molecule possessing a nucleophilic centre and an epoxide allows cyclisation via intramolecular ring opening of the epoxide. If the epoxide is asymmetric, this method offers the potential of generating two sterocentres per single step in elaboration of the skeletal framework of a molecule. The literature shows precedence for this methodology. Nitrile anions, sulfone anions, amide enolates and ester enolates are some of the nucleophiles that have been used for this purpose.[43-55]

For instance, the key step in the synthesis of (+)-brefeldin A by Taber *et al.* is the construction of a cyclopentane by the intramolecular opening of an enantiomerically enriched epoxide by an amide enolate.[52]

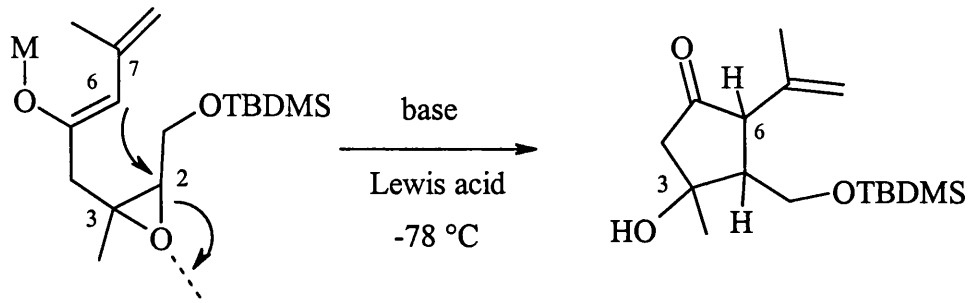


The formation of the intermediate **3.12** in Cory's synthesis of ishwarone is another example.[53] A mixture of products was isolated.



3.12

In the present synthetic study, it was envisaged that reaction of a base such as LDA with keto-epoxide **3.11** would form an anion at C-6. Enolate formation at this position would be favourable due to the presence of the allylic group at C-7. The epoxide, with the aid of a Lewis acid, could then be opened intramolecularly.



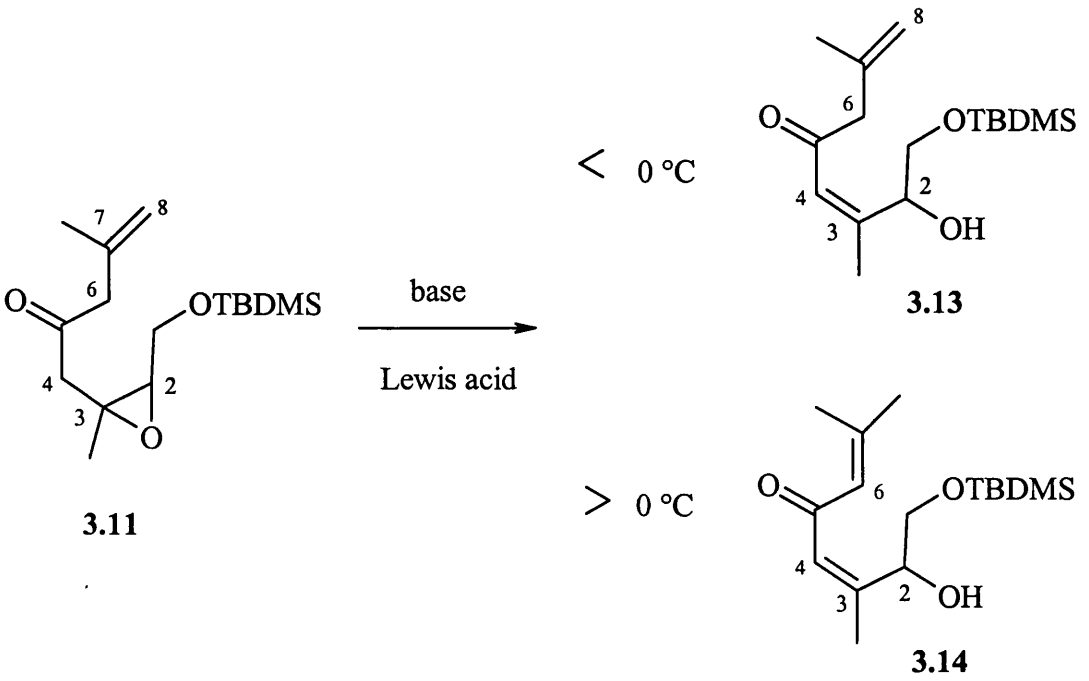
3.11 LA M= metal LA= Lewis acid

In the event itself, the general protocol for reaction was: a solution of the keto-epoxide and a Lewis acid (between 1 and 2 equivalents) in THF was added to a lithium amide base (1 equivalent) at -78 °C, the mixture stirred for a period of time (a range between 2 and 4 h) and subjected to the usual aqueous/organic work-up after a quench at -78 °C. The dilution of the reaction mixture was maintained at several levels between 0.05-0.2 M. Various Lewis acids such as Et_2AlCl, $ZnCl_2$, $Sc(OTf)_3$, $BF_3.Et_2O$ and lithium amide bases such as LDA and LHMDS were used. Unfortunately, the expected cyclised product was not formed under any of the conditions attempted. In most cases the starting epoxide was recovered.

Other variations in the reaction protocol were not successful either. For instance, adding an excess of the Lewis acid in the case of Et_2AlCl to generate an aluminium enolate[56] did not promote cyclisation. Formation of titanium and boron enolates using $TiCl_4$ and Bu_2BOTf did not open the epoxide.[57,58] A reaction with only LHMDS or LDA base was also not productive and neither was the method of Crotti *et al.* to open epoxides with lithium enolates of simple ketones in the presence of $LiClO_4$.[59] Mimicking the conditions used by Cory in synthesis of the ishwarone intermediate produced only a multi-component mixture.

Following these unsuccessful attempts with different reagents, variation in the reaction temperature was then investigated. It was found that if the reaction was allowed to warm up to 0 °C from -78 °C, the conjugated enone **3.13** was isolated as a minor product. This compound results from the formation of an anion at C-4, which then opens the epoxide. The ^1H NMR spectrum for **3.13** shows a signal at 6.47 ppm for a single proton and at 2.08 ppm for 3 protons corresponding to the proton at C-4

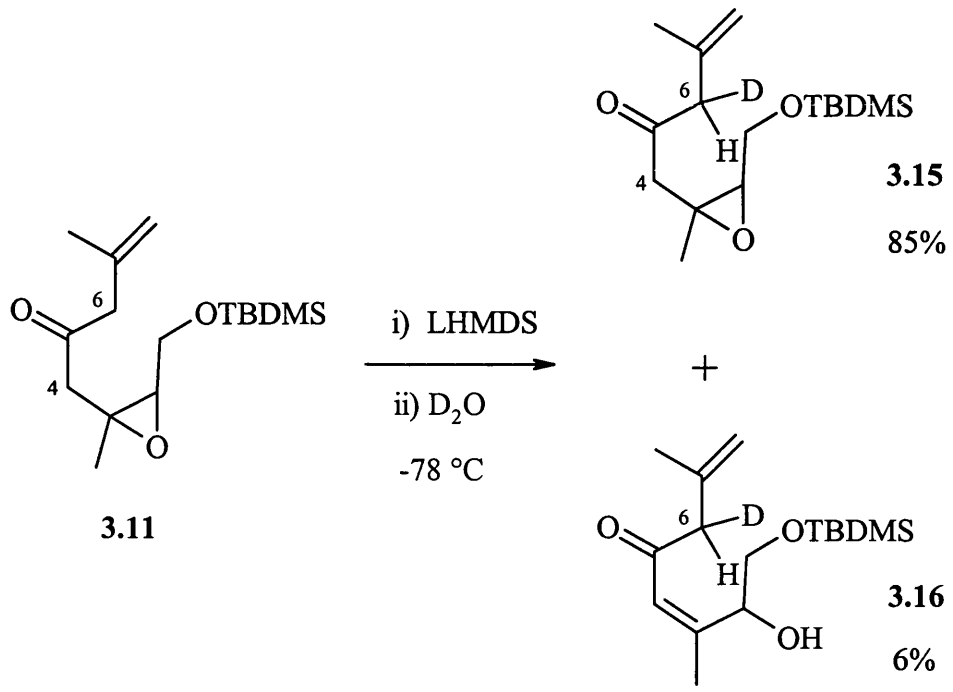
and the methyl at C-3 respectively. A shift in the carbonyl frequency from that of the starting keto-epoxide at 1718 cm^{-1} to 1686 cm^{-1} of the enone was observed in the IR spectrum. The starting keto-epoxide was recovered as the major component.



When the reaction was warmed to room temperature, the doubly-conjugated enone **3.14** was isolated. None of the starting keto-epoxide was recovered. Signals at 6.11 and 6.37 ppm, corresponding to the two protons either side of the carbonyl and for three methyl groups at 1.88, 2.10 and 2.16 ppm were observed in the ^{1}H NMR spectrum. There was an absence of signals matching those observed for protons at C-8 in the keto-epoxide. The IR spectrum showed a further shift to 1673 cm^{-1} in the carbonyl frequency. The expected carbon signals for the vinyl carbons were present in the ^{13}C NMR spectrum.

D_2O studies were carried out to check whether the required anion was formed at -78 °C. A solution of the keto-epoxide was added to LHMDS at -78 °C. After stirring for

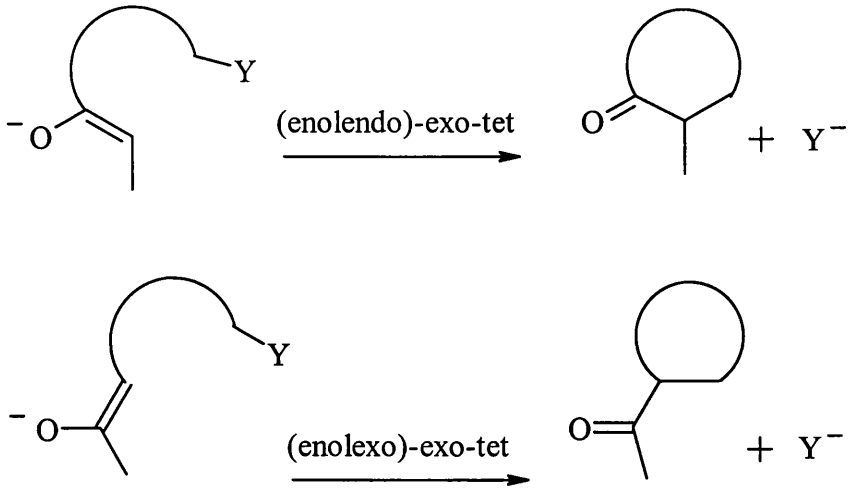
15 min, the mixture was quenched with D_2O. Two products were isolated from this reaction; deutrated keto-epoxide **3.15** and some rearranged compound **3.16**. The keto-epoxide was the major component.



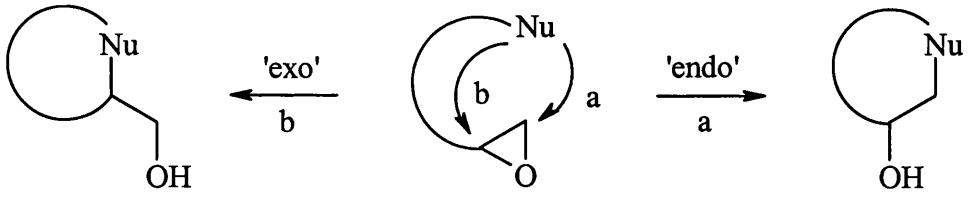
The ^1H NMR spectrum indicates deutration on both compounds at position C-6. The signal for the two protons at C-6 in the keto-epoxide **3.11** appears as a singlet at 3.12 ppm. In the products **3.15** and **3.16**, there appear signals for only one proton each at 3.04 and 3.08 ppm respectively. This study shows that the anion does form and at the expected position in the molecule. So why does cyclisation not take place?

Baldwin has designated that cyclisation of enolates can take place in an 'enolendo' mode, where the enolate C-C bond is endocyclic to the ring being formed or 'enolexo' mode, where enolate C-C bond is exocyclic to the ring being formed.[60]

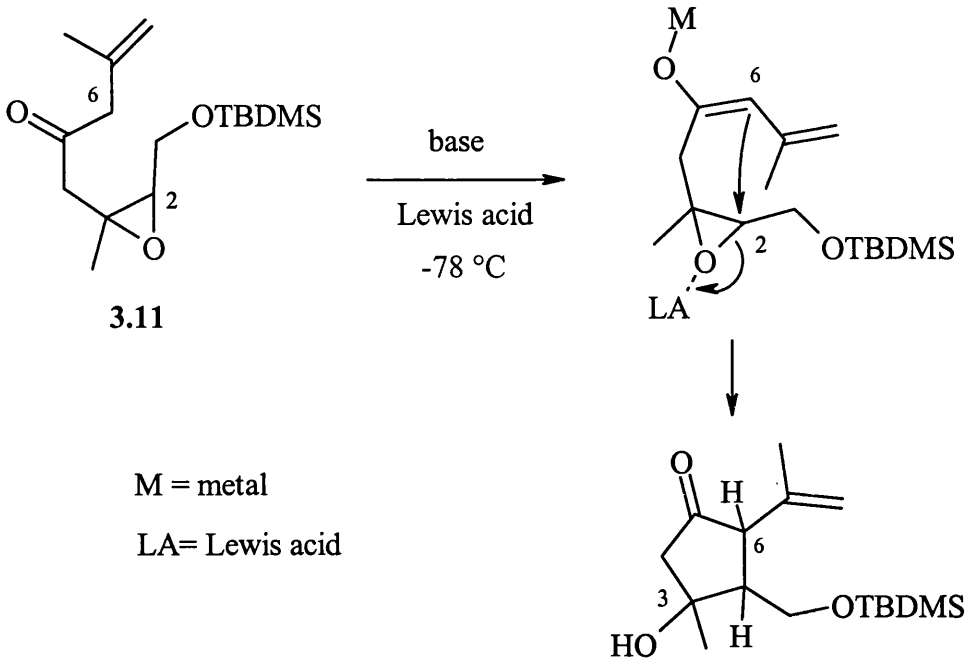
Schematic examples of 'enolendo' and 'enolexo' cyclisations are given below, where the ring-closure is exo-tet with respect to the C-Y terminus.



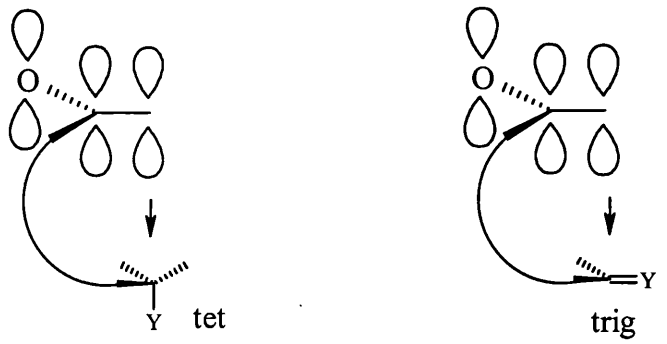
Similarly, ring-opening of an epoxide can take place either in an 'exo' or 'endo' mode.[43]



Based on this terminology, cyclisation of **3.11** would involve an 'enolendo' in terms of the enolate C-C bond and 'endo' in terms of epoxide opening.

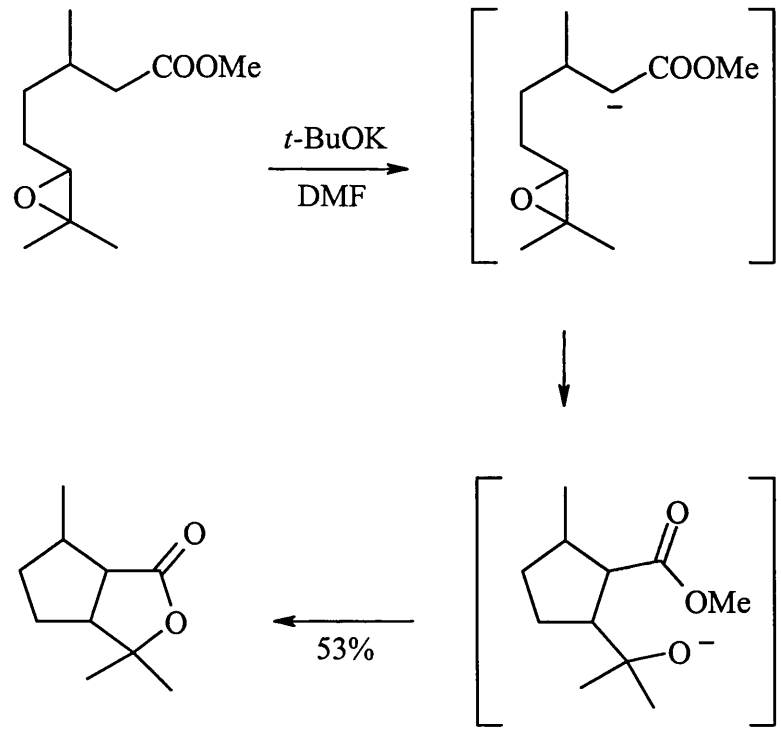


Baldwin noted that when the enolate C-C bond is endocyclic to ring formation, the planarity of the enolate system reduces the freedom of movement of the chain of atoms between the reacting sites. Also, considering the enolate terminus for an attack on a trig or tet C-Y terminus, the approach of the electrophilic carbon, is on a trajectory perpendicular to the enolate plane at the α-carbon. Both these factors determine the success of cyclisation, and 3-5-(enolendo)-exo-tet and 3-5-(enolendo)-exo-trig are considered to be disfavoured processes.[60]

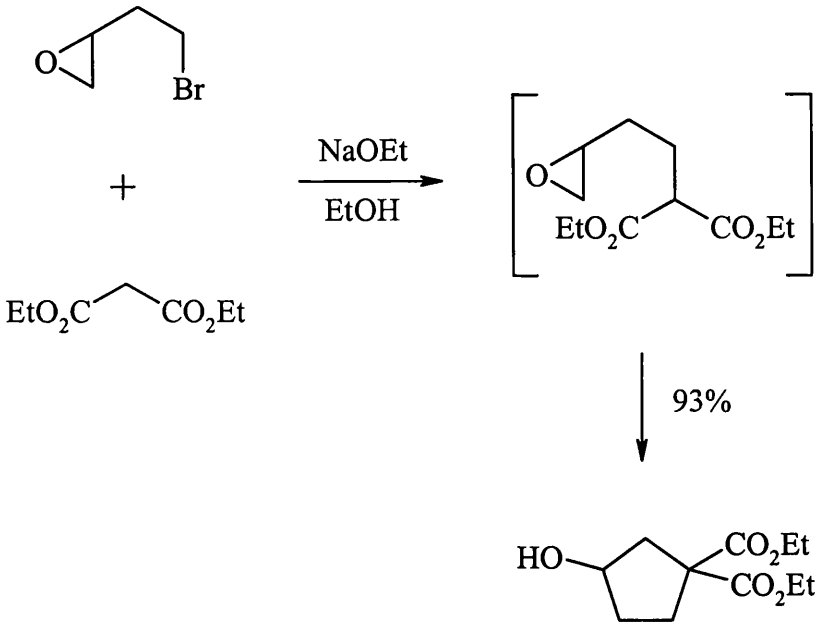


Considering the epoxide terminus independently for normal cyclisation 5-6 endo-tet and 3-5-endo-trig are also disfavored.[61]

Based on these observations, one would expect no cyclisation to take place. However, Baldwin's rules are only guidelines and epoxides are not strictly classified as trig or tet termini. The literature does show precedence for formation of cyclopentane systems by enolate opening of epoxides. One such example was seen earlier, in the formation a cyclopentane by-product in Cory's synthesis of ishwarone. Another early example is the cyclisation of methyl 6,7-epoxycitronellate to a methylcyclopentane derivative.[54]

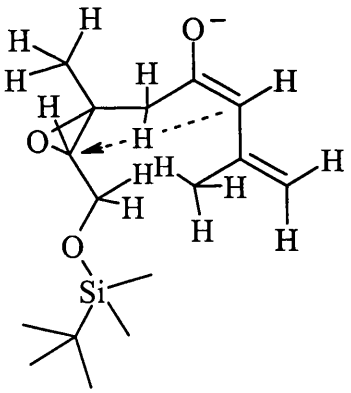


Cruickshank and Fishman have also formed a cyclopentanol system by ring-opening an epoxide with a malonate nucleophile.[55]



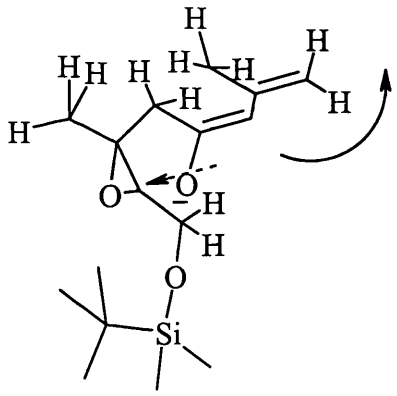
Early work on cyclisation of epoxy-nitriles by Stork and co-workers, lead to the conclusion that when the epoxide was equally substituted, the epoxy-nitrile cyclised to yield the smaller ring (exo mode). This was due to the ready co-planar arrangement of the C-nucleophile, epoxide carbon and oxide leaving group.[43] However, other studies have shown that regioselectivity can be controlled by the stereochemistry of the substituents on either side of the epoxide[50] and choice of experimental conditions.[51]

Returning to the present problem of the persistent refusal of keto-epoxide **3.11** to cyclise. Bearing in mind all studies carried out on cyclisations and epoxide opening reactions, it could perhaps be concluded that the geometric constraints imposed by the enolate, do not allow enough distortion in the plane of the enolate for a favourable alignment of nucleophile and epoxide carbon to allow a back-side attack on the epoxide.

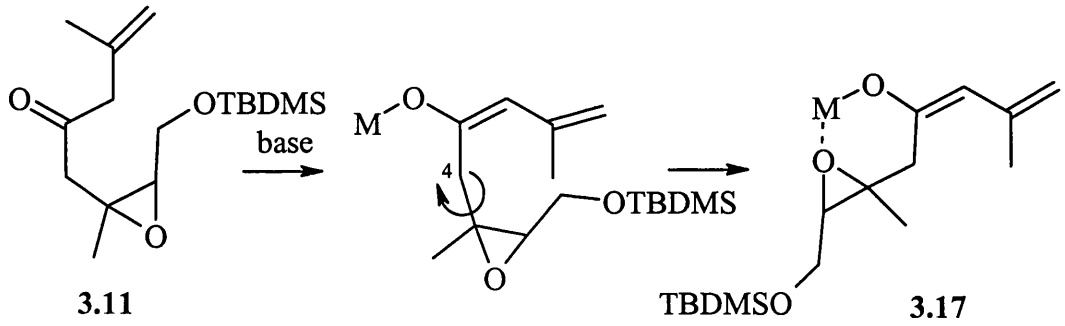


Even if distortion was allowed, the epoxide and enolate substituents may generate steric interactions that do not favour the approach of the nucleophile.

However, O-alkylation would perhaps be easier as orbitals on oxygen would be easier to align for a backside attack on the epoxide. Sterically demanding groups are out of the way for a nucleophilic attack.

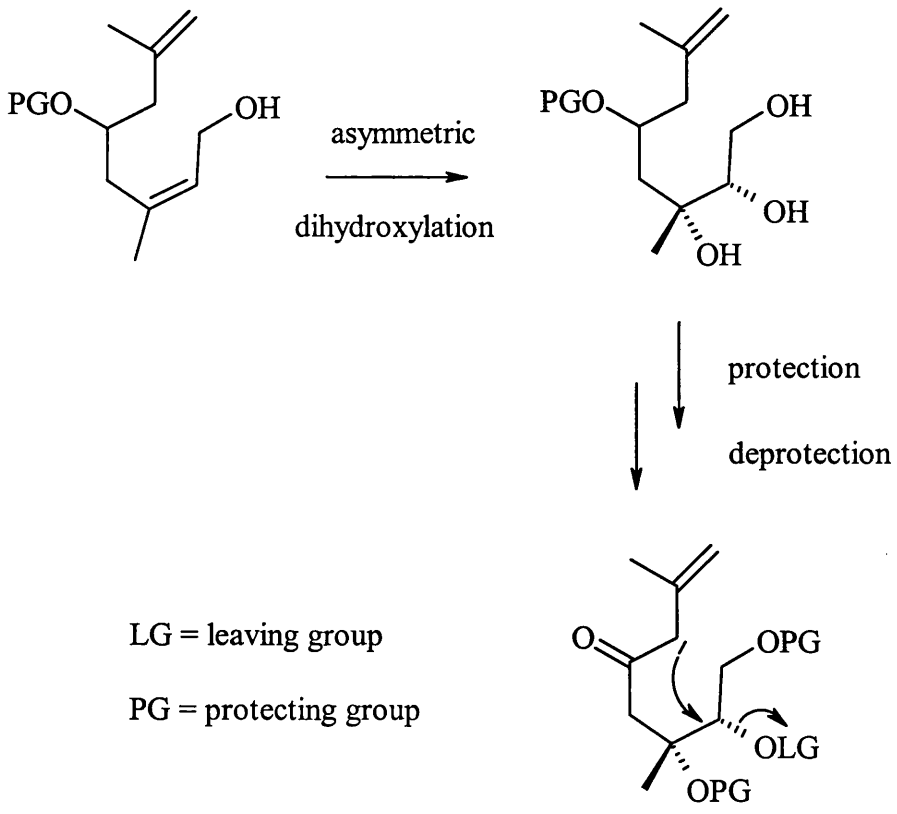


No products from either an inter- or intramolecular O-alkylation were isolated. This could suggest a stable enolate intermediate such as the chelated enolate **3.17**, accounting for the lack of reactivity.



3.11 3.17

Based on the conclusion that the anion is being formed, another possible route into this part of the molecule is shown below.



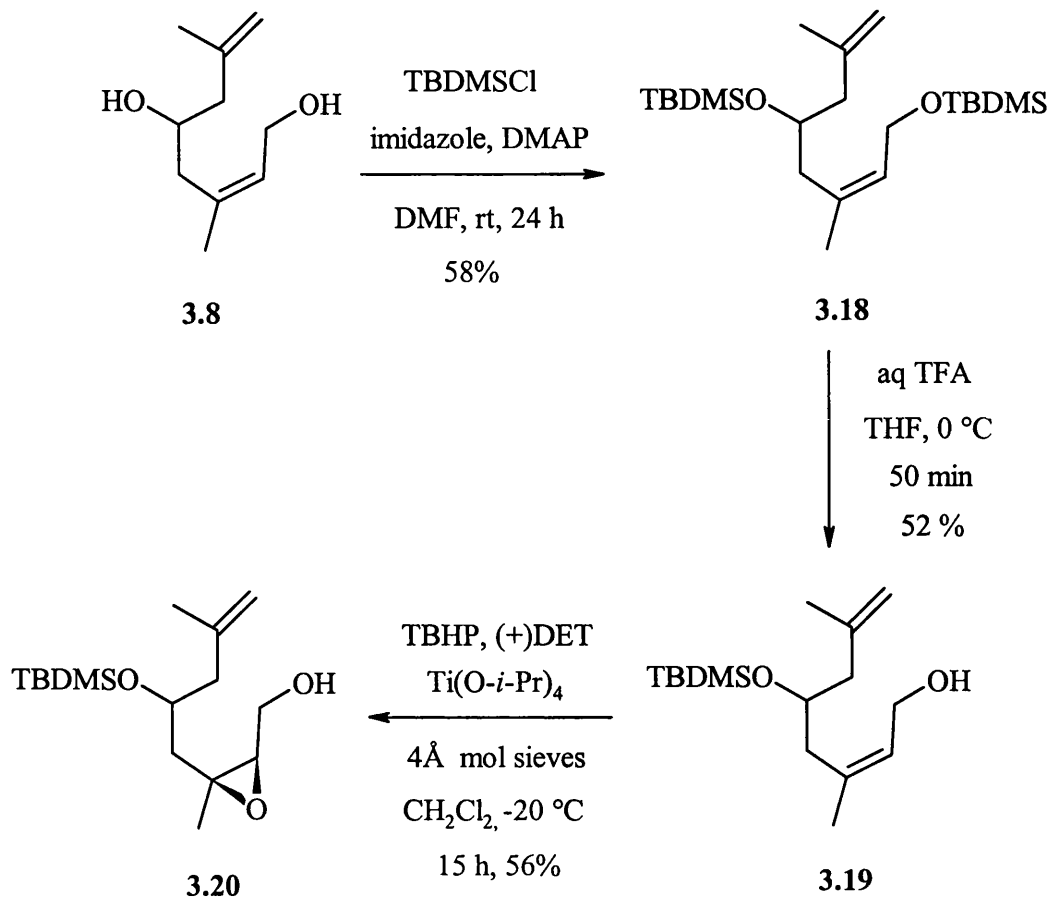
In a strategy similar to the one discussed in the preceding section, asymmetric dihydroxylation can be utilised instead of asymmetric epoxidation to achieve stereocontrol. The resulting triol could then undergo a selective protection/deprotection protocol, where the primary and tertiary alcohols are

protected and the secondary is deprotected and converted into a good leaving group such as mesylate or triflate. Cyclisation could then be achieved by generating the anion as before and this would displace the leaving group in an S_Ni fashion. It is anticipated that a protected tertiary alcohol will prevent a Payne-type rearrangement similar to that observed in the formation of minor product **3.16**. A stable, chelated enolate is not expected to form and there is expected to be a greater freedom of movement of the chain of atoms between the two reacting termini.

3.5 Stereochemical studies

Epoxidation under Sharpless conditions[62] was also looked at briefly to examine the stereochemical aspects of the synthesis.

Sharpless epoxidation on allylic alcohol **3.8** proceeded smoothly. (Some cyclised by-product, as seen in the preceding racemic synthesis, was also isolated.) However, ^1H and ^{19}F NMR spectra of an MTPA ester of the resulting epoxy-alcohol were not conclusive. Hypothetically, if the ee of a Sharpless epoxidation on **3.8** was 100%, there would still be two diastereomers in a 1:1 ratio due to the presence of the racemic, secondary homoallylic alcohol. The ^{19}F NMR spectra of the MTPA ester of epoxy-alcohol shows three broad signals with shoulder peaks, giving inconclusive data. This may perhaps be due to the alcohol on position C-5 binding to the titanium during reaction and so giving lower enantioselectivity for allylic alcohol epoxidation. This alcohol could also form an MTPA ester itself, in addition to the primary MTPA ester, thus giving multiple peaks in the spectra. So the alcohol was protected prior to the epoxidation reaction.



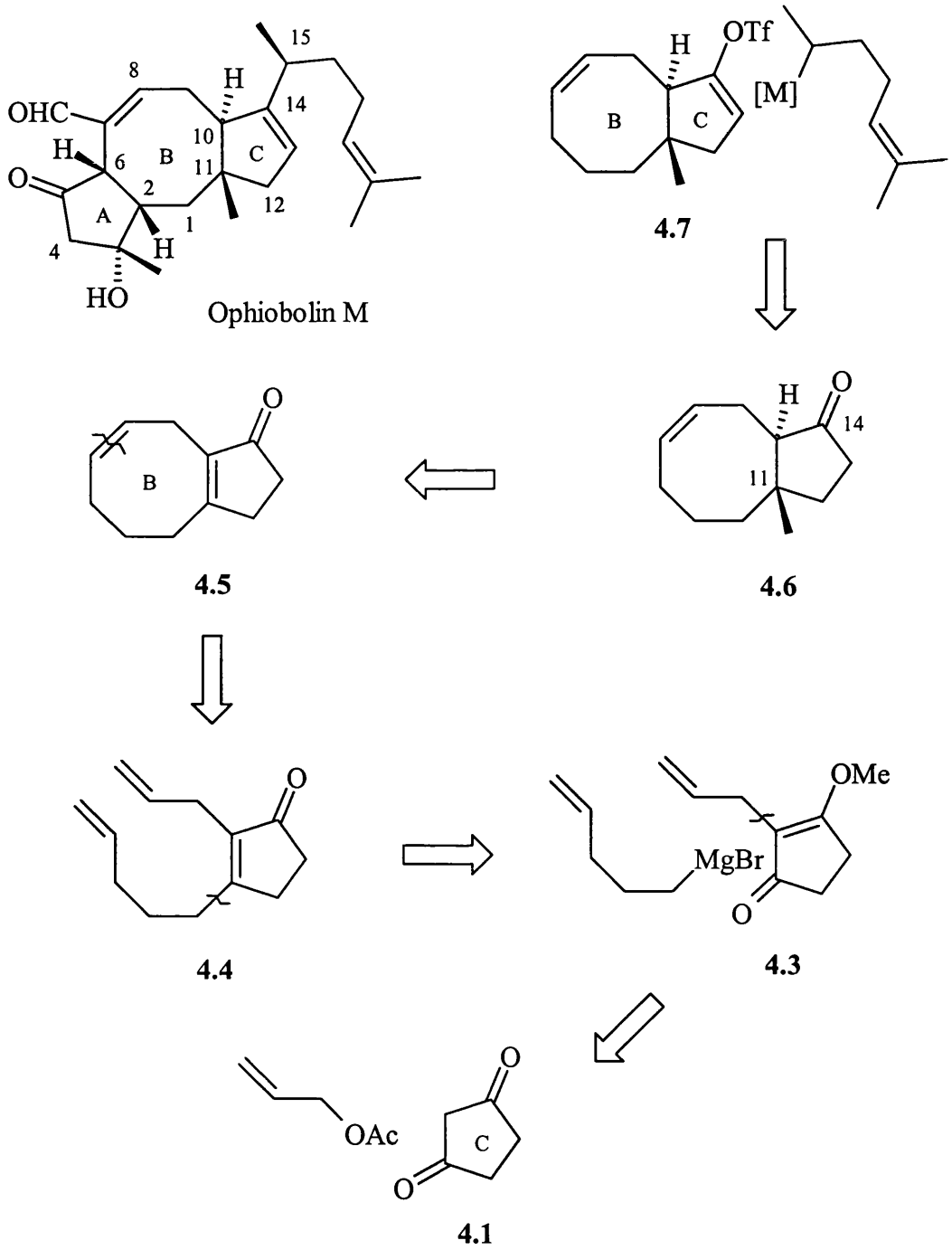
Double protection of the diol **3.8** with *t*-butyldimethylsilylchloride, followed by selective deprotection with aqueous TFA of the protected diol **3.18**, gave the mono-protected allylic alchol **3.19** in moderate yield.[63] The reactions were not optimised.

Sharpless epoxidation on the protected allylic alcohol gave the epoxide, as well as the previously observed side product. The ^{1}H and ^{13}C NMR spectra of the epoxy-alcohol show presence of isomers in an approximately 5:2 ratio. However, the ^{1}H and ^{19}F NMR spectra of the MTPA ester of the epoxy-alcohol **3.20** were still not conclusive. Over 4 signals were observed in the ^{19}F NMR spectrum due to the $-CF_3$ and only 2 signals in the ^{1}H NMR spectrum due to the -OMe groups present the MTPA ester.

As cyclisation on the racemic keto-epoxide did not give the desired results, stereochemical studies on this part of the molecule were not pursued any further.

4. SYNTHESIS OF RINGS B AND C

4.1 Retrosynthetic analysis



Synthetic studies towards acquiring rings B and C were based on the retrosynthetic analysis shown above.

Ring A can be viewed as an exocyclic group attached on the skeleton of the central 8-membered ring B, and as such, model studies to form ring B can be conducted without the presence of ring A.

The B/C sub-unit of the ophiobolin has two exocyclic groups, a heptenyl chain at C-14 and a quaternary methyl group at the B/C ring junction.

The heptenyl chain could be attached via an appropriate metal catalysed reaction between a vinyl triflate such as **4.7** and a heptenyl organometallic.[64] The heptenyl organometallic could be obtained by transformation of 6-methyl-5-hepten-2-one which is commercially available. Stereochemistry at this position could be achieved by use of a chiral ligand or by converting the vinyl triflate into a vinyl anion which would displace an enantiomerically pure halide/mesylate derived from the methyl heptenone in an S_N2 fashion.

The vinyl triflate **4.7** can be procured from bicyclic ketone **4.6**. In a forward sense this could be achieved by trapping the kinetic enolate generated from reaction of ketone **4.6** with a base such as lithium diisopropylamide as a vinyl triflate.

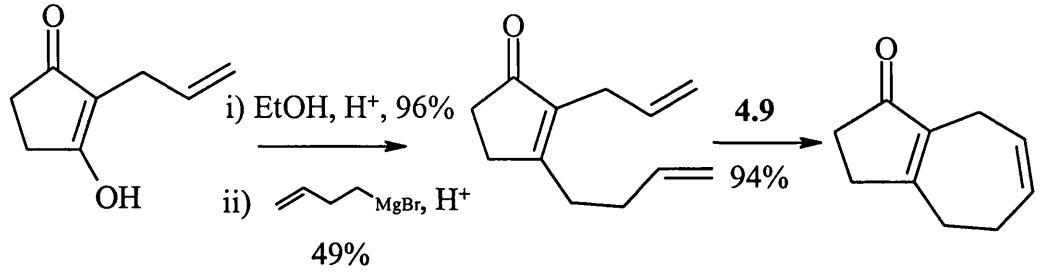
The bicyclic ketone **4.6**, with the methyl at C-11, could be obtained from the bicyclic enone **4.5**. This transformation would involve a 1,4-conjugate addition reaction on the enone **4.5** with a methyl cuprate which would furnish the C-11 methylated bicyclic B/C sub-unit **4.6**.[65-67] The stereochemistry at this position could be controlled by use of a chiral ligand.

The core 8-5 sub-unit **4.5** could be acquired from the key monocyclic triene intermediate **4.4**, by a ring-closing metathesis reaction.[68]

The triene **4.4** can be generated by reaction between the methyl ether intermediate **4.3** and an organometallic derived from pentenyl bromide. Pentenyl bromide makes an appropriate model reagent for this part of the molecule as both termini of the molecule have the same functional groups as would ring A when the real molecule was connected to ring C and ring-closed to form ring B.

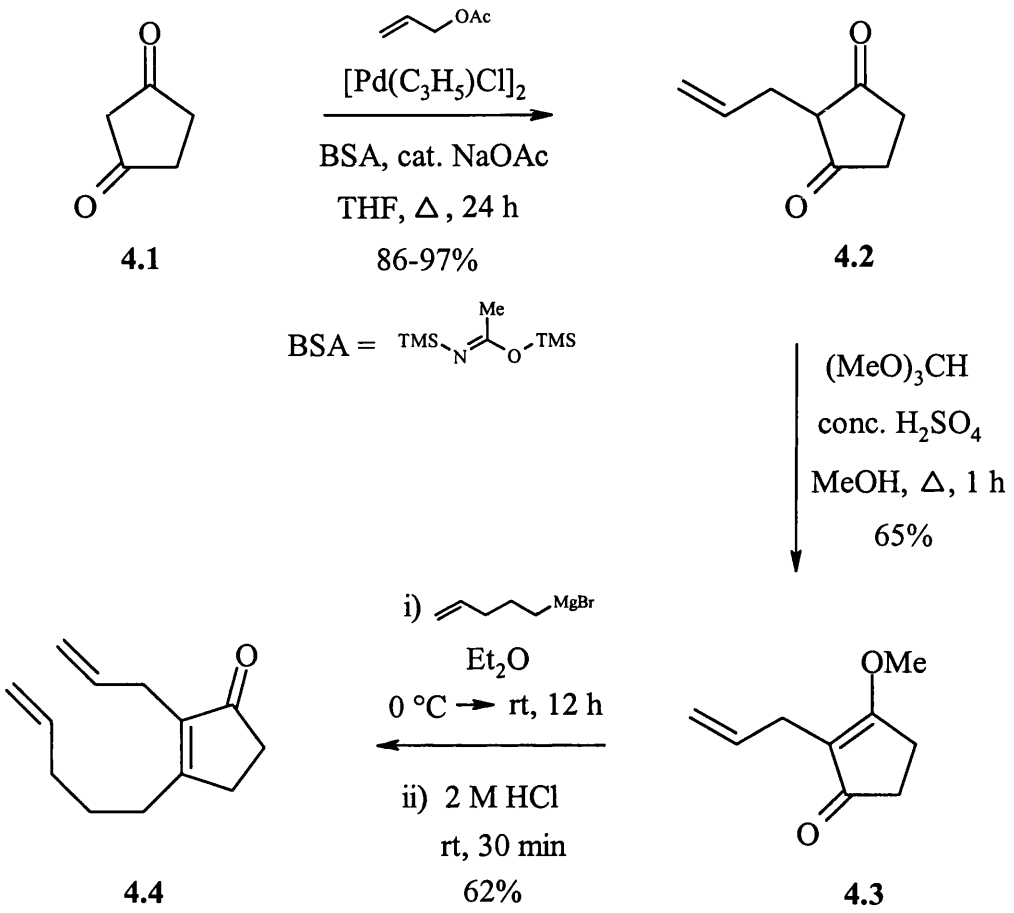
The methyl enol ether **4.3** can be obtained from an allylated precursor derived from commercially available 1,3-cyclopentanedione, **4.1**.

A similar scheme to form a 5-7 ring system has appeared in the literature.[69] Blechert and co-workers formed a triene system similar to **4.4** starting from an allylated-cyclopentanedione (scheme shown below). The later was prepared by Blechart based on multi-step literature procedure.[70]



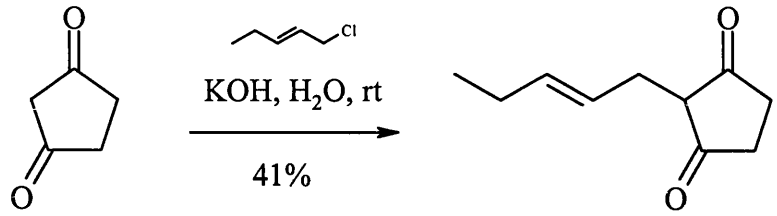
4.2 Synthesis of triene intermediate 4.4

The scheme below shows the synthetic route followed to form the monocyclic triene intermediate.



Synthesis of the triene intermediate **4.4** commenced with the one-step palladium catalysed allylation of 1,3-cyclopentanedione. Literature procedure for the synthesis of 2-allyl-1,3-cyclopentanedione involves cyclisation of an acyclic precursor.[70] The synthesis and chemistry of 2-alkyl-1,3-cyclopentanediones has been reviewed.[71]

Direct alkylations of 1,3-cyclopentanedione give low to moderate yields.[71] For instance reaction of 1,3-cyclopentanedione with an allylic halide in the presence of potassium hydroxide gave only a 41% yield.[72]



Fortunately, this transformation in the present synthesis using palladium catalysed allylic substitution[73] gave nearly quantitative yields of the allylated cyclopentanedione **4.2** in a single step. The ^{1}H NMR spectrum in d_4-methanol shows that the cyclopentanedione exists its the enol form. The signal due to the methylene in the allyl moiety appears as a doublet at 2.92 ppm. A broad singlet, partly overlapped by the terminal alkene proton signals, appears at 5.10 ppm. This is most likely due to the enol proton. A carbon signal due to an alkyl methine is not observed in the ^{13}C NMR spectrum.

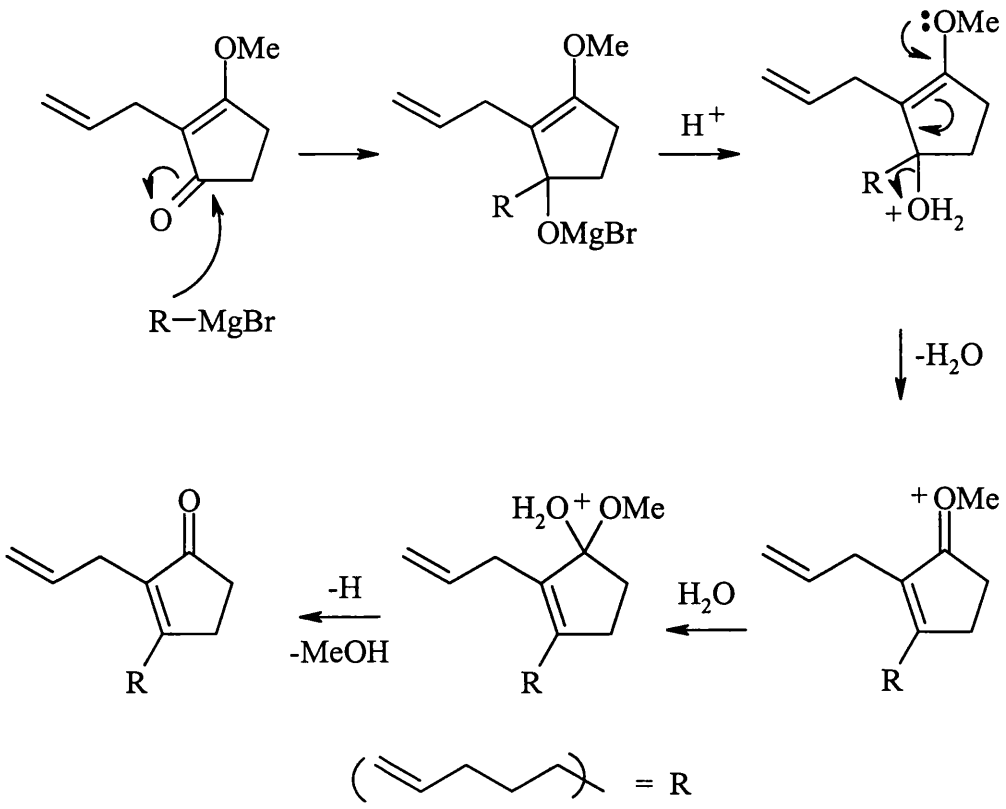
The allylated cyclopentanedione readily formed the methyl enol ether **4.3** in refluxing methanol in the presence of acid and trimethyl orthoformate.[74] The methylene signals for the protons at C-4 and C-5 now appear individually in the ^{1}H NMR spectrum.

The methyl enol ether proved to be moisture-sensitive. A neat sample of the oil stored in a stoppered flask overnight at room temperature, solidified. The solid was shown to be the starting allylated cyclopentanedione by TLC and ^{1}H NMR spectrum.

Solutions in dichloromethane showed more stability and could be stored in stoppered flasks for several days and neat samples stored under nitrogen in the fridge were stable for about a year.

To avoid problems of instability of the methyl enol ether, when reaction was done on a small scale the enol ether was used further without purification after work-up. Product from a large scale reaction was purified by flushing quickly, with diethyl ether, through a silica column basified with triethylamine.

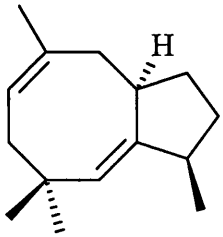
The methyl enol ether was then reacted with the Grignard reagent derived from pentenyl bromide. Initial investigative reactions showed that low yields of the product formed when the Grignard reagent was added to the enol ether or when just over stoichiometric amounts of the enol ether were used or when the reaction was carried out at -78 °C. The protocol used in the reaction was that a solution of 2 equivalents of the enol ether **4.3** in diethyl ether was added to a solution of the pentenylmagnesium bromide at 0 °C, the mixture was warmed to room temperature and stirred overnight before quenching and subjecting it to an acidic work-up. By this method yields of up to 62% of the desired triene intermediate **4.4** were realised. A possible mechanism of the reaction is illustrated overleaf.[71]



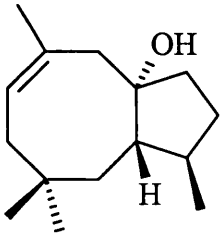
4.3 Synthesis of the B/C sub-unit - Ring-Closing Metathesis to form 8-membered ring B

The next step in the synthesis was the generation of the 8-membered ring B in the B/C sub-unit.

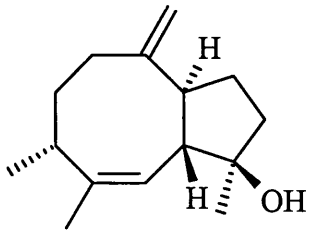
The cyclooctanoid system, not only prevails in the ophiobolins, but several other classes of natural products. Examples of some simple C15 8-5 rings are shown overleaf.[75]



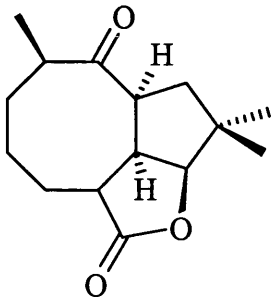
Precapnelladiene



Dactylol



Dumortenol

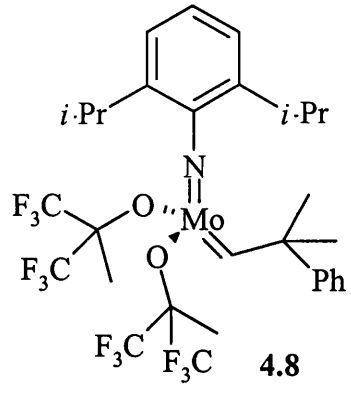


Asteriscanolide

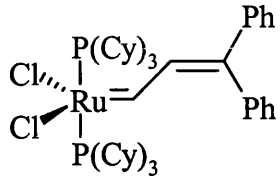
Construction of 8-membered rings by traditional methods of ring formation has proven to be challenging, probably due to the various conformations and energies associated with the cyclooctanoid systems. The synthesis of these 8-membered carbocycles and applications to natural product synthesis has been summarised in two key reviews.[76,77] The strategies used to access this ring system are similar to those seen in the earlier discussion of methods to gain entry into the central 8-membered ring of the ophiobolane sesterterpenes, namely those of cyclisation, ring expansion, polycycle fragmentation and cycloadditions.

Ring-closing metathesis (RCM) is a very powerful technique of ring formation which has come into play in the last few years.[68,78,79] This technique of metal catalysed alkene metathesis, is widely used in industry to access alkenes of various lengths. It has seen a revival in synthetic organic chemistry since Shrock[80] and

Grubbs[81] developed the molybdenum and ruthenium complexes, **4.8** and **4.9** respectively, shown below.

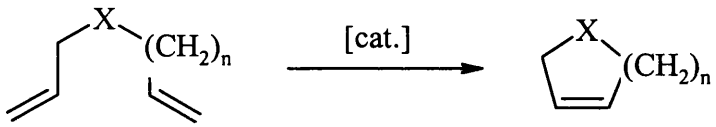


4.8



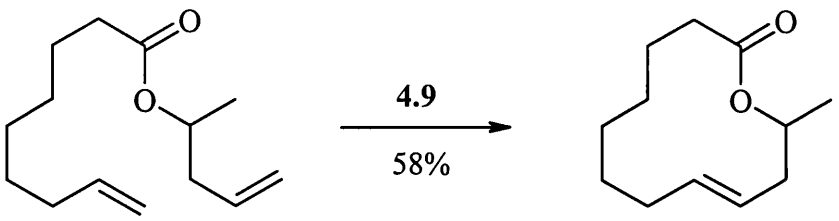
4.9

These complexes have been used to construct five-, six- and seven-membered carbo- and heterocycles with ease from suitable di-alkene precursors.[68,78,79]



X= CH_2, O, NR n=1,2,3

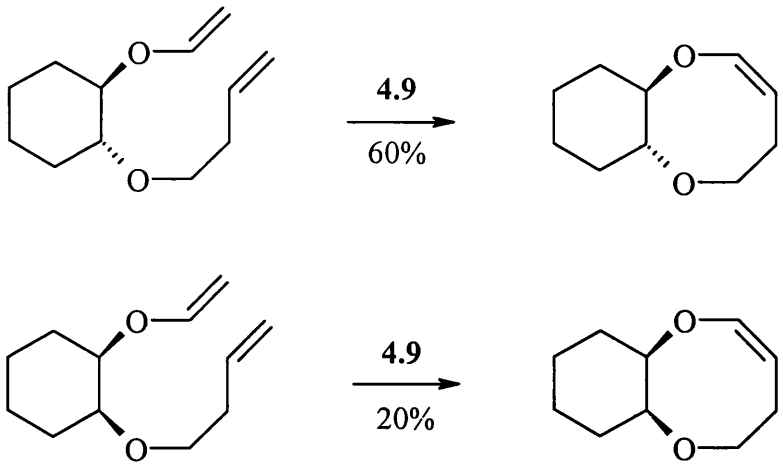
Medium sized rings and higher macrocycles have also been constructed.[82,83] An example of a macrocycle synthesis by Fürstner and Langemann is illustrated below.[82]



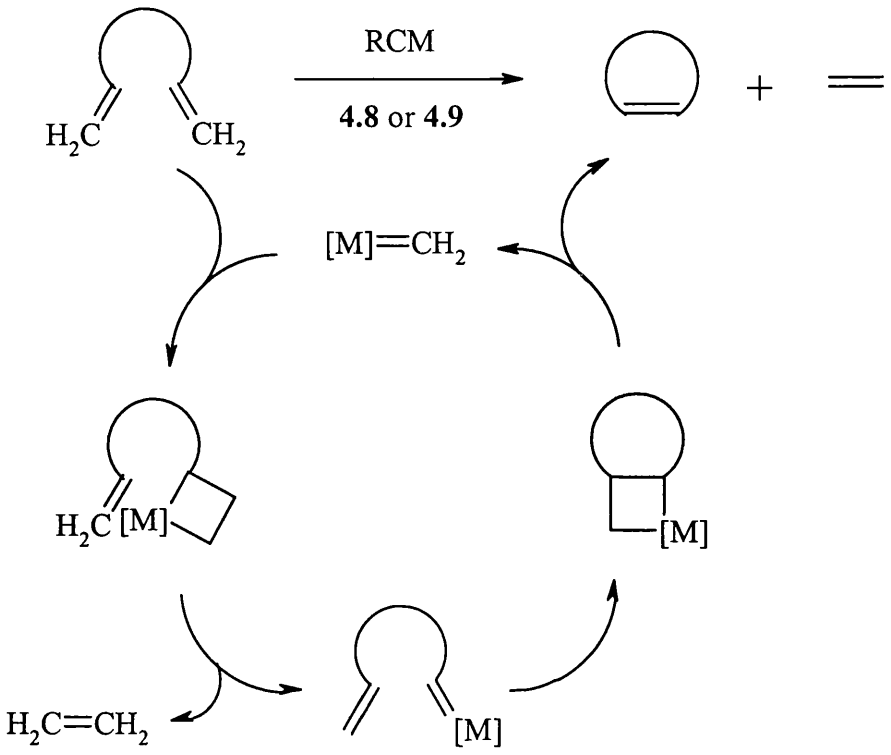
Synthesis of larger rings is usually carried out in diluted solutions to suppress intermolecular metathesis.[82]

A particular challenge has been the synthesis of 8-membered rings, probably due to the energies involved in ring-closure and those in the ring itself. Cyclooctene is a starting material for ring-opening metathesis polymerisation reaction.[68] In spite of the potential drawbacks for the formation of 8-membered rings by RCM, their synthesis has been achieved via this reaction. Fürstner and Langemann synthesised the 8-membered ring in dactylol by this method using the molebdenum catalyst.[84] However, most synthetic studies towards acquiring the cyclooctanoid system have been done using the ruthenium catalyst.[85,86]

Grubbs has demonstrated that a certain amount of constraint in the acyclic diene precursor due to an existing functional group or fused ring favours the formation of an 8-membered ring.[85] This was demonstrated by ring closure of the bis-allyl ethers shown below. The *trans*-fused bicycle was formed in a much higher yield than the *cis*-fused one.



The general mechanism for the ring-closing metathesis reaction is illustrated below.

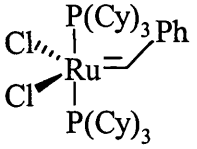


The reaction is believed to proceed via formal [2+2] cycloaddition/reterocycloaddition sequences, with evolution of the volatile ethylene.[87]

In general, it is observed that Shrock's molybdenum catalyst is more reactive than Grubbs' ruthenium one and will successfully cyclise dienes with sterically demanding and electron withdrawing substituents such as *t*-Bu and CO_2Me. This high activity is accompanied by a lower tolerance for common functional groups, and a requirement of very high levels of purity in both solvents and substrates.[88] On the other hand, the ruthenium catalyst shows tolerance to most functional groups, to

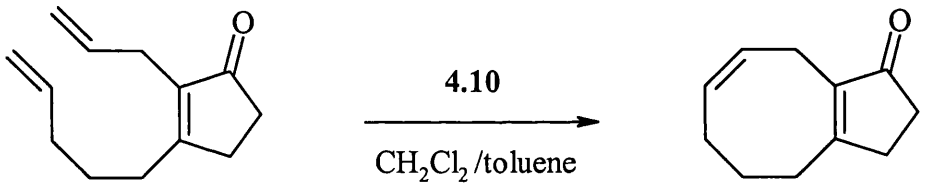
air and water, thus requiring far less rigorous conditions. In practical terms, this makes its use more desirable.

In the present synthesis, it was hoped to use RCM to form ring B of the 8-5 B/C sub-unit. Grubbs' ruthenium catalyst, **4.10**, which is commercially available from Strem chemical company, was used.



4.10

A series of reactions was carried out at various temperatures and concentrations in either toluene or dichloromethane. The general protocol for reaction was that a solution of the catalyst in degassed, distilled solvent, was added via cannula to a solution of the monocyclic triene **4.4** in the same solvent. The mixture was stirred at the required temperature for a period of time. The solvent was removed and the residue was purified by chromatography on silica to isolate a mixture of monocycle and bicycle. The conversion from the monocycle into the bicycle was determined from the ^{1}H NMR spectrum. The signal from the alkenyl proton nearest the carbonyl on the bicyclic **4.5**, appears as a multiplet at 5.43-5.51 ppm and from the four protons on the terminal alkenes of the monocycle appears as a separate multiplet at 4.95-5.07 ppm. Results from these reactions are summarised in Table **4.1**.



4.4 **4.5**

Table 4.1

Solvent	mol% **4.10**	Temp. 0 °C	Conc. M	Time	[a]B:M	[b]Yield %
CH_2Cl_2	6	rt	0.02	24 h	29:71	23
CH_2Cl_2	8	45	0.02	24 h	62:38	38
CH_2Cl_2	8	45	0.01	2½ d	96:4	34
CH_2Cl_2	10	45	0.01	3 d	92:8	48
toluene	8	rt	0.02	24 h	22:78	11
toluene	8	65	0.02	24 h	78:22	43
toluene	8	65	0.01	4 d	83:17	61
toluene	8	65	0.075	4 d	91:9	30
toluene	8	103	0.01	3 d	97:3	49

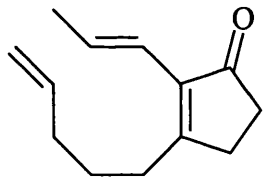
a B:M = monocycle:bicycle ratio

b Yield of bicycle before separation

In general, it was observed that there was a higher rate of conversion from the monocycle into bicycle at elevated temperatures. At 103 °C, the ratio was 97:3 in favour of the bicycle. The optimum concentration of solution was 0.01M. Reactions in dichloromethane proceeded more cleanly and were easier to work-up than those done in toluene. Some of the volatile product was lost if the reaction mixture was left

for a prolonged period under reduced pressure when excess solvent was evaporated. Hence, the optimum reaction conditions for ring closure of the triene monocycle **4.4** using Grubbs ruthenium catalyst, were those using a 0.01M solution of the triene in dichloromethane, with 8-10 mol% of the catalyst and the reaction heated at reflux.

About 10% of a by-product was isolated in most of the reactions studied. The amount isolated increased slightly at higher temperatures. The by-product had a higher R_f value than the mixture spot of the monocycle and bicycle. Its structure could not be deduced conclusively from its ^1H and ^{13}C NMR spectra. Signals corresponding to protons on a terminal alkene and two multiplets at 6.03-6.08 and 6.71-6.81 ppm, amongst others, were observed in the proton spectra. There was an absence of a signal at 2.95 ppm associated with the methylene protons of the allylic moiety in the monocycle. The ^{13}C spectra shows the presence of a methyl, five alkyl CH_2, one alkenyl CH_2 and three alkenyl CH carbons. A suspected structure for the by-product is given below arising probably from isomerisation of the allylic bond in the triene **4.4**.



Since the monocycle and bicycle co-eluted on normal phase silica, the mixture was separated by flash chromatography on silver nitrate-doped silica.[89] A slurry prepared by mixing silica with a solution of silver nitrate in acetonitrile was dried in a hot oven to give the silver nitrate-doped silica. The mixture could be also be separated

on silver nitrate impregnated TLC plates prepared by dipping glass-backed TLC plates in a silver nitrate/acetonitrile solution and drying. It was fortunate that the R_f values of the monocycle and bicycle differed significantly to make their separation relatively easy as elution had to be fairly rapid once the mixture was loaded onto the column. Slow elution lead to isolation of several products, most of which did not co-spot with product and starting material spots on TLC. Recovery of separated compounds was usually good, for instance, 97 mg of a 92:8 bicycle:monocycle ratio, separated to afford 83 mg of the bicycle and 6 mg of the unreacted triene.

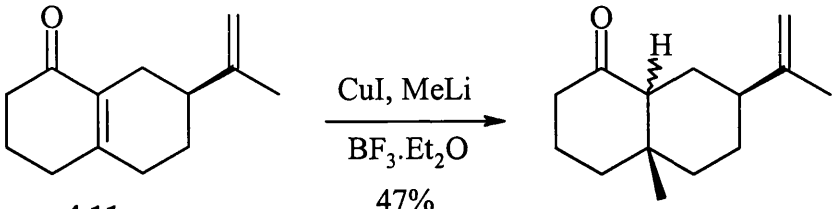
4.4 1,4-Conjugate addition of methyl at C-11 of the ophiobolin

Once the bicyclic enone was in hand, the addition of the methyl at C-11 of the ophiobolin was investigated. Its addition was envisaged to be via an appropriate methyl cuprate reagent. Racemic addition of the methyl cuprate was investigated in the first instance.

1,4-Conjugate addition of organocuprate reagents to α,β-unsaturated enones is now a well established synthetic procedure for the formation of C-C bonds.[65-67] However, a single protocol that can be universally applied to any substrate is not available and as such, various copper sources, solvents, Lewis acid activation and stoichiometries of reagents, have to be explored. This is especially so in the case of highly hindered β,β-substituted enones such as bicyclic compounds, where reagent reactivity is usually low. In such cases, Yamamoto's method of $BF_3.Et_2O$-organocopper has proven to be successful.[90,95] Trimethylchlorosilane has been used by Nakumura *et al.* to mediate 1,4-conjugate additions to hindered enones, although not bicyclic

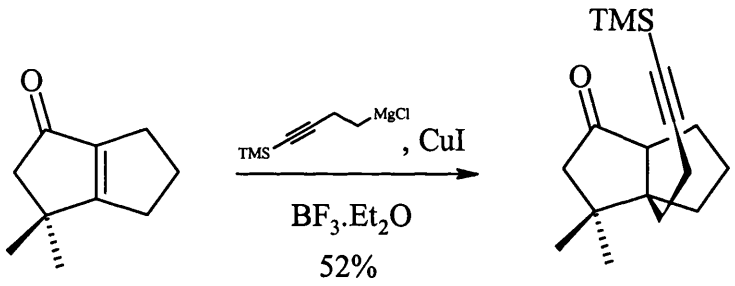
enones.[91] Some examples demonstrating 1,4-additions on bicyclic compounds are shown below.

Bhupathy and co-workers achieved 1,4-addition of methyl to **4.11** via an organocopper-Lewis acid reagent in a moderate yield.[93]



4.11

In Paquette's synthesis of the natural product modhephene, synthesis of the intermediate **4.12** was achieved once again, by use of an organocopper-Lewis acid reagent.[94]

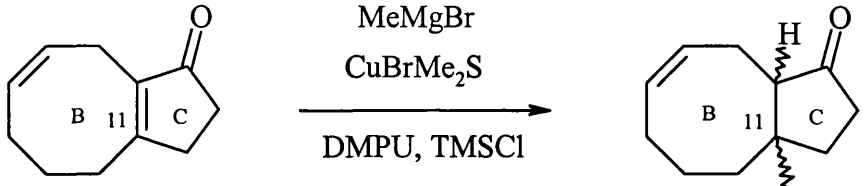


4.12

There seems to be no precedence in the literature for a similar reaction on larger bicyclic systems such as the present 8-5 enone.

In the present synthesis, methyl addition at the B/C ring junction was accomplished by using either Nakumura and co-workers[91] method of chlorosilane mediated addition, or by Yamamoto's[95] method of $BF_3.Et_2O$-organocopper system.

The chlorosilane reaction gave a yield that compares well with other 1,4-conjugate addition reactions on bicyclic enones.[92]



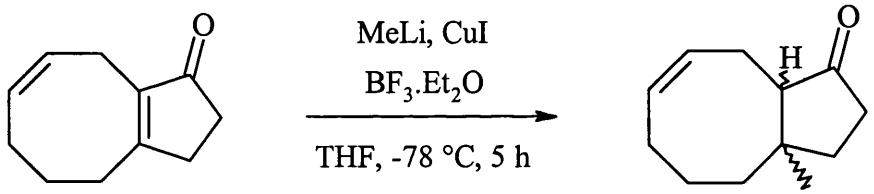
4.5 **4.6**

The reaction protocol was that a solution of the enone **4.5** and trimethylchlorosilane in THF was added to a suspension of methyl cuprate and DMPU in THF at -78 °C. The suspension was stirred for 5 h and subjected to the usual work-up and purification. Some diastereoselectivity was realised in this reaction. The ^1H NMR spectrum of **4.6** shows two peaks for the added methyl at 0.91 and 1.14 ppm in a 28:72 ratio. The expected four isomers could be separated on a chiral GC column. The de was 30% by GC. A shift in the carbonyl frequency from 1697 cm^{-1} due to the enone **4.5**, to 1739 cm^{-1} in the bicyclic ketone **4.6**, was observed in the IR spectrum.

The yields from this reaction were not consistent. The reaction protocol used, involved the addition of DMPU to the methyl cuprate suspension. It was found that sometimes on addition of DMPU, the fine reaction suspension became gelatinous and less mobile. The yield seemed to depend upon the mobility of the reaction

mixture and might simply mean that a gelatinous reaction mixture did not 'expose' enough methyl cuprate for reaction. The original protocol by Nakamura called for the use of HMPA where reactions were seen to proceed at much higher rates in the presence of trimethylchlorosilane and HMPA. The latter was not used due the harmful properties associated with it and DMPU seemed to be a suitable substitute. A change of solvent from THF to diethyl ether did not yield any product.

Yamamoto's procedure using $BF_3.Et_2O$ was generally better yielding and more consistent.



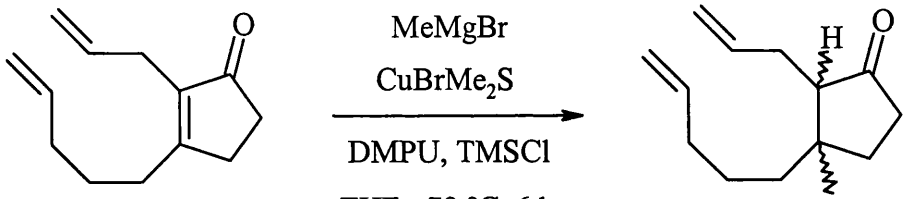
4.5 **4.6**

The reaction procedure was a straightforward sequential addition of MeLi, $BF_3.Et_2O$, and bicyclic enone to a slurry of CuI in diethyl ether at -78 °C. The mixture was stirred at -78 °C for 5 h, worked-up and purified. Yields up to 58% were realised in some cases. The de of the methyl addition product was similar to that seen earlier in the preceding reaction. Unreacted enone was recovered in most cases for both reaction types.

Three equivalents of all reagents were used in the $BF_3.Et_2O$ procedure, whereas only 1.4 equivalents of the methyl Grignard were used in the trimethylchlorosilane

procedure. However, the amount of excess reagent was not deemed to be important as the methyl moiety does not come from a precious source.

1,4-Conjugate addition was also carried out on the monocyclic enone **4.4**. This was done as a model study prior to the reactions on the bicyclic enone **4.5** as the 8-5 ring was very precious.



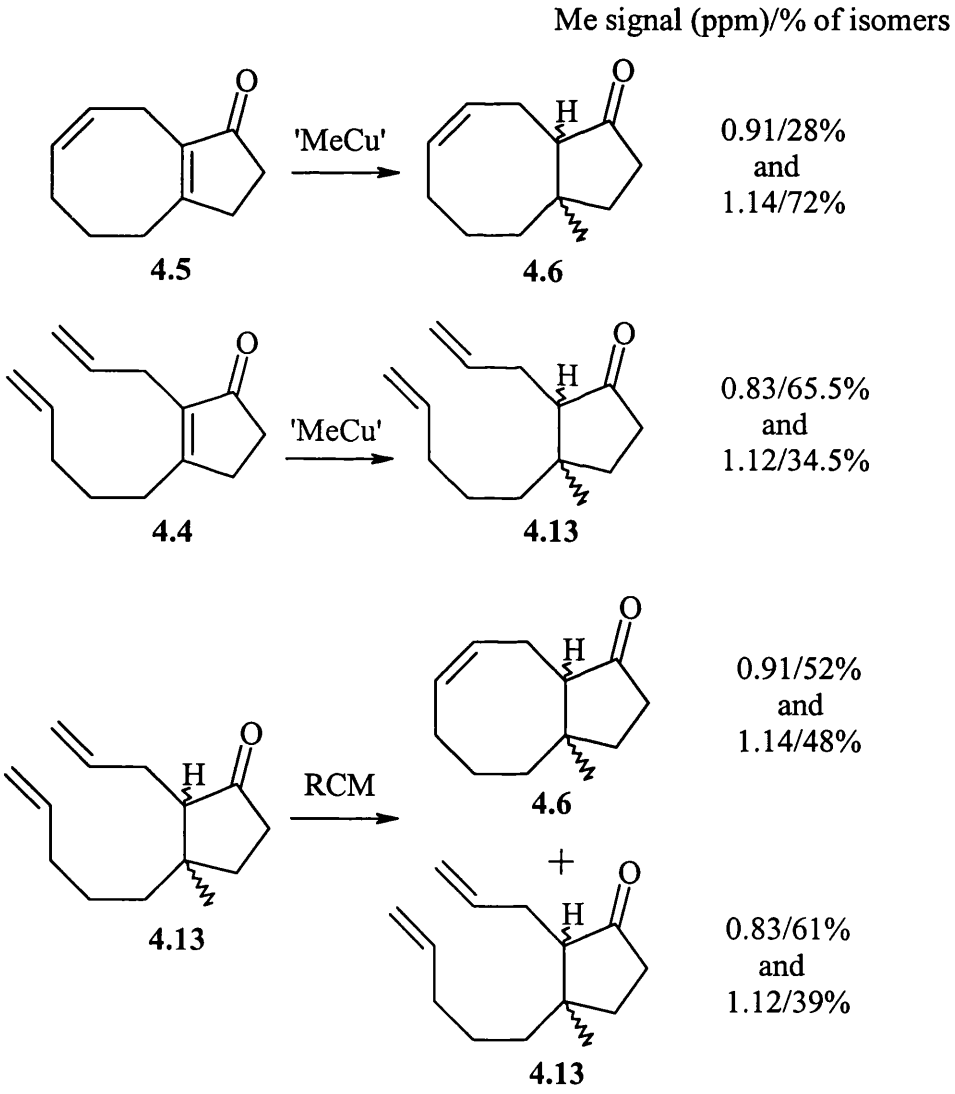
4.4 **4.13**

The ^{1}H NMR spectrum again showed two signals for the newly introduced methyl at 0.83 and 1.12 ppm. The de was lower than that from methyl addition to the bicyclic enone, but more significantly, the diastereoselectivity was opposite. The signal due to the major set of isomers (65.5%) was at 0.83 ppm and that for the minor set (34.5%) appeared at 1.12 ppm.

The addition product **4.6** could also be procured by a ring-closing metathesis reaction on the moncyclic diene **4.13**. An unoptimised RCM reaction on monocyclic diene **4.13**, where a 0.01 M solution of the diene in dichloromethane and 10 mol% of ruthenium catalyst **4.10** were heated at reflux for 24 h, gave a product where the bicycle:monocycle ratio was 1:1. Under identical conditions, other than the amount of catalyst used - 6 mol%, RCM reaction on the monocyclic triene **4.4** gave a bicycle:monocycle ratio of 2.4:1.

Signals due to the methyl in the mixture of residual monocyclic diene **4.13** and the ring-closed bicyclic **4.6**, from the ring-closing metathesis reaction on the diene **4.13**, were observed in the ^{1}H NMR spectrum.

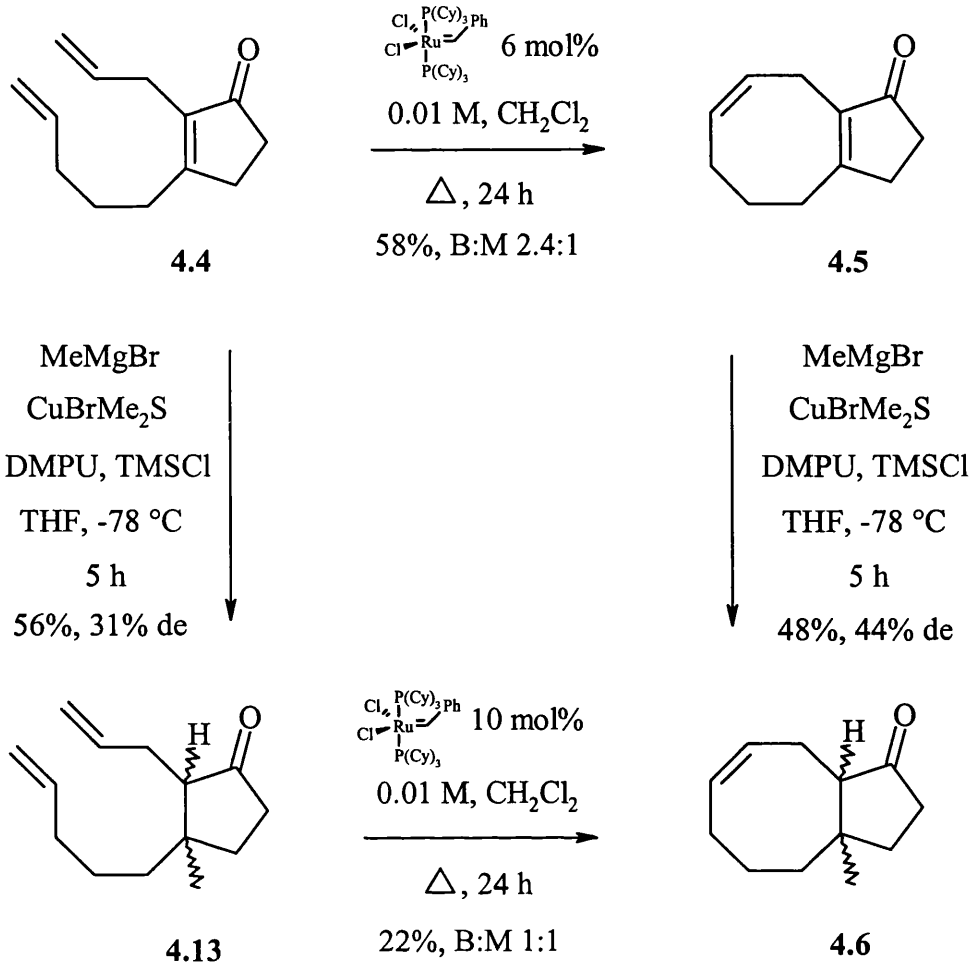
Illustrated below is a comparison of the methyl signals and isomeric ratios of compounds generated by 1,4-addition on the individual monocyclic and bicyclic enones and by RCM on the diene **4.13**.



Although the ratios of the two sets of isomers have been derived from the ^{1}H NMR spectrum and may be subject to experimental error, some inferences can be made from these results. It would seem that during RCM reaction on the methylated monocyclic diene **4.13**, one set of isomers ring-closes in slight preference to the other. The observed percentage of the residual monocycle from RCM shows that the major isomer has decreased while the minor isomer has increased, relative to the ratio of isomers seen in the starting monocycle. Bearing in mind the observations by Grubbs and co-workers, where the *trans* isomers ring-closed in preference to *cis* isomers, it could be tentatively concluded that in this case, the major set of isomers bears a *trans* configuration. It could also be concluded that the major set of isomers in the bicyclic methyl addition product **4.6** bear a *cis* configuration. The B/C ring junction requires a *trans* configuration and it could be argued that perhaps methylation followed by RCM would be the route forward. However, the yield, favourable ratio of the bicycle and hence, isolation of the product from RCM reaction on the monocyclic triene was more desirable than from RCM of the monocyclic diene. Hence the preferred route to take the synthesis forward was via RCM of the monocyclic triene, followed by 1,4-addition of methyl on the resulting bicyclic enone.

NOE studies to determine the configurations of the products resulting from the methyl addition gave only messy spectra. It was anticipated that enantioselective addition would allow an easier analysis of the configuration.

A summary scheme leading to the addition product **4.6**, via the two routes discussed so far, is given overleaf.



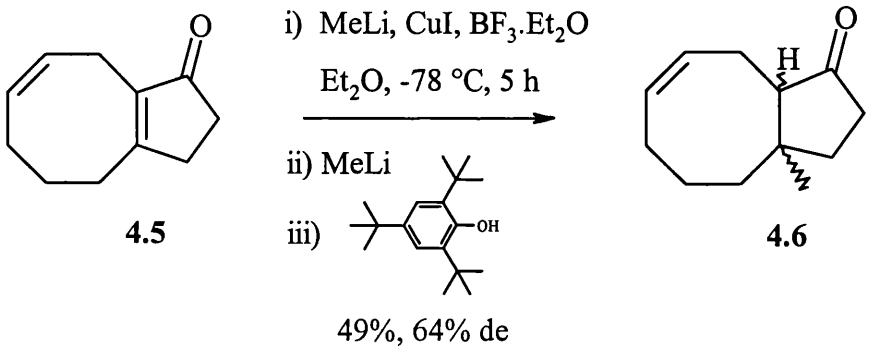
B:M = Bicycle:Monocycle ratio

4.4.1 Diastereoselectivity at B/C ring junction

Once the methyl group was added successfully to the bicyclic enone, a brief attempt was made to improve the diastereoselectivity at the B/C ring junction. At this stage, the orientation of the methyl was not that important as this would be determined by asymmetric 1,4-conjugate addition at a later stage in the synthesis.

The 1,4-conjugate addition reaction discussed in the preceding section was quenched with a solution of saturated ammonium chloride after the reaction mixture had stirred at -78 °C for 5 hours. The de observed was 44%. It was hoped that quenching with a hindered proton source, such as 2,4,6-tri *t*-butylphenol would improve the de.

A reaction protocol similar to that of methyl addition using $BF_3.Et_2O$ as discussed earlier, was followed. MeLi, $BF_3.Et_2O$, and bicyclic enone were added sequentially to a slurry of CuI in diethyl ether at -78 °C and the mixture stirred at this temperature for 5 h. It was then treated with 1.1 equivalents of MeLi, stirred for a further 30 min after which a cold (-40 °C) solution of 2,4,6-tri *t*-butylphenol in diethyl ether was added via cannula. The resulting mixture was stirred at -78 °C for 2½ h, slowly warmed to room temperature and subjected to the usual work-up and purification. Again two signals due to the methyl were observed at 0.91 and 1.14 ppm in the ^1H NMR spectrum indicating the minor and major sets of isomers respectively. The observed de was 64% by ^1H NMR and 58% by GC.



4.5 **4.6**

49%, 64% de

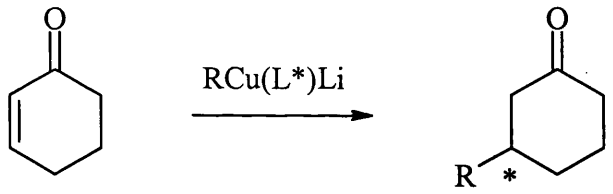
It was found that if the reaction mixture was treated directly with phenol, without the prior addition of MeLi, no improvement in de was observed. This perhaps means that

the phenol is not acidic enough to quench a boron enolate on its own, thus requiring transmetallation of boron with lithium. The reaction was not optimised.

4.4.2 Stereoselectivity at C-11

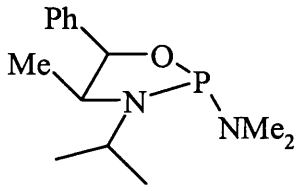
The quaternary methyl at the B/C ring junction of the 8-5 sub-unit was expected to be added stereoselectively by an asymmetric 1,4-conjugate addition mediated by chiral ligand.

There has been prolific activity in recent times to develop efficient systems for asymmetric conjugate addition reactions. This activity has been the subject of several well documented reviews.[96-100] Chirally modified organocopper compounds, RCu(L*)R, are generally used.

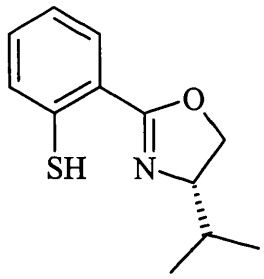


The enantiomerically pure, non-transferable ligand L*, controls the stereochemical aspects of transferring group R to the enone substrate. The ligand and copper source can be used stoichiometrically or catalytically.

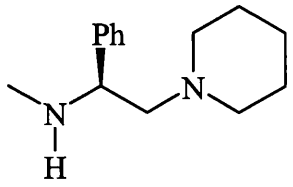
The ligands, **4.14**,[101] **4.15**[102] and **4.16**,[103] are a few of many that have shown some enantioselectivity in 1,4-conjugate additions.



4.14



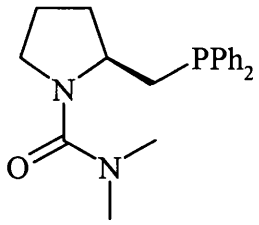
4.15



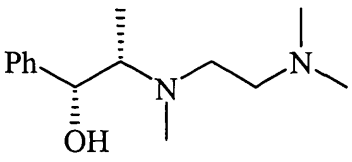
4.16

In spite of a great deal of synthetic effort being expended on this reaction, an asymmetric system, stoichiometric or catalytic, that can be applied to any acyclic or cyclic system, has yet to be found.

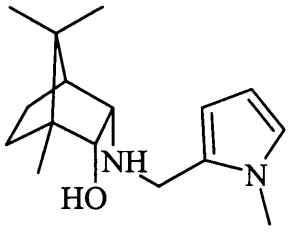
An easily accessible, highly efficient ligand was required in the present synthesis and a number of ligands, shown below were thought to be suitable.



4.17



4.18

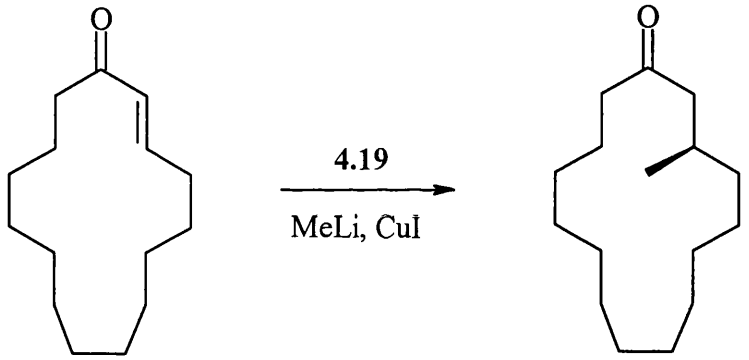


4.19

Tomioka has shown that a high enantiomeric excess, up to 98%, can be achieved with the chiral amidophosphine **4.17** mediated addition to cyclohexenone and cycloheptenone, using either a magnesium or lithium cuprate.[104]

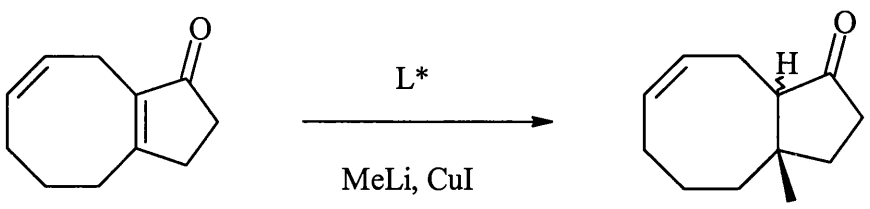
The ephedrine based amino alcohol **4.18** has been reported by Corey to show good enantioselectivity in cycloalkenones, even in cyclopentenone which traditionally shows low reactivity.[105]

A very high ee was realised by Tanaka and co-workers using the camphor based amino alcohol **4.19**. The ligand was used to form a chiral methyl alkoxy cuprate and then reacted with the fairly large macrocycle, (E)-cyclopentadec-2-enone, to give enantiomerically enriched muscone.[106] This was promising as no other precedence was found in the literature for an asymmetric addition on a sterically hindered bicyclic system such as the present B/C 8-5 sub-unit.



Muscone

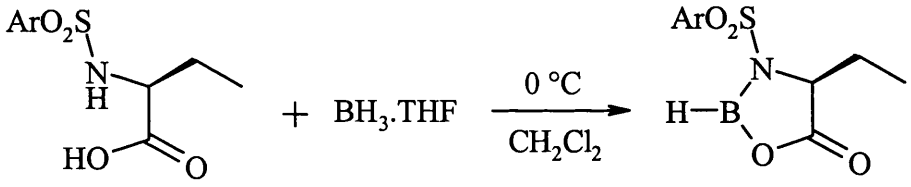
The ligands were prepared and used as directed by the authors to effect asymmetric addition.



4.5 **4.6**

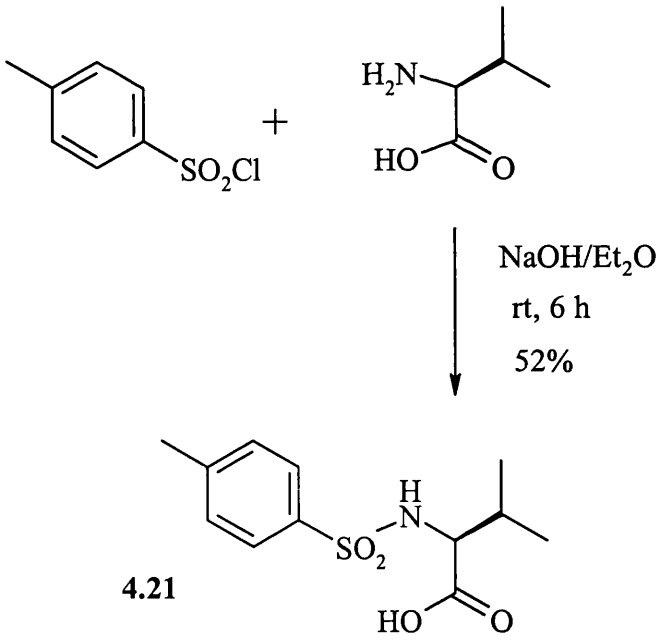
Of the three ligands, only the camphor amino alcohol, **4.19**, showed any results. Reaction with this ligand showed a trace amount of product, visible on a TLC plate, which after much persuasion showed some ee on chiral GC. In the case of the other two ligands, unfortunately, not even racemic product was isolated. This could either be due to the steric hindrance encountered in the bicycle or could once again be a demonstration of the substrate specific nature of many organocopper additions.

As discussed earlier, hindered enones sometimes require Lewis acid activation. Corey reported that O-silylation of the chiral ligand occurred at -78 °C when enantioselective conjugate addition using the ephedrine-based ligand **4.18** was carried out in the presence of trimethylchlorosilane. So perhaps the way forward in the present synthesis may be via a chiral Lewis acid and not an added achiral Lewis acid. Yamamoto has reported the synthesis of simple, easily accessible chiral boron catalysts, such as **4.20**, for Diels-Alder reactions.[107] These were prepared from sulfonamides of available amino acids.



4.20

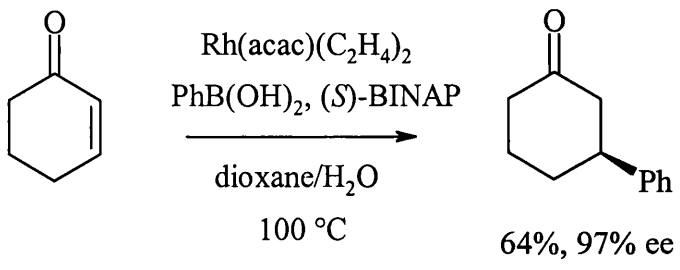
Accordingly, a sulfonamide was prepared by exposing, in this case D-valine, in sodium hydroxide solution, to *p*-toluenesulfonyl chloride in diethyl ether.



4.21

The white crystals of the sulfonamide were dissolved in THF and treated with borane.THF complex. The resulting solution was then used in a protocol similar to that used for racemic methyl addition. MeLi, borane solution and bicyclic enone **4.5** were added in sequence to a slurry of CuI in diethyl ether. No product formation, racemic or asymmetric, was observed.

As a copper based asymmetric addition gave very little joy, a different metal based addition was investigated. Hayashi and co-workers recently reported a rhodium catalysed addition where the chiral ligand used is BINAP and the added group is from a boronic acid.[108]



A similar reaction using the bicylic enone and methylboronic acid did not give the expected product.

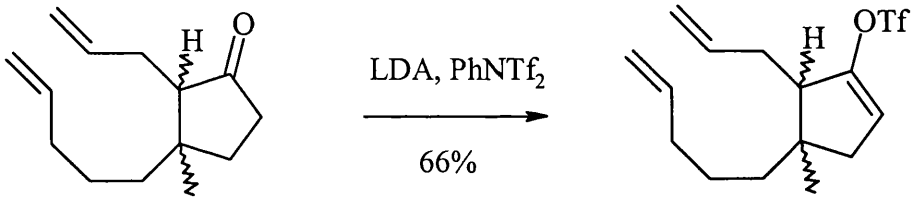
Although the desired enantiomerically enriched addition product was not realised, one of the ligands, the camphor amino alcohol **4.19**, does show promise and may form a basis for further investigation into this reaction. Also, the range of ligands used represents just a snap-shot of what is available.[96] Zinc and nickel mediated reactions could also be investigated using enantiomerically pure ligands.[96,109]

4.5 Studies to furnish ring C with the exocyclic heptenyl chain at C-14 of the ophiobolin

4.5.1 Model reactions to form an exocyclic C-C bond

The next step in the synthesis of the 8-5 sub-unit was to attach the heptenyl side-chain to the bicyclic core. Considering a racemic synthesis in the first instance, this could be achieved by a metal-mediated reaction between an organometallic precursor of the heptenyl side-chain and a vinyl triflate derived from bicyclic ketone.

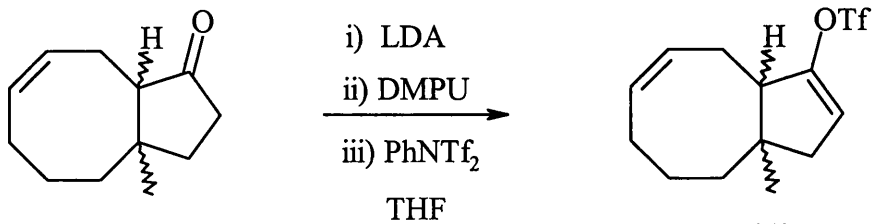
The studies began by trapping the kinetic enolate derived from ring C, as a triflate.[64] Initially the reaction was done on the more readily available monocyclic ketone **4.13**, to test the reaction, then on the bicyclic ketone **4.6**.



4.13 **4.22**

The kinetic enolate was formed by slow addition of a cold (-78 °C) THF solution of the ketone to LDA in the same solvent also at -78 °C. After 1½ h, the enolate was treated with DMPU, followed by a solution of N-phenyltrifluoromethanesulfonimide in THF, at -20 °C. The mixture was warmed to room temperature, stirred overnight and the vinyl triflate isolated by chromatography on basified silica. Yields up to 66% and 60% were realised for reactions on the monocycle and bicycle respectively. Invariably, some starting material, up to 30%, was recovered.

The initial reaction on the bicyclic ketone was done using 1.25 equivalents each, of base and N-phenyltrifluoromethanesulfonimide. 40% and 31% of product and recovered starting material were isolated. When the excess of base was increased to 2.5 equivalents and the triflating agent increased to 5 equivalents, the yield increased to 60%, while the recovered ketone was 33%.

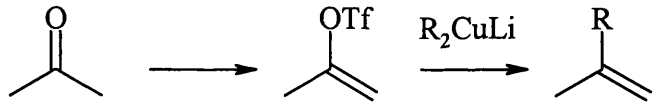


4.6 **4.7**

The ^{1}H NMR spectrum of **4.7** shows the proton signal associated with the vinylic triflate as a triplet at 5.51 ppm. The other two alkenyl protons now appear as a multiplet at 5.55-5.58 ppm, whereas, in the bicyclic ketone they appear as two separate multiplets. The carbon signals due to the vinyl triflate appear at 114.4 and 152.9 ppm in the ^{13}C NMR spectrum, corresponding to the vinylic CH and quaternary carbon respectively.

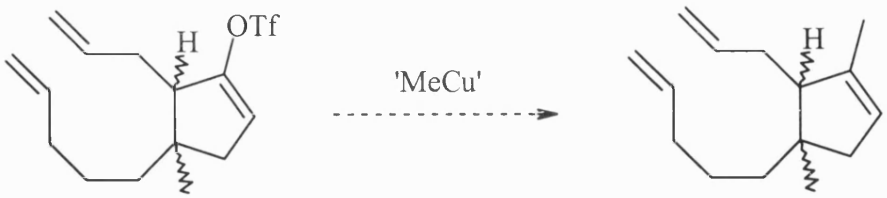
Once the vinyl triflate had been formed, some reactions to form a C-C bond by making use of this moiety were investigated. Vinyl triflates have been used to effect many synthetic transformations in organic chemistry, such as carbon-carbon bond and carbon-metal bond formation. C-C bonds can be formed by direct coupling of the vinyl triflate with organocopper reagents or by cross-coupling reactions.[64]

Several years ago, McMurry reported that vinyl triflates underwent regio- and stero-sepecific coupling in high yield with Gilman-type organocuprates.[110]



Investigations into the exocyclic C-C bond formation began with this straightforward method of forming substituted alkenes. Model studies were first conducted using the monocyclic triflate **4.22** and a methyl organometallic.

A variety of copper reagents was used to form methyl cuprate and reacted with triflate **4.22**. Reactions were carried out between -78 °C and -20 °C, and monitored by TLC. Some reaction conditions and results are shown in **Table 4.2**.



4.22 **4.23**

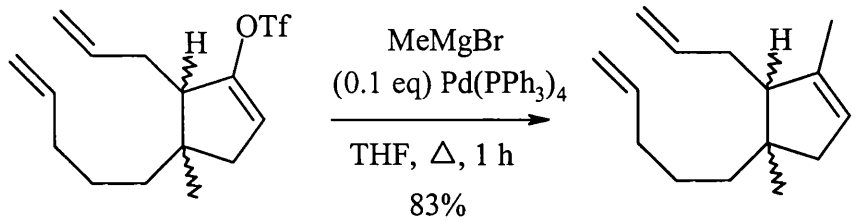
Table 4.2

Reaction condition	result
4.22, MeLi, CuI, THF, -78 °C to -20 °C	No product, messy reaction mixture
4.22, MeMgBr, CuI, LiCl, THF, -20 °C	No product, **4.22** recovered
4.22, MeMgBr, CuBrMeS, THF, -20 °C	No product, **4.22** recovered
4.22, MeLi, Li 2-ThCuCN, Et_2O, -78 °C	Some product, mainly **4.22**
4.22, MeMgBr, Li 2-ThCuCN, Et_2O, -78 °C	Some product, mainly **4.22**

As illustrated by the table, direct coupling by use of organocopper reagents was not very productive. The reactions were very messy and only those with the mixed cuprate, methyl lithium 2-thienylcyanocuprate, showed formation of any product.[111]

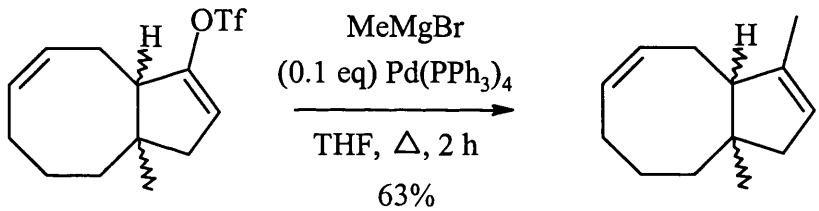
Some cross-coupling reactions were looked at next. Reaction using $Ni(acac)_2$ and MeMgBr gave some product, but a very messy reaction mixture. However, a palladium catalysed reaction proved a lot more promising. An 83% yield of product

was realised when the monocyclic triflate was reacted with methylmagnesium bromide in the presence of $Pd(PPh_3)_4$ for 1 hour.



4.22 **4.23**

A similar reaction with the bicylic triflate **4.7**, gave the methyl coupled product **4.24**. Palladium catalyst and methylmagnesium bromide were added in sequence to a solution of the bicyclic triflate in THF at room temperature. The mixture was heated at reflux for 2 hours, solvent evaporated and the product isolated in 63% yield. About 7% of the starting triflate was also recovered.

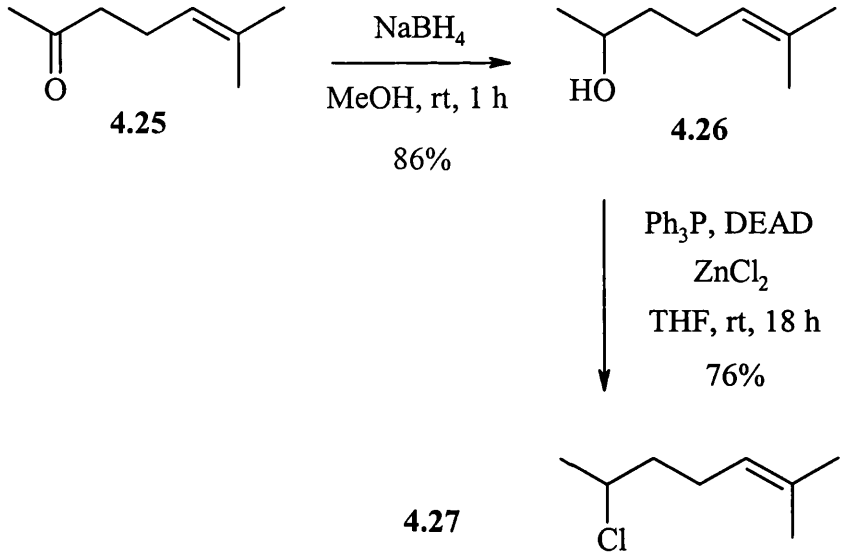


4.7 **4.24**

Two pairs methyl peaks were observed in the ^1H NMR spectrum of the coupled product at 0.96, 1.03 and 1.62, 1.67 ppm, corresponding to the ring junction and vinylic methyl groups respectively. The vinylic proton on the 5-membered ring also appeared as a split signal at 5.15 (major) and 5.22 (minor) ppm. All four isomers could be separated on chiral GC. The de was observed to be 57% by ^1H NMR spectrum and 52% by GC.

4.5.2 Investigative studies towards attaching heptenyl precursor to ring B

Once it was established that the exocyclic C-C bond could be formed, coupling of the heptenyl chain itself was investigated. It was hoped to achieve this by coupling an appropriate organometallic precursor of the heptenyl chain with the bicyclic vinyl triflate **4.7**. A heptenyl organometallic could be derived from 6-chloro-2-methylhept-2-ene, **4.27**.

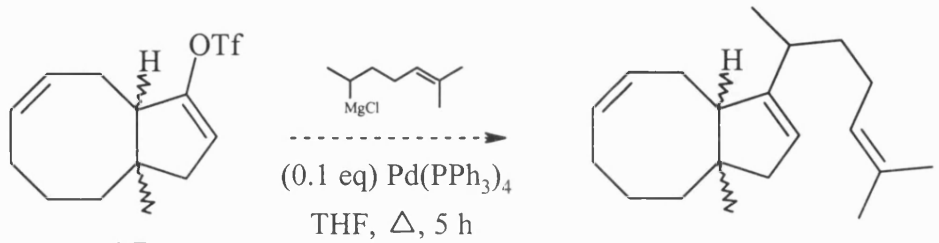


4.25 **4.26** **4.27**

Both heptenone **4.25** and heptenol **4.26** are commercially available, except that the former is much cheaper. Reduction of 6-methyl-5-hepten-2-one with sodium borohydride gave the fragrant heptenol, **4.26**. Clean conversion of the heptenol into a heptenyl chloride using the method of Ho and Davies[112] employing Mitsunobu reagents, diethyl azodicarboxylate and triphenylphosphine, in conjunction with zinc chloride, was achieved. This method was preferred due its non-cumbersome nature.

The chloride was found to be rather volatile and was lost easily when its solution in pentane was evaporated under reduced pressure.

A coupling reaction between a Grignard reagent derived from the heptenyl chloride and the bicyclic triflate **4.7**, was attempted using the same protocol as for the methyl coupling.

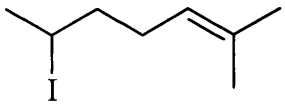


4.7 **4.28**

A small amount of product was isolated but spectroscopic data could not determine its structure. Features corresponding to either of the two halves of the expected compound **4.28** were conspicuously absent in the ^{1}H NMR spectrum. A mass ion or fragments of the desired compound **4.28** were not detected in the mass spectrum of the product.

The reaction was repeated using another palladium catalyst, $PdCl_2dppf$.[113] Again, there was no product formation. It was thought that either, the reaction was sluggish as one of the coupling partners was a secondary Grignard or the Grignard did not form in the first place. So, a THF solution of heptenylmagnesium chloride was prepared and quenched with benzaldehyde. TLC did not show formation of a UV active product, only a rather messy mixture. Perhaps a more reactive halide was

required. Iodoheptene **4.29** was prepared using a similar protocol as that used for preparation of chloroheptene.

4.29 

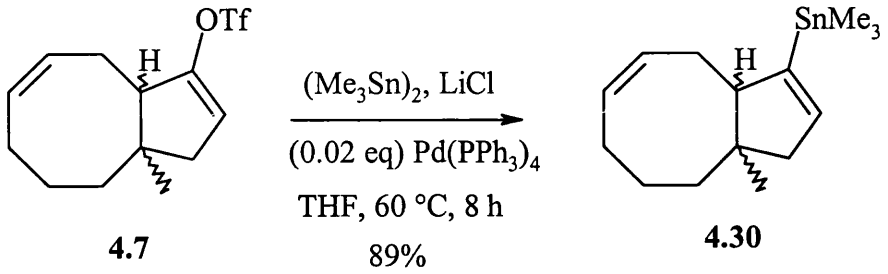
Unfortunately, no joy was derived from a cross-coupling reaction using this precursor either.

The ultimate goal in this particular reaction was to attach the side chain stereoselectively. This could be achieved by one of two methods, a Grignard cross-coupling reaction in the presence of a chiral ligand[114] or by displacement of a leaving group on an enantiomerically pure heptenyl precursor by a vinylic anion on the bicycle in an S_N2 type reaction.

Stereoselective Grignard cross-coupling reactions of secondary alkyl groups not bearing an aryl group at the chiral centre are known not to proceed with high enantioselectivity.[114] As the racemic synthesis was not giving any desirable result, it was decided not to concentrate on this particular method.

Making use of the intermediate in hand, the bicyclic triflate **4.7**, a vinylic anion could be generated by converting the vinyl triflate into a vinylstannane followed by transmetallation.

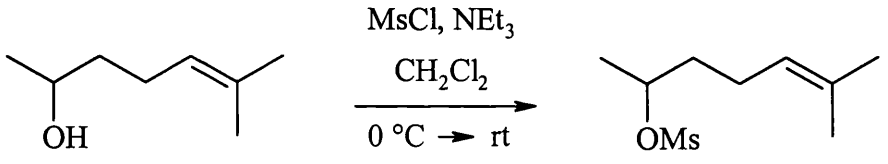
Treatment of the vinyl triflate with hexamethylditin in the presence of $Pd(PPh_3)_4$ and lithium chloride provided the vinylstannane **4.30**, in good yield.[115] A small amount of starting material was usually recovered.



4.7 **4.30**

A signal in the ^1H NMR spectrum due to trimethylstannane was observed at 0.13 ppm with appropriate satellites due to the presence of the tin isotope. The isotope effect was also seen in the appearance of the signal from the proton associated with the vinyl stannane.

Next, a displacement reaction was attempted.[115] The heptenyl source was the mesylate **4.31**, prepared by routine chemistry.



4.26 **4.31**

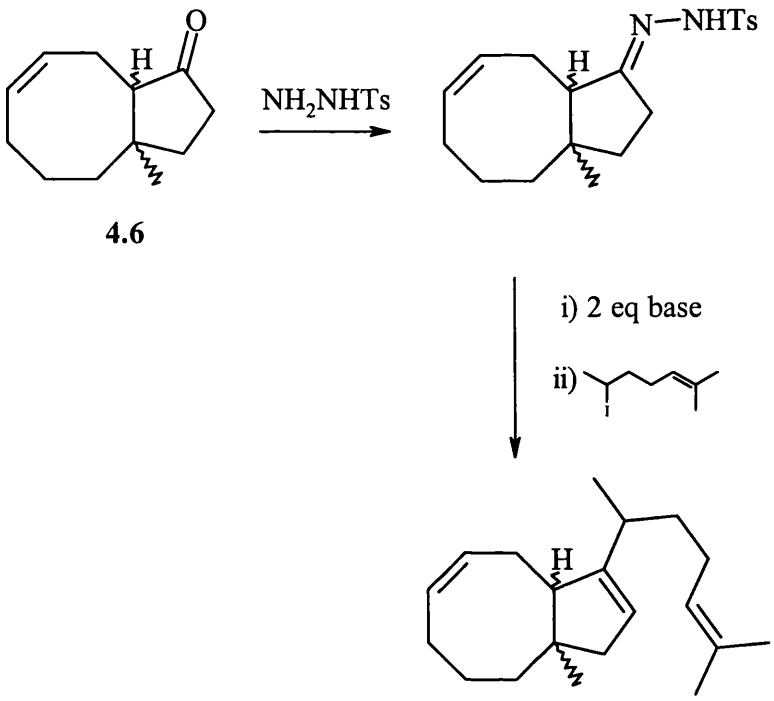
The vinyl stannane was lithiated by reaction with methyllithium and subsequently treated with heptenyl mesylate **4.31**. The reaction was carried out in THF, initially at -78 °C and then warmed to room temperature. Its progress was followed by reverse-

phase TLC using MeCN:water 7:3 as eluent. Upon lithiation, after several hours, a small amount of compound that had a lower R_f than the vinylstannane appeared. As time progressed, the relative amount of the new compound and vinyl stannane did not change. A change was not observed upon addition of the mesylate. The reaction was worked-up and chromatographed. ^{1}H NMR spectrum of the product revealed the absence of signals corresponding to the heptenyl moiety. Although methylstannane signals were observed, there were several other unidentifiable signals leading to inconclusive results.

It was thought that perhaps converting the vinyl anion into a softer cuprate anion would encourage an S_N2 displacement. Accordingly, a one-pot reaction was carried out in THF at -78 °C, where the vinyl triflate was treated with *n*-BuLi, stirred for two hours, then subjected to a sequential addition of cyano copper and heptenyl mesylate. Only some starting stannane was recovered.

Perhaps mesylate was not a good source for a displacement reaction. A similar reaction to the one above was carried out using heptenyl iodide. Again, just starting material was recovered. A change in the source of cuprate was looked at next. A reaction where vinyl cuprate was treated sequentially with MeLi, lithium 2-thienylcyanocuprate and heptenyl iodide gave only some recovered starting material.

Time factors did not allow further persuit of this reaction. The reaction could perhaps be investigated further by generating an anion via a Shapiro reaction on the bicyclic ketone **4.6** and then subsequently reacting it with a heptenyl precursor. This is shown in the scheme overleaf.



4.6

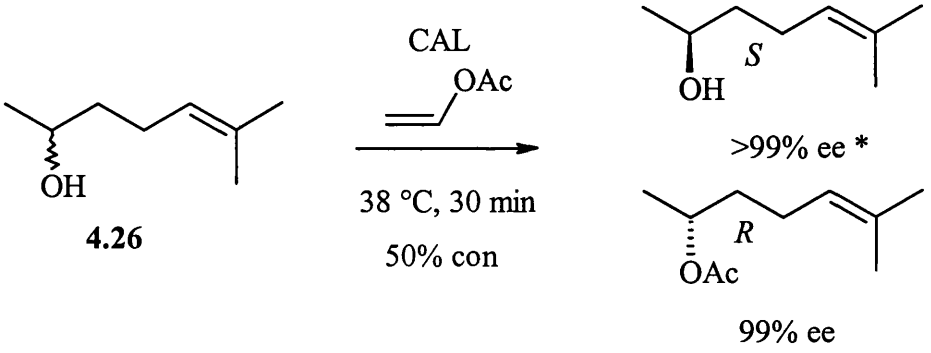
4.5.3 Synthesis of enantiomerically enriched heptenyl precursor

6-Methyl-5-hepten-2-ol or sulcatol as it commonly known, is a pheromone of a species of beetle. The sense of chirality of sulcatol is important for biological activity. Enantiomerically pure alcohols can be obtained by making use of enzymes either to enantioselectively reduce the corresponding ketone or to resolve a racemic mixture of alcohols.

Veschambre and co-workers have obtained good enantiomeric purity of the two enantiomers of 6-methyl-5-hepten-2-ol.[116] This was achieved by either enzymatic reduction of 6-methyl-5-hepten-2-one or enzymatic resolution of the racemic alcohols using lengthy, cumbersome protocols and relatively long reaction times. They resolved the racemic alcohols in 96 h by using porcine pancreatic lipase (PPL)

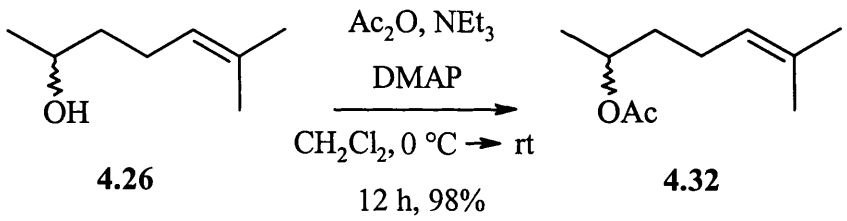
and trichloroethyl butyrate. The (*S*)-alcohol and the butyrate ester of the (*R*)-alcohol was obtained in enantiomeric excesses of >99% and 80% respectively.

Fortunately, in the present synthesis, the same resolution was easily obtained with the lipase from *Candida antartica* (CAL), in the presence of vinyl acetate, in high enantioselectivity in less than an hour.



* The other isomer was not observed by chiral GC

The ee of the heptenol **4.26** and the acetate **4.32** was determined by chiral GC and the % conversion by the ratio of signals from the methine protons, ($CH_3CH(OR)CH_2$), of the alcohol and acetate as observed in the ^1H NMR spectrum. The ee of the acetate was found to be 99%, whilst the other enantiomer of the remaining alcohol could not be seen by GC. The ^1H NMR spectrum of the mixture of alcohol and acetate gives corresponding methine ($CH_3CH(OR)CH_2$) signals at 3.81 and 4.88 ppm respectively, in a ratio of 1:1 indicating a 50% conversion. The acetate **4.32** for GC analysis was prepared routine manipulation of the alcohol **4.26**.



4.26 **4.32**

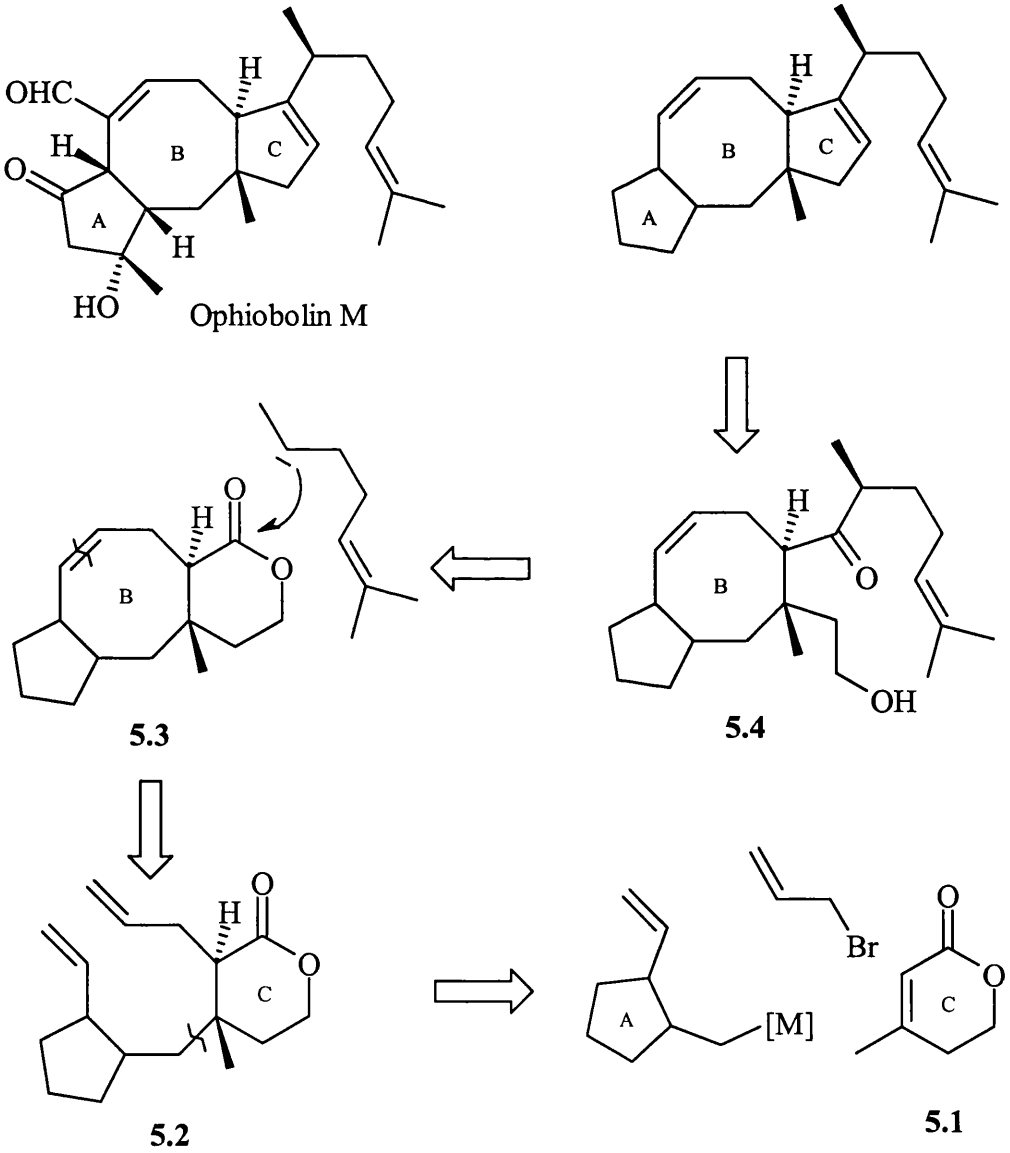
Flash column chromatography can separate the mixture of alcohol and acetate. The R_f values of the acohol and acetate are 0.1 and 0.6 respectively on a silica TLC plate with petroleum ether:diethyl ether, 9:1, as eluent. This separation was not done in the present study, as its purpose was to demonstrate the accessibility of an enantiomerically pure heptenyl precursor. Also, as the displacement reaction was not productive, further manipulation of the mixture was put on hold.

Although this resolution gives a maximum of 50% of an isomer and accessing its enantiomer would require further routine manipulation of the ester, alcohols with very high enantioselectivity can be obtained very easily, in a very short period of time and at low cost.

5. AN ALTERNATIVE APPROACH TO RHS B/C RING SYSTEM

This chapter describes and discusses some aspects of an alternative approach to access the right hand side B/C sub-unit. This explorative study was done alongside the B/C sub-unit synthesis discussed in the preceding chapter. The latter proved to be easier and shorter, and so the present study was not followed and instead looked upon as a back-up scheme.

5.1 Synthetic strategy



Generation of ring C was envisaged to be possible by a ring-contraction protocol, via opening of a 6-membered ring and its subsequent closure to a 5-membered one.

It was anticipated that ring A/B would be connected to ring C precursor, **5.1**, via a 1,4-conjugate addition of an appropriate organometallic form of ring A. Subsequent C-trapping with allyl bromide would furnish intermediate **5.2**, which is set up for synthesis of ring B.

A ring-closing metathesis reaction on intermediate **5.2** would generate the central 8-membered ring B, giving a 5-8-6 system such as **5.3**.[68]

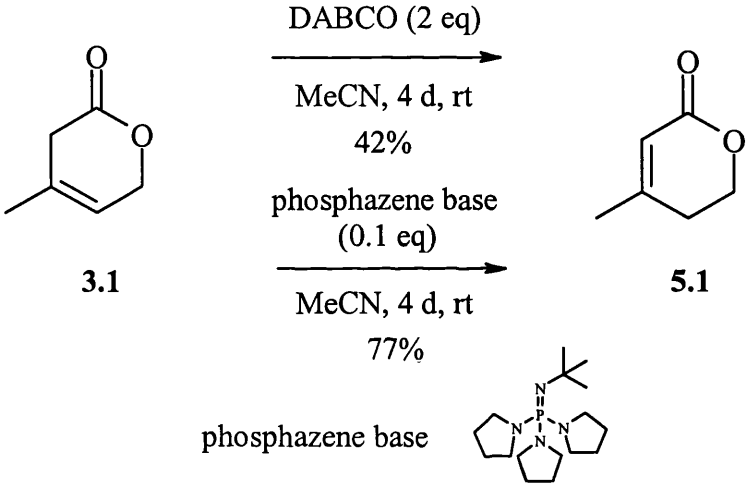
Transformation of the 6-membered precursor to ring C, would begin by its reaction with a heptenyl organometallic to provide the keto-alcohol **5.4**. Modification of the alcohol to a bromide, followed by an intramolecular Wittig[117] reaction, would close the 5-membered ring C yielding the 5-8-5 ophiobolin skeleton.

Stereoselectivity at B/C ring junction was anticipated to come via use of an external chiral ligand during 1,4-conjugate addition. Initially, it was hoped to get the chemistry right in this explorative study and then to modify the reactions to incorporate stereochemistry.

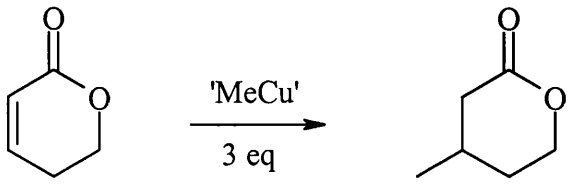
5.2 Synthetic studies

The conjugated lactone **5.1**, could be obtained from the non-conjugated lactone **3.1** which is the starting precursor in the synthesis of ring A.

Isomerisation of lactone **3.1** (see chapter **3**) proceeded cleanly in the presence of both DABCO and phosphazene base to provide lactone **5.1** in 42% and 77% yield. A shift in the carbonyl frequency from 1738 cm^{-1} to 1720 cm^{-1} was observed in the IR spectrum.



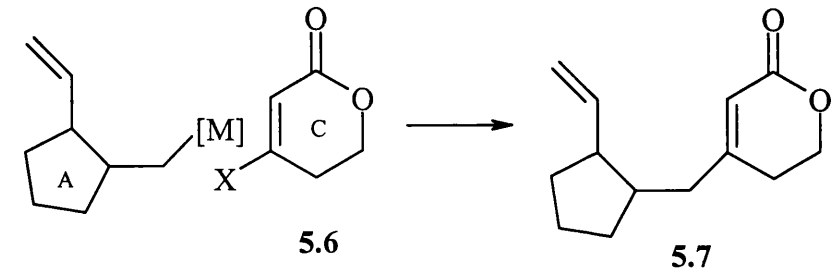
The precursor to rings A/B of the molecule was envisaged to be linked to ring C by a copper mediated 1,4-conjugate addition reaction to lactone **5.1**. Explorative studies on commercially available lactone **5.5** showed that an excess of the organocuprate was required for 1,4-addition.[118]



5.5

This was not a good protocol as in the synthesis of the real molecule, the excess moiety would be the ring A/B precursor, thus proving to be a wasteful exercise.

An alternative procedure more economical on precious reagents was considered.



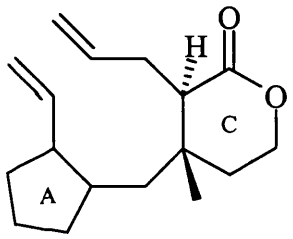
5.6

M = metal X = triflate, Cl

5.7

i) 1,4-addition of Me

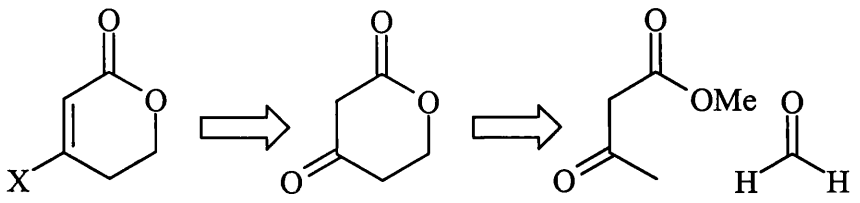
ii) *in-situ* trap of allyl



5.2

The intermediate **5.2**, could be obtained by the alternative route illustrated above. The organometallic precursor of ring A/B, could be connected to a triflate/chloride lactone such as **5.6**. 1,4-Addition of methyl cuprate, followed by an *in-situ* C-allylation would furnish the desired intermediate.

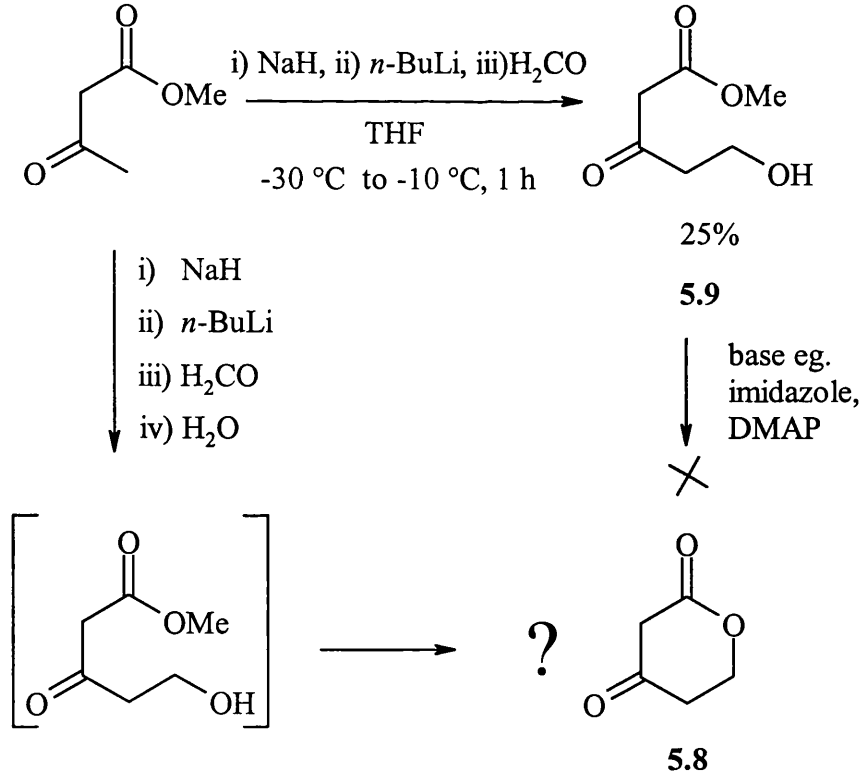
Retrosynthetically the triflate/chloride lactone **5.6** can be obtained from simple starting materials.



5.6 **5.8**

In the forward synthesis, it was hoped a dianion of methylacetoacetate would react with formaldehyde and undergo intramolecular cyclisation to give **5.8**. Its enol form could be trapped as a triflate or converted into a chloride.

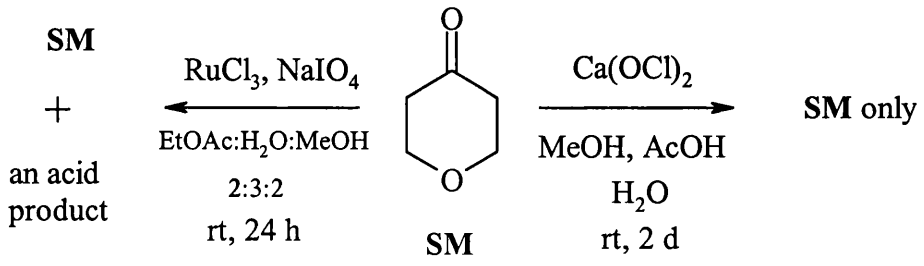
The explorative synthesis itself is summarised in the scheme below.



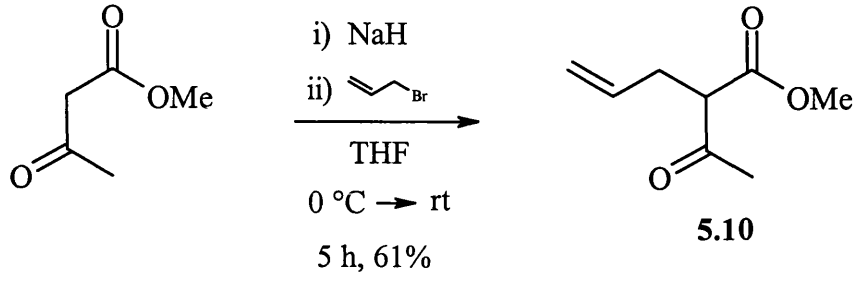
A dianion was formed by sequential reaction of sodium hydride and *n*-BuLi with methylacetoacetate. This was then treated with formaldyde, prepared from paraformaldehyde and *p*-toluenesulfonic anhydride.[119] (Reaction of the dianion with paraformaldehyde or trioxane did not yield a product.) After 20 min at -10 °C, the mixture was quenched, worked-up and a product isolated. Its ^{1}H NMR spectrum revealed that the structure was the acyclic keto-alcohol **5.9**. This compound did not cyclise in the presence of an array of mild bases.

The same reaction protocol was repeated except that after addition of formaldehyde, the reaction was slowly warmed to room temperature from -10 °C, stirred for two hours, quenched with water and stirred for a further 24 h. Work-up and purification, yielded a gooey, cream solid, the structure of which was suspected to be **5.8** by ^{1}H NMR spectrum, but could not be backed up by ^{13}C NMR spectrum, mass spectrum or CHN analysis. The product was insoluble in most solvents except MeOH and DMF, and could not be trapped as the triflate, chloride or iodide.

Direct oxidation[120] of tetrahydro-4H-pyran-4-one with either $RuCl_3/NaIO_4$ or $Ca(OCl)_2$ did not yield lactone **5.8**.

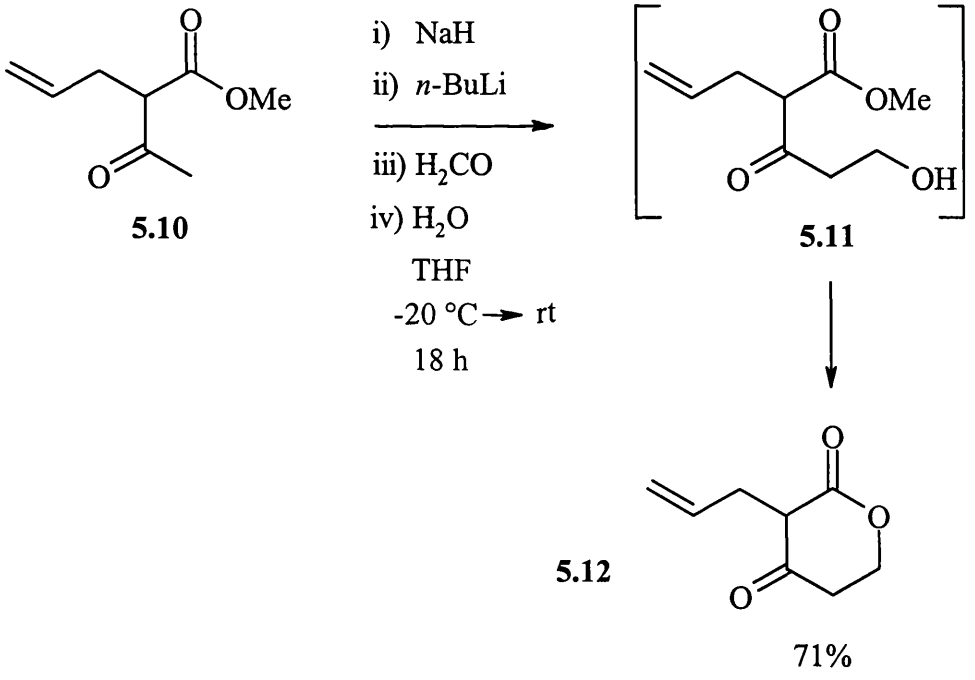


Since an allyl group at the α-position of the lactone is needed to be introduced later in the synthetic route, methylacetoacetate was allylated before formation of the lactone. Some bis-allylated product was also isolated.



5.10

The allylated methylacetoacetate was subjected to the same conditions as before.



5.10

5.11

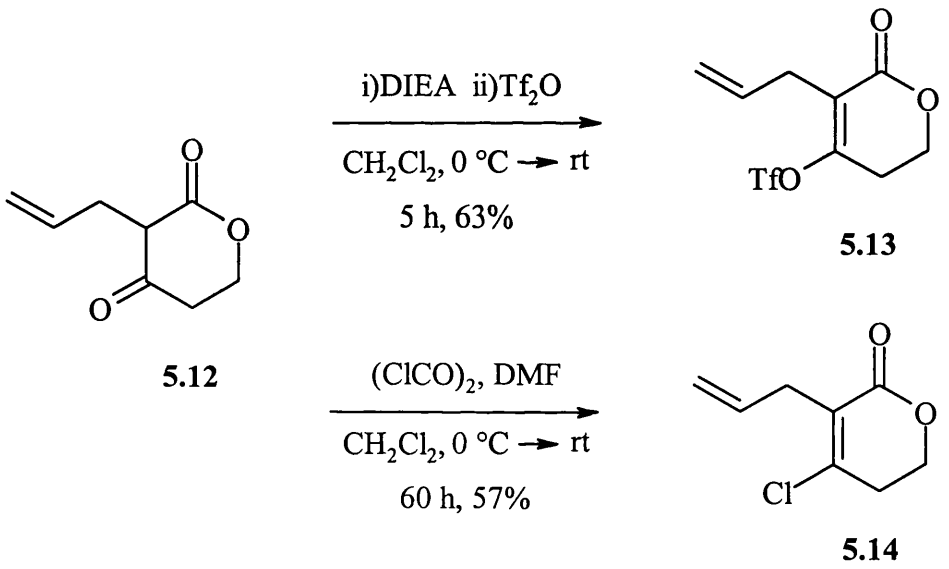
5.12

71%

The dianion from **5.10** was initially treated with a small amount of the cracked paraformaldehyde and the reaction was followed by TLC. The procedure was repeated at 15 min intervals until only a trace amount of the starting acyclic **5.10** was

visible by TLC, 8:2 petroleum ether:EtOAc. Two new compounds running close to each other on the TLC plate, 8:2 CH_2Cl_2:MeOH as eluent, were detected. The relative amount of the less polar of the two compounds increased with time and that of the more polar, decreased indicating the cyclic product **5.12** and acyclic intermediate **5.11** respectively. This also showed that allylation allowed cyclisation of the intermediate **5.11** with ease.

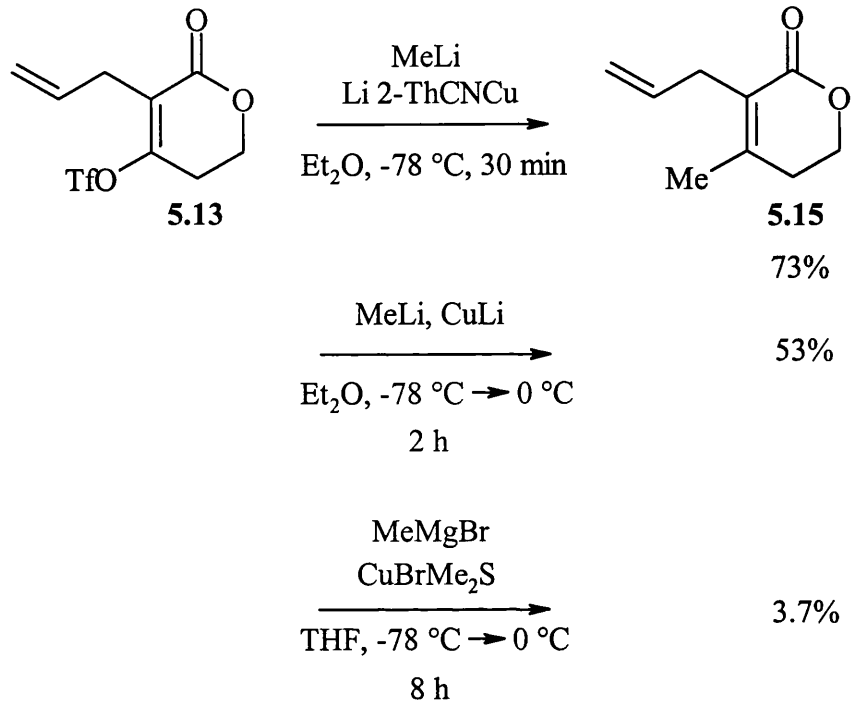
The ^1H NMR spectrum in $CDCl_3$ of the lactone **5.12** showed it to be mainly in its enol form. The enol was readily trapped as the enol triflate **5.13**[121] or converted into the vinyl chloride **5.14**.[122]



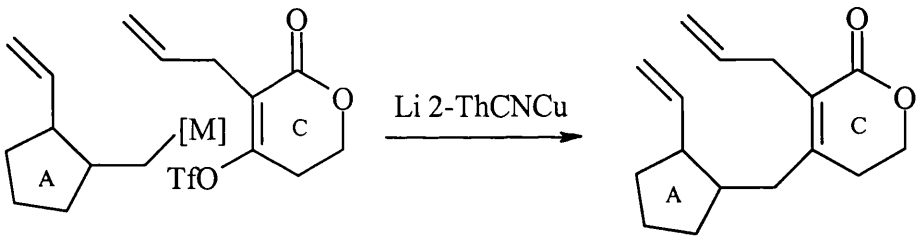
5.12 **5.13** **5.14**

Once the starting lactone was in hand, the next step was to investigate C-C bond formation at the β-position of the lactone. This was hoped to be achieved via an organocuprate reagent where the latter would add by a 1,4-conjugate addition and give the desired product by subsequent elimination of the triflate.

Methyl cuprate was used as a model reagent to demonstrate the C-C bond formation. Various copper mediated reactions were attempted.[65]



All reactions were done using just over one equivalent of the methyl and copper reagents. The best result was achieved with lithium 2-thienylcyanocuprate.[111] Reaction of the triflate lactone **5.13** with methyl cuprate, generated from methyllithium and 2-thienylcyanocuprate, at -78 °C afforded the methyl lactone product **5.15** in 15 min. C-C bond formation at the β-position of the lactone was thus achieved in an efficient and reagent economical manner. Under similar conditions, it was envisaged that an organometallic precursor of ring A/B could be attached to the triflate lactone **5.13** giving an intermediate similar to **5.7**.



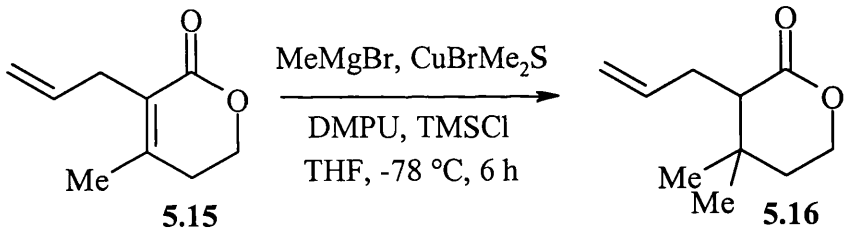
M = metal **5.13**

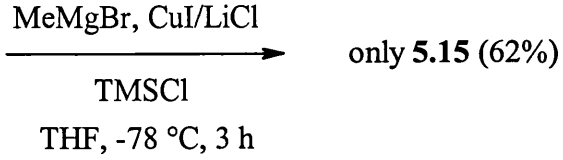
^{1}H NMR spectrum of **5.15** showed presence of a methyl substituent at 1.97 ppm. A shift in the carbonyl frequency was also observed from 1733 cm^{-1} to 1706 cm^{-1} corresponding to the triflate and methyl lactone respectively.

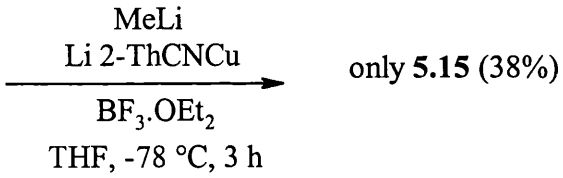
Some starting material (22%) was recovered from the low-yielding reaction using MeMgBr and $CuBrMe_2S$.

The next important reaction involving ring C is the addition of methyl to generate the quaternary centre at the B/C ring junction of the ophiobolin. This was envisaged to be via a 1,4-conjugate addition reaction.

A model study was to add a methyl group at the β-position of the methyl lactone **5.15**. Again variations of the organocuprate reaction were investigated.[65,94]

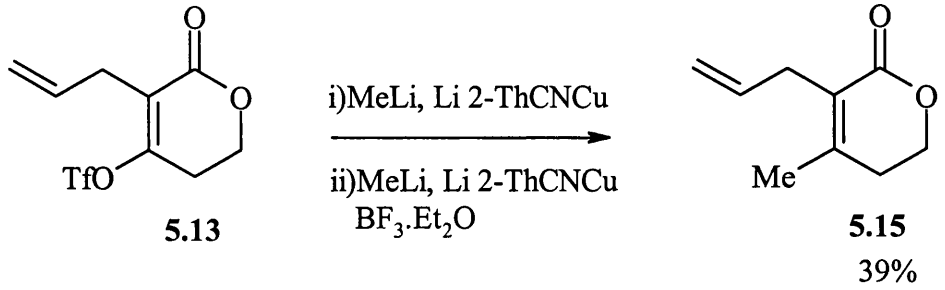






As illustrated above, the procedure of Nakamura and co-workers using MeMgBr/CuBr.MeS gave the desired product in a good yield.[91] The ^{1}H NMR spectrum showed presence of two methyl groups. These appeared as singlets at 0.99 and 1.19 ppm. A shift from 1706 to 1741 cm^{-1} was observed in the IR spectrum.

A one-pot proceedure where displacement of the triflate by one methyl substituent was followed by 1,4-conjugate addition of another methyl, did not give the bis-substituted product. Only the intermediate **5.15** was isolated.



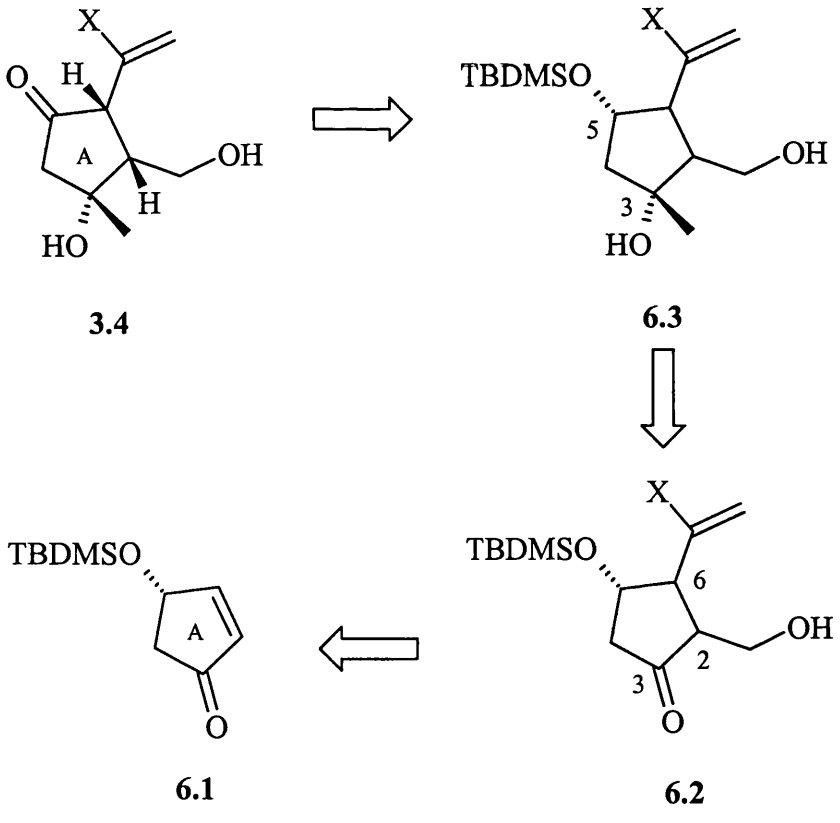
Thus far, model studies have established reaction protocols that could be used for some key chemical transformations required in accessing the right hand side of the molecule. Synthesis of a precursor to ring C, reaction protocol to attach a substituent (ring A/B organometallic in the real molecule) to the precursor and addition of a methyl at the projected B/C ring junction, have been successfully investigated.

At this stage in the synthesis the on-going parallel synthesis of the B/C sub-unit discussed in chapter **4**, seemed more promising and was made the focus of the project. The present study was thus, put on hold.

6. CONCLUSION

Model studies towards the synthesis of ophiobolin M have explored a route for the synthesis of ring A. Although cyclisation of the epoxide precursor **3.11** did not give the desired product, it has been shown that the anion required for this cyclisation does form at the correct position. This information can perhaps be used to form ring A using essentially the same chemistry as discussed in chapter **3**, except that instead of asymmetric epoxidation, asymmetric dihydroxylation can be employed.

If the dihydroxylation strategy was unsuccessful and bearing in mind the chemistry explored to assemble the B/C sub-unit, an alternative approach to ring A is suggested.



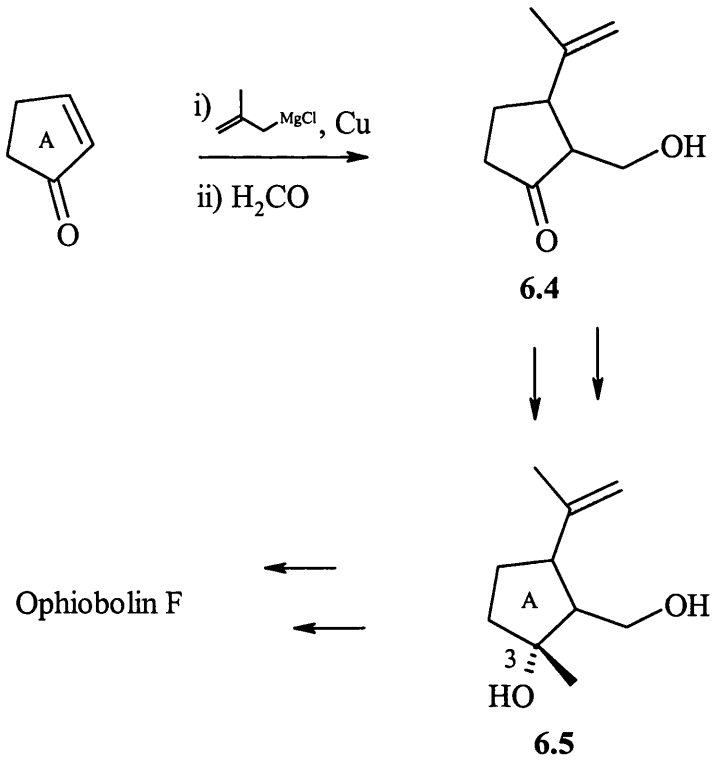
3.4 **6.3** **6.1** **6.2**

In a forward sense, the synthesis would commence with the cyclopentenone precursor **6.1**, (which is commercially available from Tyger Scientific Inc., USA). A 1,4-conjugate addition using an appropriate vinylic cuprate precursor, followed by an *in-situ* quench with formaldehyde, would give the intermediate **6.2**.[119] Stereochemistry C-6 could perhaps be explored by asymmetric 1,4-addition and at C-2 by quenching an enolate at that position with a suitable proton source.

Reaction of the C-3 carbonyl in intermediate **6.2** with a methyl nucleophile could afford a tertiary alcohol at that position affording **6.3**. Hopefully some chiral induction can be gained from the large protecting group at C-5 and the two ring junction substituents which should both point in the same direction as the silyl protecting group.

The protected alcohol at C-3 could retain that form until a point in the synthesis is reached where deprotection of the alcohol and oxidation to the carbonyl would not leave the carbonyl exposed to further attack. This would furnish ring A of the ophiobolin as depicted in **3.4**.

This route would allow access to ring A very efficiently although stereochemical issues may need more attention. A similar protocol would also allow construction of ring A of ophiobolin F.



1,4-Conjugate addition on cyclopentenone with methylvinylcuprate, followed by an *in-situ* quench with formaldehyde would afford an intermediate such as **6.4**. Reaction of a methyl nucleophile would generate the tertiary alcohol at C-3 affording the intermediate **6.5** and hopefully the ring junction substituents would give some stereochemical induction.

Studies on the 8-5, B/C sub-unit have been more successful. This right hand side of the molecule has been constructed very efficiently in seven synthetic steps starting from the monocyclic 1,3-cyclopentanedione to the bicyclic unit **4.24**, bearing an exocyclic methyl group. Some interesting chemistry was realised on route.

Efficient one-step alkylations of 1,3-cyclopentanedione at C-2 are not usually observed.[71] Palladium catalysis allowed this in very high yields.

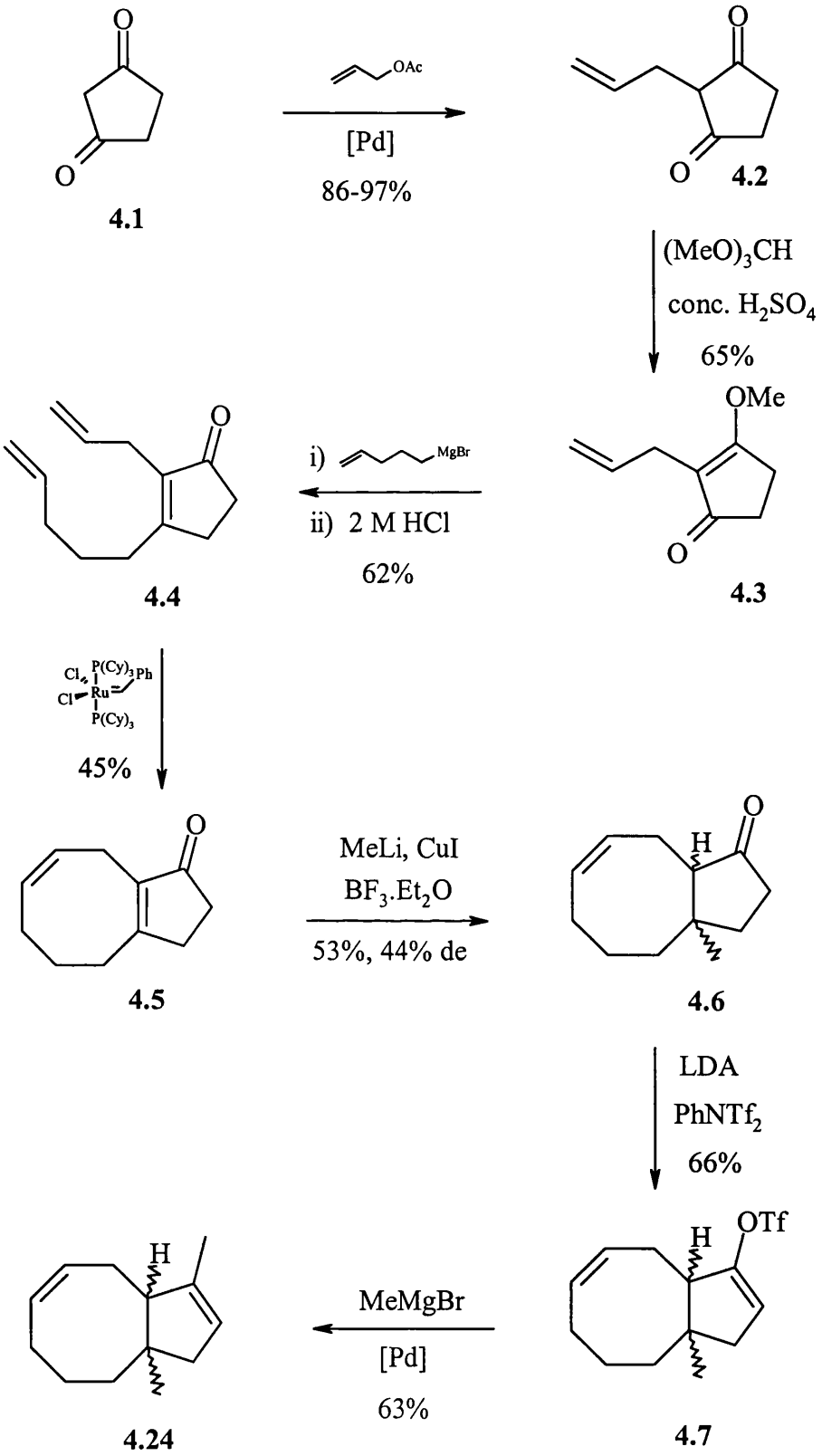
Two reactions, RCM and 1,4-conjugate addition, where ring size plays a leading role were explored and the corresponding products were obtained in very reasonable yields.

Ring-closing metathesis reaction on the monocyclic triene precursor **4.4** with allylic and pentenyl substituents gave the isolated bicyclic enone in yields up to 45%, by employing Grubbs ruthenium catalyst.

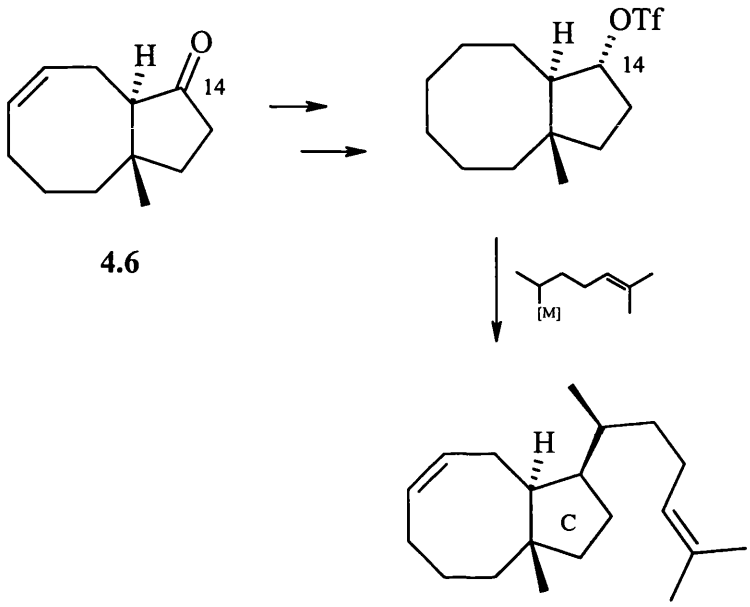
1,4-Conjugate addition of a methyl group on the resulting enone **4.5** gave addition product **4.6** in up to 58% yield. Diastereoselectivity was seen in this reaction without the help of any added ligands or selective proton quench. This can be attributed to the conformation of the bicyclic molecule. Enantioselectively of the methyl addition was investigated by use of added chiral ligand to the methyl cuprate reaction mixture. Although no major breakthrough was achieved, use of camphor based ligand (**4.19**), showed a slight amount of product with some enantioselectivity and this could perhaps be investigated further.

An exocyclic C-C bond on ring C of the molecule has been formed. Grignard cross-coupling could be investigated further by formation of a heptenyl Grignard precursor using a more activated magnesium source.[123] An alternative route to attaching the heptenyl chain enantioselectively by making using of the highly selective resolution of heptenol **4.26** has been discussed in chapter **4,** section **4.4.2**. Conjugate addition followed by RCM to form the methylated bicycle **4.6**, was also investigated but found to be less satisfactory.

A summary of the major linear synthesis for assembling the 8-5 B/C sub-unit is given below.



The 8-5 sub-unit, **4.6**, allows access to other ophiobolins. For instance, stereoselective reduction of the carbonyl, conversion of the resulting alcohol into a triflate and its subsequent displacement with a heptenyl nucleophile can furnish ring C of ophiobolins C and F.



4.6

So, the duration of the project has seen a valid strategy for assembling ring A, an efficient construction of the B/C sub-unit, addition of a quaternary methyl at a bicyclic ring junction and formation of an exocyclic C-C bond. The stereochemical aspects of the synthesis have also been explored.

An alternative approach to rings B/C has also been investigated briefly.

7. EXPERIMENTAL

General Experimental

All reactions that required an inert atmosphere were carried out under nitrogen and in glassware that was flame-dried and cooled under nitrogen. Nitrogen was passed through a calcium chloride/silica gel drying tube.

Solvents for these reactions were dried and purified by distillation prior to use. Diethyl ether, tetrahydrofuran and toluene were distilled from sodium. Dichloromethane was distilled from calcium hydride. Petroleum ether fraction used was 60:40 and was distilled before use. HPLC grade solvents were used for any other reactions.

Most reagents were used as obtained from the manufacturer but some were purified when required. The ruthenium catalyst for ring-closing metathesis reaction was purchased from Strem Chemical Inc. and used without further purification. It was stored under nitrogen at all times.

All temperatures quoted are external.

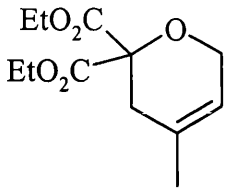
Purification of products was mainly carried out by flash column chromatography using either Merck Kieselgel 60 H silica or Aldrich florisil, 100-200 mesh. Reactions were followed by Thin Layer Chromatography using plastic backed plates coated with Merck Kieselgel G/UV_{254}. Reactions requiring reverse phase TLC were followed using aluminium backed Whatman Thin Layer Chromatography plates

coated with diphenyl-F reversed phase. TLC plates were visualised using either UV light (at 254 nm) and/or staining with PMA (prepared by dissolving phosphomolybdic acid (12 g) in EtOH (250 mL) or $KMnO_4$ (prepared by dissolving $KMnO_4$ (2.25 g), K_2CO_3 (10 g) in water (150 mL), followed by heating.

Samples for NMR spectroscopy were prepared by dissolution in $CDCl_3$ or CD_3OD. Deutrated chloroform was passed through a small alumina column and stored over 4Å molecular sieves. ^1H, ^{13}C and ^{19}F NMR spectra were recorded as stated by use of either a JEOL GX270 MHz or JEOL GX400 MHx instrument. Chemical shifts are reported downfield in parts per million (ppm) from a tetramethyl silane reference. IR spectra were recorded mainly as liquid films or KBr discs on a Perkin Elmer FT1000. Mass Spectra were recorded by use of a Finnigan MAT 8340 instrument. Elemental analysis was carried out on a Carbo Erba Stamentazione EA1506 analyser. Separation of diastereoisomers was achieved by chiral GC on a SUPELCO™ Beta-dex 120 column using samples dissolved in dichloromethane in a concentration of 2 $mgmL^{-1}$. The melting point of 2-allyl-1,3-cyclopentanedione was measured on an Electrothermal MKII mp apparatus and is uncorrected.

7.1 EXPERIMENTAL CHAPTER 3

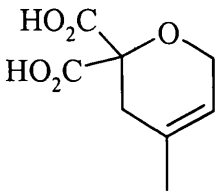
Diethyl 4-methyl-3,6-dihydro-2H-pyran-2,2-dicarboxylate, 3.5.[36]



3.5

Isoprene (25 mL, 0.25 mol) was added to a solution of diethylketomalonate (15.9 mL, 0.1 mol) and hydroquinone (110 mg, 1 mmol) in acetonitrile (30 mL) in a stainless steel reactor. The vessel was sealed and heated at 134 °C for 8 h. On cooling, excess solvent and reagent were removed under reduced pressure to afford a brown oil. Chromatography of the crude oil on silica gel with 95:5 petroleum ether:EtOAc afforded the diester adduct as a yellow-brown oil (21.9 g, 90%). The ratio of the 4-Me:5-Me regio-isomers was 12:1 by ^{1}H NMR analysis [literature ratio 4:5 11:1].[36] R_f (8:2, petroleum ether:EtOAc): 0.44; ν_{max} (film)/cm^{-1}: 2978, 2935 (CH), 1742 (C=O); δ_H (270 MHz, $CDCl_3$): 1.29 (6H, t, *J* 7.1 Hz, OCH_2CH_3), 1.59 (3H, s, 4-CH_3), 1.75 (3H, s, 5-CH_3), 2.57 (2H, s, $(CO_2Et)_2CCH_2C{=}C$), 4.27 (4H, q, *J* 7.2 Hz, OCH_2CH_3), 4.33-4.37 (2H, m, $C{=}CHCH_2$-O), 5.38 (1H, broad s, $C{=}CHCH_2$-O); δ_C (270 MHz, $CDCl_3$): 13.9 (CH_3), 22.8 (CH_3), 33.5 (CH_2), 61.9 (CH_2), 63.8 (CH_2), 79.4 (quaternary), 118.1 (=CH), 129.5 (quaternary), 168.1 (quaternary); *m/z* (EI) 242 (22%, M^+), 169 (27, M - CO_2Et), 95 (100), ($C_{12}H_{18}O_5$ requires *M*, 242.1154. Found: M^+, 242.1149).

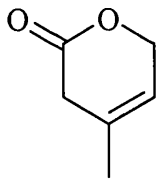
4-Methyl-3,6-dihydro-2H-pyran-2,2-dicarboxylic acid, 3.6.[36]



3.6

A THF (260 mL) solution of the diester adduct **3.5** (21.6 g, 0.089 mol) was stirred with aqueous KOH (2.7 mol, 10 M) for 30 h at room temperature. The resulting white suspension was acidified, with cooling, using 2 M HCl to pH 1 and extracted thoroughly with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$) and solvent removed under reduced pressure to afford di-acid **3.6** as a viscous golden oil (15.9 g, 96%) which was used further without purification. Various attempts to crystallise the di-acid did not yield any solid. Ratio of the 4-Me:5-Me regio-isomers was 13:1 by ^1H NMR analysis. R_f (1:1 EtOAc:MeOH): product just lifts off the baseline; ν_{max} (film)/cm^{-1}: 3500-3000 (broad, -COOH), 2916 (CH), 1732 (C=O); δ_H (400 MHz, $CDCl_3$): (major isomer) 1.76 (3H, s, 4-CH_3), 2.63 (2H, s, $(CO_2H)_2CCH_2C$=C), 4.39 (2H, s, C=CHCH_2-O), 5.41 (1H, m, C=CHCH_2-O), 10.45 (broad s, CO_2H), (minor isomer) 1.62 (3H, s, 5-CH_3), 2.72 (2H, s, $(CO_2H)_2CCH_2C$=C), 4.27 (2H, broad s, C=CHCH_2-O), 5.51-5.56 (1H, m, C=CHCH_2-O); δ_C (400 MHz, $CDCl_3$): (major isomer) 22.7 (CH_3), 33.2 (CH_2), 63.9 (CH_2), 79.2 (quaternary), 118.1 (=CH), 129.6 (quaternary), 171.6 (quaternary), (minor isomer) 18.1 (CH_3), 28.8 (CH_2), 66.1 (CH_2), 78.1 (quaternary), 115.6 (=CH), 131.6 (quaternary), 172.5 (quaternary); *m/z* (FAB): 209 (70%, M^+ + Na), 187 (100, M^+ + H); ($C_8H_{10}O_5$ requires *M* + *H*, 187.0606. Found: M^+ + H, 187.0604).

4-Methyl-3,6-dihydro-2H-pyran-2-one, 3.1.[36]



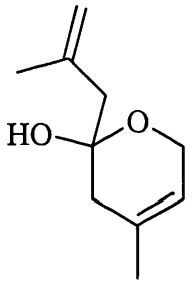
3.1

Water (50 mL) was added dropwise over one hour, via a syringe pump, to a clear orange coloured solution of the di-acid **3.6** (2 g, 10.7 mmol) and ceric ammonium nitrate (29.4 g, 53.6 mmol) in acetonitrile (150 mL) at ambient temperature. The mixture was stirred for a further 1 h during which the clear orange solution became a lighter orange, gelatinous mixture. Acetonitrile was removed under vacuum using a cool (20 °C) water bath. CH_2Cl_2 (20 mL) was added to the concentrate and the mixture stirred vigorously for 5 min. $MgSO_4$ was then added until the aqueous layer formed a thick slurry. The mixture was allowed to stand for about 15 min during which the slurry solidified further leaving a clear organic layer which was filtered through a thick pad of celite. The solid was washed several times with CH_2Cl_2 (5 × 50 mL). The combined organic phase was dried with more $MgSO_4$ and solvent removed under reduced pressure. The residue was chromatographed (silica, 9:1 petroleum ether:EtOAc) to give lactone **3.1** as a light brown oil (0.71 g, 59.2%).[†] Ratio of the 4-Me:5-Me regio-isomers was 12:1 by ^1H NMR analysis. R_f (7:3 petroleum ether: EtOAc): 0.31; ν_{max} (film)/cm^{-1}: 2917 (CH), 1738 (C=O); δ_H (270 MHz, $CDCl_3$): (major isomer) 1.79 (3H, s (singlet with fine splitting), 4-CH_3), 2.98

[†] organic/aqueous work-up gave a gelatinous, inseparable mixture which led to a low yield of recovered product.

(2H, s (singlet with fine splitting), C=CMeCH_2CO), 4.82-4.87 (2H, m, C=CHCH_2-O), 5.58-5.62 (1H, m, C=C*H*CH_2-O), (minor isomer) 1.71-1.76 (3H, m, 5-CH_3), 3.01-3.09 (2H, m, C=CMeCH_2CO), 4.74-4.79 (2H, m, C=CHCH_2-O), 5.50-5.55, (1H, m, C=C*H*CH_2-O); δ_C (270 MHz, $CDCl_3$): (major isomer) 21.3 (CH_3), 34.7 (CH_2), 68.6 (CH_2), 116.0 (=CH), 130.5 (quaternary), 169.4 (quaternary), (minor isomer, some signals observed) 15.1 (CH_3), 34.0 (CH_2), 65.7 (CH_2); *m/z* (EI): 112 (71%, M^+), 84 (88, M - CO), 41 (100), ($C_6H_8O_2$ requires *M*, 112.0525. Found: M^+, 112.0524).

4-Methyl-2-(2-methyl-2-propenyl)-3,6-dihydro-2H-pyran-2-ol, 3.7.

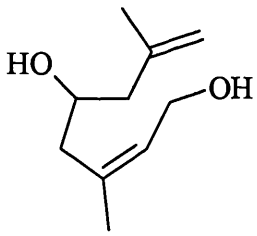


3.7

2-Methylallylmagnesium chloride (3.3 mL of 0.5 M solution in THF, 1.6 mmol) was added dropwise to a stirred solution of lactone **3.1** (0.18 g, 1.6 mmol) in dry Et_2O (3.2 mL) under nitrogen at -78 °C. After 25 min at this temperature, the mixture was poured into ammonium chloride solution (15 mL) and extracted with EtOAc (3 × 10 mL). The organic extract was washed with brine, dried ($MgSO_4$) and solvent evaporated under reduced pressure. The residue was purified by chromatography (silica, 97:3 hexane:EtOAc) to give a yellow oil (0.21 g, 78%). [A trace amount of starting lactone was also recovered.] R_f (8:2 hexane:EtOAc): 0.38; ν_{max} (film)/cm^{-1}:

3414 (OH), 3073 (=CH), 2927 and 2853 (CH), 1645 (C=C); δ_H (400 MHz, $CDCl_3$): 1.71 (3H, s, CH_2*Me*C=CH), 1.88 (3H, d, *J* 1 Hz, H_2C=C*Me*CH_2), 1.91 (1H, d, *J* 17 Hz, HC=CMeC*H*HC(OH)), 2.27 (1H, d, *J* 17 Hz, HC=CMeCH*H*C(OH)), 2.41 (2H, q, *J* 17 Hz, C(OH)CH_2CMe=CH_2), 2.81 (1H, d, *J* 1.5 Hz, OH), 4.06 (1H, d, *J* 16 Hz, MeC=CHC*H*H-O), 4.29 (1H, d, *J* 16 Hz, MeC=CHCH*H*-O), 4.85 (1H, s, MeC=C*H*H), 5.01 (1H, s (singlet with fine splitting), MeC=CH*H*), 5.42-5.47 (1H, m, MeC=C*H*CH_2-O); δ_C (400 MHz, $CDCl_3$): 23.6 (CH_3), 25.2 (CH_3), 39.6 (CH_2), 49.8 (CH_2), 61.0 (CH_2), 95.2 (quaternary), 116.3 (=CH_2), 118.9 (=CH), 129.4 (quaternary), 142.3 (quaternary); *m/z*: M^+ not observed in EI mass spectrum analysis, but some fragments by FAB mass spectrum, 151 (24%, M - OH), 113 (95, M - CH_2CMe=CH_2), 57 (100).

(2Z)-3,7-Dimethyl-2,7-octadiene-1,5-diol, 3.8.

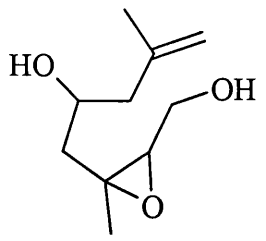


3.8

Sodium borohydride (0.35 g, 9.1 mmol) was added in portions to a cooled (ice-bath), stirred solution of the lactol **3.7** (1.4 g, 8.3 mmol) in MeOH (16 mL). The cooling bath was removed after 10 min and the cream coloured heterogeneous reaction mixture stirred at room temperature for 1 h. After this time, the mixture was acidified with 2 M HCl to pH 1 and some of the solvent evaporated under reduced pressure. The residue was poured into water (20 mL) and extracted with CH_2Cl_2 (3 × 100 mL).

The extract was washed (brine), dried ($MgSO_4$) and solvent removed under reduced pressure. Chromatography (silica, 8:2 petroleum ether:EtOAc) afforded the diol **3.8** (1.3 g, 93%) as very pale yellow oil. R_f (7:3 petroleum ether:EtOAc): 0.16; ν_{max} (film)/cm^{-1}: 3333 (OH), 3075 (=CH), 2967 and 2934 (CH), 1648 (C=C); δ_H (400 MHz, $CDCl_3$): 1.77 (3H, s, *Me*C=CHCH$_2$OH), 1.80 (3H, s, H$_2$CC*Me*=CH$_2$), 2.01 (1H, dd, *J* 2.8 and 13.4 Hz, CH=CMeC*H*HCH(OH)), 2.22 (2H, d, *J* 6.1 Hz, CH(OH)C*H*$_2$CMe=CH$_2$), 2.49 (1H, dd, *J* 9.6 and 13.5, CH=CMeC*H*HCH(OH)), 2.56 (2H, broad s, 2 × OH), 3.80-3.86 (1H, m, CH$_2$C*H*(OH)CH$_2$), 3.90 (1H, dd, *J* 7.2 and 12.0 Hz, CMe=CHC*H*H(OH), 4.15 (1H, dd, *J* 8.0 and 12.0 Hz, CMe=CHCH*H*(OH), 4.82 (1H, t, *J* 0.9, MeC=C*H*H), 4.90 (1H, dd, *J* 1.5 and 3.3, MeC=CH*H*), 5.72-5.74 (1H, m, CMe=C*H*CH$_2$OH); δ_C (400 MHz, $CDCl_3$): 22.3 (CH_3), 23.8 (CH_3), 39.3 (CH_2), 46.5 (CH_2), 57.6 (OCH_2), 65.6 (CH(OH)), 113.8 (=CH_2), 126.8 (=CH), 138.1, (quaternary), 142.3 (quaternary); *m/z* (FAB): 341 (26%, $2M^+$ + H), 193 (18, M^+ + Na), 171 (21, M^+ + H) 97 (100), ($C_{10}H_{18}O_2$ requires *M* + *H*, 171.1385. Found: M^+ + H, 171.1377).

3,7-Dimethyl-2-oxiranyl-7-octen-1,5-diol, 3.9.[41]

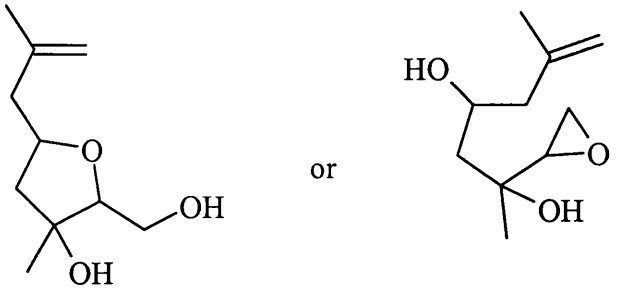


3.9

Allylic alcohol **3.8**, (0.4 g, 2.4 mmol) was added to a stirred solution of vanadyl acetylacetone (64 mg, 0.24 mmol) and sodium hydrogencarbonate (0.38 g, 4.4

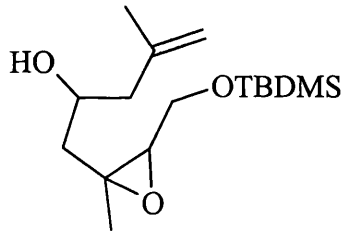
mmol) in dry toluene (75 mL). The turquoise coloured mixture was stirred at room temperature for 5 min, after which *t*-butyl hydroperoxide (0.83 mL of a 5.5 M solution in decane, 4.6 mmol) was added dropwise. The colour altered rapidly leaving a rusty red solution. The reaction mixture was stirred for 2 h during which the colour changed to a paler red. The mixture was then filtered through a pad of celite which was washed several times with EtOAc. The filtrate was dried ($MgSO_4$) and solvent evaporated under reduced pressure. The residue was purified by chromatography (silica, 65:35 petroleum ether:EtOAc) to give a pale yellow oil as a mixture of isomers in a ratio of 88:12 (0.23 g, 56.3%). [53 mg of a side product was also isolated. R_f (1:1 petroleum ether:EtOAc): 0.38.] R_f (1:1 petroleum ether:EtOAc): 0.28; ν_{max} (film)/cm^{-1}: 3387 (broad, OH), 3075 (=CH), 2977 and 2962 (CH), 1675 (C=C); δ_H (400 MHz, $CDCl_3$): 1.42 (3H, s, *Me*-epoxide), 1.63 (1H, dd, *J* 8.9 and 14.5 Hz, CH(OH)C*H*HCMe-epoxide), 1.77 (3H, s, C*Me*=CH_2), 1.81 (1H, dd, *J* 3.1 and 14.8 Hz, CH(OH)CH*H*CMe-epoxide), 2.20 (2H, ddd, *J* 6.4, 13.6 and 40.2 Hz, CH(OH)CH_2C=), 2.54 (1H, broad s, CH_2OH), 2.77 (1H, broad s, CH(O*H*)), 2.98 (1H, dd, *J* 4.6 and 6.2 Hz, $HOCH_2CH$-epoxide), 3.74 (1H, dd, *J* 6.2 and 12.1 Hz, HOC*H*HCH-epoxide), 3.82 (1H, dd, *J* 4.6 and 12.1 Hz, HOCH*H*CH-epoxide), 4.10-4.16 (1H, m, $CH_2CH(OH)CH_2$), 4.78 (1H, s, CMe=C*H*H), 4.87 (1H, s, CMe=CH*H*), [Signals due to the minor isomer overlap except for: 4.83 (1H, s, CMe=C*H*H), 4.91 (1H, s, CMe=CH*H*)]; δ_C (400 MHz, $CDCl_3$): 22.8 (CH_3), 23.6 (CH_3), 38.7 (CH_2), 46.5 (CH_2), 61.1 (quaternary), 61.3 (CH_2OH), 63.6 (CH-O-), 67.1 (CH-OH), 113.7 (=CH_2), 142.2 (quaternary); *m/z* (FAB): 209 (100%, M^+ + Na), 187 (17, M^+ + H) 171 (13, M - OH), 131 (44, H_2C=$CMeCH_2CHOH$-), ($C_{10}H_{18}O_3$ requires *M* + *Na*, 209.1154. Found: M^+ + Na, 209.1152).

Side-product of epoxidation.



δ_H (400 MHz, $CDCl_3$): 1.41, (3H, s), 1.58 (1H, dd, *J* 11.1 and 14.2 Hz), 1.78 (3H, s), 1.93 (1H, dd, *J* 1.9 and 14.2 Hz), 2.16 (1H, dd, *J* 9.2 and 13.4 Hz), 2.24 (1H, dd, *J* 3.6 and 13.4 Hz), 2.53 (1H, broad s, OH), 3.00-3.03 (1H, m), 3.42-3.50 (1H, m), 3.91-3.97 (2H, m); δ_C (400 MHz, $CDCl_3$): 20.4 (CH_3), 22.2 (CH_3), 39.5 (CH_2), 46.8 (CH_2), 59.0 (quaternary), 60.7 (CH_2), 62.2 (CH), 65.8 (CH), 114.7 (=CH_2), 141.6 (quaternary).

TBDMS-protected alcohol 3.10.[42]

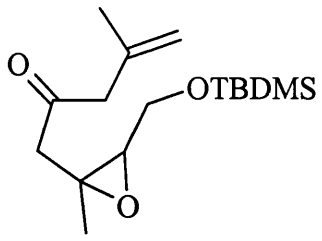


3.10

t-Butyldimethylsilyl chloride (0.18 g, 1.18 mmol) was added in one portion to a stirred solution of the epoxy-alcohol **3.9** (0.2 g, 1.07 mmol), triethylamine (0.17 mL, 1.23 mmol) and DMAP (39 mg, 0.3 mmol) in CH_2Cl_2 (1mL) under nitrogen at room temperature. The reaction mixture was stirred for 1.5 h, poured into water and

extracted with CH_2Cl_2 (3 × 10 mL). The extract was washed (brine), dried (Na_2SO_4) and solvent removed under reduced pressure. Chromatography (silica, 95:5 petroleum ether: EtOAc) to give a colourless oil (0.27 g, 84%). R_f (9:1 petroleum ether:EtOAc): 0.28; ν_{max} (film)/cm^{-1}: 3442 (OH), 3075 (=CH), 2956 and 2930 (CH), 1646 (=CH), 1256 and 838 (*t*-BuSiMe$_2$); δ_H (270 MHz, $CDCl_3$): 0.00 (3H, s, $SiMe_2$), 0.01 (3H, s, $SiMe_2$), 0.82 (9H, s, *t*-BuSi), 1.33 (3H, s, *Me*-epoxide), 1.47 (1H, dd, *J* 9.3 and 14.5 Hz, CH(OH)C*H*HCH-epoxide), 1.68 (1H, dd, *J* 2.9 and 14.5 Hz, CH(OH)CH*H*CH-epoxide), 1.69 (3H, s, C*Me*=CH_2), 2.05 (1H, d, *J* 7.1 Hz, CH(OH)C*H*HC=), 2.17 (1H, d, *J* 7.7 Hz, CH(OH)CH*H*C=), 2.67 (1H, d, *J* 1.7 Hz, OH), 2.83 (1H, t, *J* 5.49 Hz, epoxide-C*H*CH_2OSi-), 3.68 (2H, d, *J* 5.49 Hz, epoxide-CHC*H*$_2$OSi-), 4.03-4.13 (1H, m, CH_2CH(OH)CH_2), 4.68-4.70 (1H, s, CMe=C*H*H), 4.76-4.79 (1H, s, CMe=CH*H*); δ_C (270 MHz, $CDCl_3$): -5.3 (CH_3, $SiMe_2$), -5.2 (ÇH$_3$, $SiMe_2$), 18.2 (quaternary, *t*-BuSi), 22.5 (=CCH_3), 23.0 (epoxide-CH_3), 25.8 (CH_3, *t*-BuSi), 38.1 (CH_2), 46.1 (CH_2), 60.5 (quaternary), 61.7 (CH_2OSi), 63.5 (CH-epoxide), 66.9 (CH-OH), 113.3 (=CH_2), 142.3 (quaternary); *m/z* (FAB): 323 (44%, M^+ + Na), 301 (14, M^+ + H), 283 (70, M - OH), 73 (100), ($C_{16}H_{32}O_3Si$ requires *M* + *Na*, 323.2018. Found: M^+ + Na, 323.2009).

Synthesis of keto-epoxide 3.11.[41]

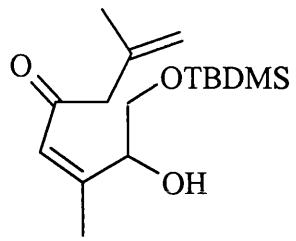


3.11

A CH_2Cl_2 (1 mL plus 2 × 0.5 mL for rinses) solution of epoxy-alcohol (0.17 g, 0.56 mmol) was added to a stirred suspension of pyridinium chlorochromate (0.30 g, 1.4 mmol), NaOAc (0.23 g, 2.8 mmol) and powdered, activated 4Å molecular sieves (0.25 g) in CH_2Cl_2 (3 mL). The mixture was stirred at room temperature for 18 h and filtered through a pad of celite. The pad was washed with more CH_2Cl_2 (4 × 20 mL) and the combined filtrate was evaporated. The keto-epoxide was isolated from the residue by chromatography (silica, 97:3 petroleum ether:EtOAc) as a yellow oil (0.15 g, 87%). R_f (95:5 petroleum ether:EtOAc) 0.29; ν_{max} (film)/cm^{-1}: 3079 (=CH), 2956 and 2930 (CH), 1718 (C=O), 1649 (C=C) 1256 and 838 (*t*-BuSiMe_2); δ_H (270 MHz, $CDCl_3$): 0.05 (3H, s, SiMe_2), 0.06 (3H, s SiMe_2), 0.88 (9H, s, *t*-BuSi), 1.35 (3H, s, *Me*-epoxide), 1.74 (3H, s, C*Me*=CH_2), 2.62 (1H, d, *J* 16.9 Hz, epoxide-CMeC*H*HCO), 2.88 (1H, d, *J* 17.0 Hz, epoxide-CMeCH*H*CO), 2.95 (1H, dd, *J* 3.8 and 6.0 Hz, epoxide-C*H*CH_2OSi), 3.12 (2H, s, COCH_2CMe=CH_2), 3.57 (1H, dd, *J* 6.2 and 11.9 Hz, epoxide-CHC*H*HOSi), 3.86 (1H, dd, *J* 3.8 and 11.9 Hz, O-CHCH*H*OSi), 4.82 (1H, broad s, CMe=C*H*H), 4.95 (1H, t, *J* 1.6 Hz, CMe=CH*H*); δ_C (270 MHz, $CDCl_3$): -5.4 (CH_3, SiMe_2), -5.3 (CH_3, SiMe_2), 18.3 (quaternary, *t*-BuSi), 22.5 (=CCH_3), 23.2 (epoxide-CH_3), 25.8 (CH_3, *t*-BuSi), 46.0 (CH_2), 52.6 (CH_2), 57.6 (epoxide, quaternary), 62.0 (CH_2-O), 63.7 (CH-O), 115.4 (=CH_2), 138.7 (quaternary), 205.4 (quaternary); *m/z* (FAB): 321 (17%, M^+ + Na), 299 (36, M^+ + H), 281 (32, M - OH), 241 (59, M - $C(CH_3)_3$), 73 (100), ($C_{16}H_{30}O_3Si$ requires *M* + *H*, 299.2042. Found: M^+ + H, 299.2043).

Side -product 3.13 from keto -epoxide cyclisation.

(5Z)-8-{[*t*-Butyl(dimethyl)silyl]oxy}-7-hydroxy-2,6-dimethyl-1,5-octadien-4-one, 3.13.

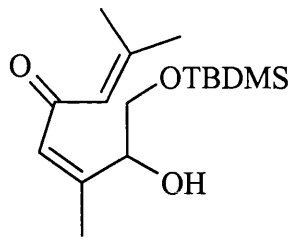


3.13

Purification by chromatography (silica, 97:3 petroleum ether:EtOAc); R_f (92:8 petroleum ether:EtOAc): 0.18; ν_{max} (film)/cm^{-1}: 3444 (broad, OH), 2929 and 2857 (CH), 1686 (C=O), 1624 (C=C), 1256 and 838 (*t*-BuSiMe$_2$); δ_H (270 MHz, $CDCl_3$): 0.07 (3H, s, $SiMe_2$), 0.08 (3H, s, $SiMe_2$), 0.89 (9H, s, *t*-BuSi), 1.75 (3H, s, C*Me*=CH_2), 2.08 (3H, s (singlet with fine splitting), (OH)CHC*Me*C=), 2.81 (1H, d, *J* 3.6 Hz, OH), 3.16 (2H, s, COC*H*$_2$CMe=CH_2), 3.45 (1H, dd, *J* 7.1 and 9.9 Hz, CH(OH)C*H*H-OSi), 3.80 (1H, dd, *J* 3.7 and 9.9 Hz, (CH(OH)CH*H*-OSi), 4.10-4.16 (1H, m, C=CMeC*H*(OH)CH_2), 4.82 (1H, broad s, CMe=C*H*H), 4.93-4.95 (1H, m, CMe=CH*H*), 6.47 (1H, s (singlet with fine splitting), CMe=C*H*$COCH_2$); δ_C (400 MHz, $CDCl_3$): -5.4 (CH_3, $SiMe_2$), 18.2 (quaternary, *t*-BuSi), 22.6 (CH_3), 25.7 (CH_3, *t*-BuSi), 29.7 (CH_3), 53.8 (CH_2), 65.6 (CH_2OSi), 76.0 (CHOH), 114.8 (=CH_2), 121.7 (=CH), 139.6 (quaternary, (Me)$_2$*C*=CH_2), 155.1 (quaternary, (CHOH)(Me)*C*=CHCO), 198.9 (quaternary, C=O); *m/z* (FAB): 299 (6%, M$^+$ + H), 281 (15, M - OH), 243 (53, M - $CH_2C(CH_3)$=CH_2), 115 (14, *t*-BuSiMe$_2$), 73 (100), ($C_{16}H_{30}O_3Si$ requires *M* + *H*, 299.2042. Found: M$^+$ + H, 299.2036).

By-product 3.14 from cyclisation of keto-epoxide.

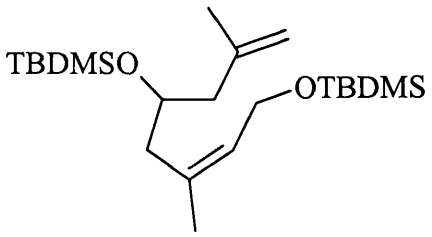
(5Z)-8-{[*t*-Butyl(dimethyl)silyl]oxy}-7-hydroxy-2,6-dimethyl-2,5-octadien-4-one, 3.14.



3.14

Purification by chromatography (silica, 96:4 petroleum ether:EtOAc); R_f (9:1 petroleum ether:EtOAc): 0.23; ν_{max} (film)/cm^{-1}: 3448 (broad, OH), 2954 and 2929 (CH), 1673 (C=O), 1630 (C=C), 1254 and 837 (*t*-BuSiMe$_2$); δ_H (270 MHz, $CDCl_3$): 0.07 (6H, s, $SiMe_2$), 0.08 (6H, s, $SiMe_2$), 0.89 (9H, s, *t*-BuSi), 1.89 (3H, s (singlet with fine splitting), =CMe), 2.10 (3H, d, *J* 1.3 Hz, =CMe), 2.16 (3H, s, =CMe), 2.81 (1H, d, *J* 3.3 Hz, OH), 3.4 (1H, dd, *J* 7.6 and 10.0 Hz, CH(OH)C*H*H-OSi), 3.77 (1H, dd, *J* 3.6 and 10.0 Hz, CH(OH)CH*H*-OSi), 4.11-4.16 (1H, m, C*H*(OH)), 6.11 (1H, s (singlet with fine splitting), C=CHC=O) 6.37 (1H, s (singlet with fine splitting), C=CHC=O); δ_C (270 MHz, $CDCl_3$): -5.41 (CH_3, $SiMe_2$), -5.38 (CH_3, $SiMe_2$), 16.1 (CH_3), 18.2 (quaternary, *t*-BuSi), 20.6 (CH_3), 25.8 (CH_3, *t*-BuSi), 27.7 (CH_3), 65.9 (CH_2OSi), 76.2 (CH(OH)), 125.1 (=CH), 126.3 (=CH), 153.2 (quaternary, =C), 155.1 (quaternary, =C), 191.7 (quaternary, C=O); *m/z* (FAB): 597 (86%, $2M^+ + H$), 299 (37, $M^+ + H$), 281 (46, M - OH), 115 (12, *t*-BuSiMe$_2$), 73 (100), ($C_{16}H_{30}O_3Si$ requires *M* + *H*, 299.2042. Found: $M^+ + H$, 299.2046).

Di-TBDMS protected alcohol 3.18.

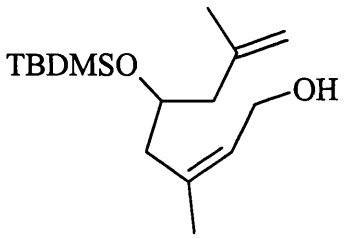


3.18

t-Butyldimethylsilyl chloride (165 mg, 1.1 mmol) was added to a solution of diol **3.8** (67 mg, 0.39 mmol), imidazole (81 mg, 1.18 mmol) and DMAP (29 mg, 0.24 mmol) in DMF (0.8 mL) at room temperature and stirred for 24 h. The resulting cream suspension was partitioned between brine (20 mL) and EtOAc (20 mL). The phases were separated and the aqueous re-extracted with EtOAc (3 × 20 mL). The combined extract was washed several times with brine to remove excess DMF, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was chromatographed (silica, petroleum ether) to afford the TBDMS-protected diol **3.18** as a yellow oil (90 mg, 58%). R_f (99:1 petroleum ether:EtOAc): 0.23; ν_{max} (film)/cm^{-1}: 3075 (=CH), 2955 and 2930 (CH), 1648 (C=C), 1255 and 835 (*t*-BuSiMe_2), 1073 (s); δ_H (400 MHz, $CDCl_3$): 0.01 (3H, s, $SiMe_2$), 0.03 (6H, s, $SiMe_2$), 0.06 (6H, s, $SiMe_2$), 0.86 (9H, s, *t*-BuSi), 0.89 (9H, s, *t*-BuSi), 1.73 (6H, s, 2 × =CMe), 2.12 (2H, dd, *J* 3.1 and 6.1 Hz, C*H*$_2$CH(OSi*t*-BuMe_2)), 2.16 (2H, d, *J* 6.4 Hz, C*H*$_2$CH(OSi*t*-BuMe_2)), 3.88 (1H, quintet, *J* 6.4 Hz, CH_2C*H*(OSi*t*-BuMe_2), 4.17 (2H, ddd, *J* 6.6, 12.7 and 27.8 Hz, =CHC*H*$_2$OSi*t*-BuMe_2), 4.71 (1H, s, MeC=C*H*H), 4.78 (1H, s, MeC=CH*H*), 5.38 (1H, t, *J* 6.1 Hz, =C*H*CH_2OSi*t*-BuMe_2); δ_C (400 MHz, $CDCl_3$): -4.9 (CH_3, $SiMe_2$), -4.3 (CH_3, $SiMe_2$), 18.0 (quaternary, *t*-BuSi), 18.4 (quaternary, *t*-BuSi), 22.9 (CH_3), 24.3 (CH_3), 25.8 (CH_3, *t*-BuSi), 26.0 (CH_3, *t*-BuSi), 40.1 (CH_2), 46.3 (CH_2), 60.1

(CH_2OSi), 69.8 (CHOSi), 113.1 (=CH_2), 127.3 (=CH), 134.5 (quaternary), 142.6 (quaternary); *m/z* (FAB): 397 (12%, M^+ + H), 341 (22, M^+ - $C(CH_3)$), 199 (39), 73 (100), (accurate mass was unobtainable).

(2Z)-5-{[*t*-Butyl(dimethyl(dimethyl)silyl]oxy}-3,7-dimethyl-2,7-octadien-1-ol, 3.19.[63]

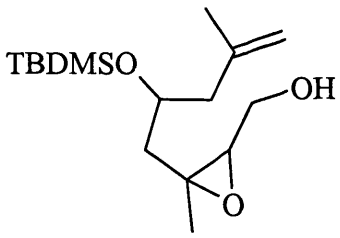


3.19

Aqueous TFA (9:1 TFA:H_2O, 0.2 mL) was added slowly, at room temperature, to a stirred solution of the di-TBDMS protected alcohol **3.18** (75 mg, 0.19 mmol) in THF (1 mL). After addition was complete the reaction mixture was submerged in an ice-bath and stirred for a further 20 min. TLC (96:4 petroleum ether:EtOAc) of the mixture showed that some starting material was still present. More aqueous TFA (0.2 mL) was added and after stirring for 30 min, the mixture was diluted with CH_2Cl_2 (5 mL), poured into water (10 mL) and extracted with more CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with sodium hydrogencarbonate solution (2 × 20 mL), dried (Na_2SO_4) and solvent removed under reduced pressure. The residue was chromatographed (95:5 petroleum ether:EtOAc) to afford the allylic alcohol **3.19** as a pale yellow oil (28 mg, 52.4%). [The diol **3.8**, where both the silyl groups were cleaved off, was also isolated (11 mg, 34.3%).] R_f (9:1 petroleum ether:EtOAc): 0.29; ν_{max} (film)/cm^{-1}: 3332 (OH), 3075 (=CH), 2955 and 2930 (CH),

1648 (C=C), 1255 and 835 (*t*-BuSiMe$_2$), 1086 (s); δ_H (270 MHz, $CDCl_3$): 0.02 (3H, s, $SiMe_2$), 0.06 (3H, s, $SiMe_2$), 0.86 (9H, s, *t*-BuSi), 1.73 (6H, s, 2 × =CMe), 2.05-2.29 (4H, m, C*H*$_2$CH(OSi*t*-BuMe_2)C*H*H, OH), 2.34 (1H, dd, *J* 9.0 and 13.6 Hz, CH_2CH(OSi*t*-BuMe_2)CH*H*), 3.89-3.98 (1H, m, CH_2C*H*(OSi*t*-BuMe_2)), 4.09-4.17 (2H, m, C*H*$_2$OH), 4.72 (1H, s, =C*H*H), 4.78 (1H, s, =C*H*H), 5.61 (1H, t, *J* 7.0 Hz, =C*H*CH_2OH); δ_C (270 MHz, $CDCl_3$): -4.4 (CH_3, $SiMe_2$), -4.7 (CH_3, $SiMe_2$), 18.0 (quaternary, *t*-BuSi), 22.8 (CH_3), 23.5 (CH_3), 25.8 (CH_3, *t*-BuSi), 39.3 (CH_2), 46.7 (CH_2), 58.5 (CH_2OSi), 68.9 (CHOSi), 113.3 (=CH_2), 126.7 (=CH), 137.6 (quaternary), 142.2 (quaternary); *m/z* (FAB): 569 (50%, $2M^+$ + H), 285 (21, M^+ + H), 267 (8, M^+ - OH), 199 (100), ($C_{16}H_{32}O_2Si$ requires *M* + *H*, 285.2249. Found: M^+ + H, 285.2237).

Asymmetric epoxidation to synthesise epoxy-alcohol 3.20.[62]



3.20

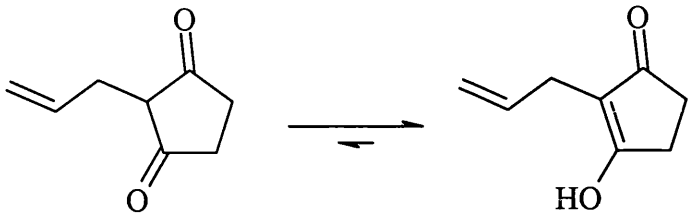
To a reaction flask equipped with a nitrogen inlet, were added CH_2Cl_2 (0.2 mL) and 4Å powdered, activated molecular sieves (5 mg). The flask was purged with nitrogen twice. L-(+)-Diethyl tartrate (23 mg, 0.109 mmol) and Ti(O-*i*-Pr)$_4$ (27 µl, 0.09 mmol) were added sequentially with stirring. The reaction flask was submerged in a dry ice/acetone bath at -20 °C and stirred for 10 min. Meanwhile, some *t*-butylhydroperoxide (~ 0.6 mL of 5.0 M solution in decane) was added into a vial

containing some 4Å activated molecular sieve pellets. The vial was stoppered and after 5 min, 27 μl (0.137 mmol) was transfered via a syringe to the cooled (-20 °C) reaction mixture. The resulting mixture was stirred for a further 20 min. Allylic alcohol **3.19**, was dissolved in CH_2Cl_2 (0.2 mL) and a couple of 4Å activated molecular sieve pellets were added to it. After 15 min, the dried alcohol (plus 3 × 0.2 mL CH_2Cl_2 for rinses) was added dropwise to the reaction mixture. The reaction flask was then stored in the freezer (-20 °C) for 15 h, warmed to 0 °C and the mixture poured into a cooled (0 °C), vigorously stirred aqueous solution of $FeSO_4$/tartaric acid[62] (5 mL). After stirring for 10 min, the aqueous phase was extracted with CH_2Cl_2 (3 × 0.2 mL). The combined extracts were dried (Na_2SO_4) and solvent removed under reduced pressure. Chromatography (silica, 95:5 petroleum ether:EtOAc) of the residue afforded the epoxy-alcohol **3.20** (15 mg, 55.5%) as a pale yellow oil. R_f (8:2 petroleum ether:EtOAc): 0.34; ν_{max} (film)/cm^{-1}: 3426 (OH), 3075 (=CH), 2957 and 2930 (CH), 1648 (C=C), 1255 and 835 (*t*-BuSiMe$_2$), 1095 (s); δ_H (400 MHz, $CDCl_3$): [Two sets of signals, possibly for diastereomers, in a ratio of 5:2, were observed.] (major isomer) 0.13 (3H, s, SiMe$_2$), 0.16 (3H, s, SiMe$_2$), 0.90 (9H, s, *t*-BuSi), 1.35 (3H, s, Me-epoxide), 1.51 (1H, dd, *J* 10.7 and 14.3 Hz, epoxide-C*H*HCH(OSi)), 1.72 (3H, s, C*Me*=CH$_2$), 1.84 (1H, dd, *J* 7.0 and 14.3 Hz, epoxide-CH*H*CH(OSi)), 2.06-2.22 (1H, m, CH(OSi)C*H*HCMe=), 2.36 (1H, dd, *J* 4.1 and 13.3 Hz, CH(OH)CH*H*CMe=), 2.82 (1H, dd, *J* 4.5 and 7.4 Hz, epoxide-C*H*CH$_2$OH), 3.61-3.68 (1H, m, epoxide-CHC*H*HOH), 3.79-3.87 (1H, m, epoxide-CHCH*H*OH), 4.00-4.07 (1H, m, CH$_2$C*H*(OTBDMS)), 4.71 (1H, s, =C*H*H), 4.80 (1H, s, =CH*H*), (minor isomer) 0.06 (3H, s, SiMe$_2$), 0.07 (3H, s, SiMe$_2$), 0.88 (9H, s, *t*-BuSi), 1.38 (3H, s, Me-epoxide), 1.40 (1H, d, *J* 5.8 Hz, epoxide-C*H*HCH(OSi)), 1.67 (1H, dd, *J* 5.3 and 14.5 Hz, epoxide-CH*H*CH(OSi)), 1.72 (3H, s, C*Me*=CH$_2$), 1.95 (1H, dd, *J*

2.9 and 14.5 Hz, CH(OSi)C*H*HC=), 2.06-2.22 (1H, m, CH(OSi)CH*H*C=), 2.92 (1H, dd, *J* 4.5 and 7.4 Hz, epoxide-C*H*CH_2OH), 3.61-3.68 (1H, m, epoxide-CHC*H*HOH), 3.79-3.87 (1H, m, epoxide-CHCH*H*OH), 3.95 (1H, quintet, *J* 6.7 Hz, CH_2C*H*(OTBDMS)), 4.71 (1H, s, =C*H*H), 4.80 (1H, s, =CH*H*); δ_C (400 MHz, $CDCl_3$): (major isomer) -4.6 (CH_3, $SiMe_2$), -3.9 (CH_3, $SiMe_2$), 18.0 (quaternary, *t*-BuSi), 22.1 (CH_3), 23.9 (CH_3), 25.9 (CH_3, *t*-BuSi), 38.6 (CH_2), 47.2 (CH_2), 59.3 (quaternary, epoxide), 61.5 (CH_2OH), 63.1 (CH-epoxide), 69.2 (CHOSi), 113.8 (=CH_2), 141.4 (quaternary), (minor isomer) -4.5 (CH_3, $SiMe_2$), -4.4 (CH_3, $SiMe_2$), 17.9 (quaternary, *t*-BuSi), 22.7 (CH_3), 22.8 (CH_3), 25.8 (CH_3, *t*-BuSi), 40.2 (CH_2), 46.4 (CH_2), 60.7 (quaternary, epoxide), 61.2 (CH_2OH), 63.6 (CH-epoxide), 68.9 (CHOSi), 113.5 (=CH_2), 142.2 (quaternary); *m/z* (FAB): 323 (16%, M^+ + Na), 301 (19, M^+ + H), 199 (92), 73 (100), ($C_{16}H_{32}O_3Si$ requires *M* + *H*, 301.2199. Found: M^+ + H, 301.2202).

7.2 EXPERIMENTAL CHAPTER 4

2-allyl-1,3-cyclopentanedione, 4.2.[73]



4.2

$[Pd(C_3H_5)Cl]_2$ (0.09 g, 0.25 mmol, 2.5 mol%)[‡] was added to dppe (0.4 g, 1 mmol) in a reaction flask equipped with a nitrogen line and a water condenser. The reaction flask was purged with nitrogen twice. The solid reagents were dissolved in THF (25 mL) and allyl acetate (1.08 mL, 10 mmol) added. To the yellow-orange solution 1,3-cyclopentanedione (1.5 g, 15 mmol), BSA (3.7 mL, 15 mmol) and CsOAc (0.05 g, 0.25 mmol) were added sequentially. The mixture was refluxed for 24 h, after which it was cooled, diluted with MeOH (20 mL) and stirred for 15 min. A cream solid precipitated which was removed by filtering the suspension through a pad of celite. The pad was washed with more MeOH (3 × 10 mL) and the combined washings were reduced to about third of the original volume, under reduced pressure. Silica (4 g) was added to the concentrate and solvent evaporated. The pre-adsorbed crude

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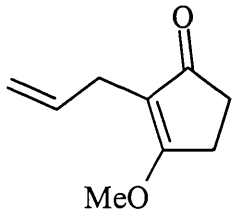
[‡] The commercially bought greenish-yellow Pd dimer was purified by dissolving in a small quantity of CH_2Cl_2 and refluxing gently with a heat gun. This solution was then passed through a small column of silica which was rinsed several times with CH_2Cl_2. The combined washings were then evaporated to give a bright yellow solid.

mixture was chromatographed (silica, 98:2 CH_2Cl_2:MeOH) to isolate allylated cyclopentanedione **4.3** as an off-white solid which was recrystallised from hot EtOAc as shiny white needles (1.19 g, 86%). Mp 152.9-153.3 °C; R_f (95:5 CH_2Cl_2:MeOH): 0.27, ν_{max} (KBr)/cm^{-1}: 3414 (w, OH), 3077 (=CH), 2970 and 2929 (CH), 2400 (broad, strong), 1868 (broad, strong), 1675 (C=O), 1640 (C=C); δ_H (270 MHz, CD_3OD): 2.58 (4H, s, CH_2CH_2CO), 2.92 (2H, d, *J* 6.0 Hz, CH_2=CHCH_2C), 4.99-5.08 (2H, m, CH_2=CHCH_2C), 5.10 (1H, broad s, OH), 5.87 (1H, ddt, *J* 6.0, 10.0 and 17.2 Hz, CH_2=C*H*CH_2C); δ_C (270 MHz, CD_3OD): 26.2 (CH_2, CH_2CO), 31.5 (CH_2), 115.1 (=CH_2), 116.6 (quaternary), 136.4 (=CH), 199.2 (quaternary, CO); *m/z* (EI): 138 (100%, M^+), 95 (47), ($C_8H_{10}O_2$ requires *M*, 138.0681. Found: M^+, 138.0680); ($C_8H_{10}O_2$ requires C, 69.5; H, 7.3%. Found: C, 69.3; H, 7.3%).

The reaction was repeated on large scale using stoichiometric amounts of allyl acetate and cyclopentanedione using essentially the same procedure as above: $[Pd(C_3H_5)Cl]_2$ (1.05 g, 2.87 mmol, 2 mol%), dppe (4.6 g, 11.5 mmol, 8 mol%), allyl acetate (14.8 mL, 0.138 mol), 1,3-cyclopentanedione (14 g, 0.138 mol), BSA (34.1 mL, 0.138 mol) and NaOAc (0.55 g, 2.87 mmol, 2 mol%) in THF (300 mL). The mixture was refluxed for 24 h, after which it was cooled, diluted with MeOH (170 mL) and stirred for 15 min. A precipitate did not form. Solvent was evaporated and the resulting solid was titurated with EtOAc to give white needles (5.5 g). The supernatant was titurated again and stored in the fridge overnight to give a second crop of white crystals (7.6 g). The residual supernatant was diluted with MeOH and pre-adsorbed onto silica. Chromatography (silica, 98:2 CH_2Cl_2:MeOH) of the pre-adsorbed material gave more allylated product as an off-white solid (5.4 g). Total yield: 97%.

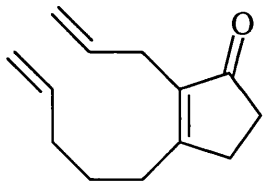
2-Allyl-3-methoxy-2-cyclopenten-1-one, 4.3.[74]



4.3

Conc. H_2SO_4 (4 mL) was added to a solution of 2-allyl-1,3-cyclopentanedione (10.0 g, 0.07 mol) and $(MeO)_3CH$ (45.9 mL, 0.42 mol) in MeOH (140 mL). The mixture was refluxed for 1 h and after cooling, most of the MeOH was carefully removed under vacuum. The residue was brought to pH 8 with saturated sodium hydrogencarbonate solution and extracted with Et_2O (6 × 200 mL). The combined extracts were dried (Na_2SO_4) and solvent removed under reduced pressure. The residual brown oil was flushed quickly with Et_2O through a column of silica, basified with Et_3N, to afford the methyl enol ether **4.3** as a yellow brown oil (7.1 g, 64.5%) which was stored under an atmosphere of nitrogen in the frigde. R_f (Et_2O): 0.12; ν_{max} (film)/cm^{-1}: 3483 (w), 3078 (=CH), 2952 (CH), 1686 (C=O), 1625 (C=C), 1360 (s), 1261 (s); δ_H (400 MHz, $CDCl_3$): 2.45-2.47 (2H, m, CH_2), 2.68 (2H, t, *J* 4.6 Hz, CH_2), 2.90 (2H, d, *J* 6.4 Hz, H_2C=CHCH_2C), 3.96 (3H, s, OMe), 4.93-5.03 (2H, m, CH_2CH=CH_2), 5.83 (1H, ddt, *J* 6.3, 10.0 and 17.1 Hz, CH_2CH=CH_2); δ_C (400 MHz, $CDCl_3$): 24.6 (CH_2), 25.5 (CH_2), 33.3 (CH_2), 56.4 (CH_3), 114.7 (=CH_2), 118.0 (quaternary), 134.9 (=CH), 184.9 (quaternary), 204.2 (quaternary); *m/z* (EI): 152 (100%, M^+), 137 (47, M^+ - Me), 95 (43), 43 (44), ($C_9H_{12}O_2$ requires *M*, 152.0837. Found: M^+, 152.0833).

2-Allyl-3-(4-pentenyl)-2-cyclopenten-1-one, 4.4.



4.4

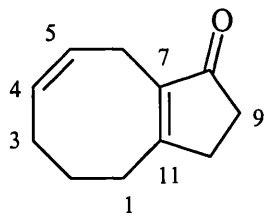
Magnesium turnings (84 mg, 3.4 mmol) in a 3-necked, 25 mL round bottom flask equipped with a nitrogen line and water condenser, were mechanically stirred under nitrogen for 2 h and then suspended in dry Et_2O (7 mL). Bromopentene (0.39 mL, 3.28 mmol) was then added dropwise. Initially, ~ 0.1 mL was added and the mixture gently refluxed for about 5 min, after which the reflux was maintained simply by the addition of more bromopentene. After the addition was complete, the reagent mixture was stirred at room temperature for 15 min, cooled to 0 °C, and a solution of methylenol ether **4.3** (0.25 g, 1.6 mmol) was added dropwise. The resulting yellow-brown suspension was stirred at room temperature for 8 h, then quenched very carefully with 2 M HCl (10 mL) solution and stirred at room temperature for a further 30 min. The mixture was poured into water and extracted with Et_2O (4 × 15 mL). The extract was dried (Na_2SO_4), solvent evaporated under reduced pressure and residue chromatographed (silica, CH_2Cl_2) to afford the triene **4.4** as a yellow oil (0.19 g, 62.4%). R_f (9:1 CH_2Cl_2): 0.2; ν_{max} (film)/cm^{-1}: 3078 (=CH), 2928 (CH), 1698 (CO), 1641 (C=C); δ_H (400 MHz, $CDCl_3$): 1.59-1.71 (2H, m, CH_2), 2.07-2.16 (2H, m), 2.39-2.41 (2H, m), 2.44 (2H, t, *J* 7.8 Hz), 2.53 (2H, t, *J* 4.6 Hz), 2.95 (2H, d, *J* 6.4 Hz, H_2C=CHC*H*$_2$C), 4.95-5.07 (4H, m, CH_2CH=C*H*$_2$), 5.72-5.85 (2H, m, CH_2CH=CH_2); δ_C (400 MHz, $CDCl_3$): 26.5 (CH_2), 27.3 (CH_2), 29.2 (CH_2), 30.6 (CH_2), 33.6 (CH_2), 34.2 (CH_2), 115.2 (=CH_2), 115.4 (=CH_2), 134.9 (=CH), 137.7

CH_2CH=CH_2); δ_C (400 MHz, $CDCl_3$): 26.5 (CH_2), 27.3 (CH_2), 29.2 (CH_2), 30.6

(=CH), 138.0 (quaternary), 174.8 (quaternary), 209.2 (quaternary, CO); *m/z* (FAB): 191 (100%, M^+ + H), ($C_{13}H_{18}O$ requires *M* + *H*, 191.1436. Found: M^+ + H, 191.1439).

The reaction was repeated on large scale using 7g of methylenol ether.

Bicyclo-[6.3.0]-undecane, 4.5.[85]

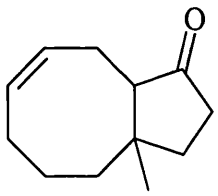


4.5

Note: Preparation[89] **of silver nitrate-impregnated silica for the chromatographic separation of monocyclic and bicyclic compounds from RCM reaction:** Reagents, silica, MeCN and $AgNO_3$, were used in a ratio of 3:3:1, w:v:w, respectively. A solution of $AgNO_3$ (for example, 5 g) in MeCN (15 mL) was added to silica (15 g). The moist silica was mixed thoroughly for 5 min, the vessel covered with aluminium foil and dried in a hot oven (70 °C) for 4 h. The dry, silver-doped silica was stored in a dark place. **Preparation of silver nitrate-impregnated silica TLC plates:** Reagent ratio was $AgNO_3$:MeCN, 1:3 w:v. Glass-backed silica TLC plates, cut to appropriate sizes, were soaked in a solution of $AgNO_3$ (for example, 1 g) in MeCN (3 mL) for 5 min and then dried in a hot oven for 5-10 min. The dry, silver-doped plates were covered in aluminium foil and stored in the dark. Compounds on the TLC plate were observed using PMA stain and then heating.

A solution of $RuCl_2(=CHPh)(PCy_3)_2$ (95 mg, 0.115 mmol, 10 mol%) in dry, degassed CH_2Cl_2 (0.5 mL plus 0.25 × 2 mL for rinses), was added via cannula to a solution of triene **4.4** (0.22 g, 1.15 mmol) in dry, degassed CH_2Cl_2 (114 mL). The reaction flask was placed in an oil bath and the light purple solution (0.01 M) refluxed for 72 h. The solvent was removed under reduced pressure and the dark residue was chromatographed (silica, 92:8 petroleum ether:Et_2O) to afford a mixture of monocycle and bicycle as an oil (yield: 97 mg; ratio monocycle:bicycle 8:92); R_f (8:2 petroleum ether:Et_2O): 0.11). The mixture of compounds was separated by further chromatography (1 × 10 cm silver-doped silica column) using 1:1 petroleum ether:Et_2O as eluent to isolate the bicycle **4.5** as a pale yellow oil (83 mg, 44.5%) and Et_2O as eluent to recover unreacted triene (6 mg, 2.7%); R_f (Et_2O, silver-doped silica TLC plate): bicycle 0.68, monocycle 0.42. Bicycle **4.5**: ν_{max} (film)/cm^{-1}: 3015 (=CH), 2934 (CH), 1697 (C=O), 1640 (C=C); δ_H (400 MHz, $CDCl_3$): 1.61-1.67 (2H, m, H_2), 2.09-2.17 (2H, m, H_3), 2.35-2.38 (2H, m, H_9), 2.46-2.49 (2H, m, H_{10}), 2.62 (2H, t, *J* 6.2 Hz, H_1), 2.98 (2H, dd, *J* 1.9 and 5.0 Hz, H_6), 5.43-5.51 (1H, m, H_4), 5.77 (1H, quintet, *J* 5.4 Hz, H_5); δ_C (400 MHz, $CDCl_3$): 22.3 (C_2, CH_2), 24.3 (C_6, CH_2), 25.5 (C_3, CH_2), 29.2 (C_1, CH_2), 31.6 (C_{10}, CH_2), 34.2 (C_9, CH_2), 127.9 (C_5, =CH), 128.6 (C_4, =CH), 140.2 (C_{11}, quaternary), 172.6 (C_7, quaternary), 209.1 (C_8, quaternary); *m/z* (FAB): 325 (7%, $2M^+ + H$), 163 (100%, $M^+ + H$), ($C_{11}H_{14}O$ requires *M* + *H*, 163.1123. Found: $M^+ + H$, 163.1127).

Methylated bicycle 4.6.



4.6

Method A[95]

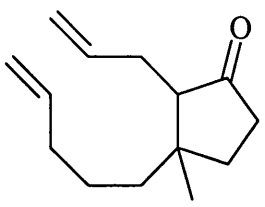
MeLi (0.37 mL of a 1.5 M solution in Et_2O, 0.55 mmol) was added dropwise to a stirred suspension of CuI (105 mg, 0.55 mmol) in Et_2O (0.6 mL) under nitrogen at -40 °C. After stirring at this temperature for 5 min, the yellow slurry was cooled to -78 °C and $BF_3.Et_2O$ (71 μL, 0.57 mmol) was added. The thick, deep-yellow slurry was stirred for a further 5 min before the dropwise addition of a solution of pre-dried (with a couple of 4Å molecular sieve pellets) enone **4.5** (30 mg, 0.18 mmol) in Et_2O (0.2 mL plus 0.1 × 2 mL for rinses). The mixture was stirred at -78 °C for 5 h, quenched with saturated NH_4Cl solution, the phases separated and the aqueous re-extracted with Et_2O (5 × 2 mL). The combined organic extracts were dried (Na_2SO_4), solvent evaporated under reduced pressure and residue chromatographed (silica). Elution with 99:1 petroleum ether:Et_2O afforded the addition product **4.6** as a yellow oil (17 mg, 53%) and with 92:8 petroleum ether:Et_2O, the unreacted enone **4.5** (13 mg, 43.3%). The addition product was isolated as a mixture of isomers with a de of 42% by ^1H NMR and 30% by chiral GC. R_f (9:1 petroleum ether:Et_2O): 0.48; ν_{max} (film)/cm^{-1}: 3015 (=CH), 2933 (CH), 1739 (C=O); δ_H (270 MHz, $CDCl_3$): 0.91 (Me, minor - 29%, s), 1.14 (Me, major - 71%, s), 1.34-1.61 (2H, m), 1.63-1.86 (5H, m), 1.93-2.17 (1H, m), 2.20-2.49 (5H, m, CHC=CHCH_2C*H*COCH_2), 5.54-5.60 (1H, m,

C*H*C=CHCH$_2$CHCO), 5.70-5.76 (1H, m, CHC=C*H*CH$_2$CHCO); δ_C (270 MHz, $CDCl_3$): (major isomer) 20.3 (CH_2), 24.6 (CH_2), 24.7 (CH_2), 25.3 (CH_3), 33.8 (CH_2), 34.4 (CH_2), 38.3 (CH_2), 42.3 (quaternary), 59.7 (CH), 128.2 (=CH), 129.4 (=CH), 221.9 (quaternary, C=O), (minor isomer) 16.8 (CH_3), 24.5 (CH_2), 25.0 (CH_2), 26.6 (CH_2), 34.3 (CH_2), 36.7 (CH_2), 37.7 (CH_2), 42.1 (quaternary), 63.9 (CH), 129.2 (=CH), 130.7 (=CH), 217.6 (quaternary, C=O); *m/z* (EI): 178 (100%, M^+), 163 (54, M^+ - Me), ($C_{12}H_{18}O$ requires *M*, 178.1358. Found: M^+, 178.1356); GC (155 °C, 2 mg/mL): retention time (% area), 38.47 (3.415), 38.92 (3.435), 39.49 (1.847), 40.38 (1.801).

Method B[91]

The same procedure as for the monocyclic enone was followed using $CuBrMe_2S$ (8 mg, 0.036 mmol), MeMgBr (0.1 mL of a 2.5 M solution in Et_2O, 0.25 mmol) in THF (0.7 mL), DMPU (54 μl, 0.44 mmol), a mixture of enone **4.5** (30 mg, 0.18 mmol) and TMSCl (46 μL, 0.36 mmol) in THF (0.2 mL plus 0.1 × 2 mL for rinses) to generate the methyl addition product **4.6** (16 mg, 48.5%, 44% de). A small amount of starting enone was also recovered (1 mg, 3.3%).

2-Allyl-3-methyl-3-(4-pentenyl)-2-cyclopentanone, 4.13.[91]

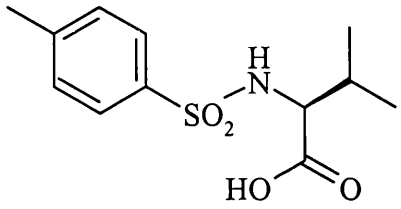


4.13

$CuBrMe_2S$ (0.21 g, 1 mmol) was added in one portion to a stirred solution of MeMgBr (2.9 mL of a 2.5 M solution in Et_2O, 7.3 mmol) in THF (20 mL) under nitrogen at -78 °C, followed by a slow dropwise addition of DMPU (1.5 mL, 12.6 mmol). The cream, gelatinous mixture was stirred at -78 °C for 5 min and then submerged in an ice-bath for 15 min. During this time the mixture became more mobile and translucent. It was then cooled down to -78 °C and after 10 min, a mixture of enone **4.4** (1 g, 5.2 mmol) and TMSCl (1.3 mL, 10.5 mmol) in THF (4 mL) was added slowly, dropwise. The yellow suspension was stirred at -78 °C for 6 h, quenched with saturated ammonium chloride solution and the phases separated. The aqueous phase was re-extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were dried (Na_2SO_4), solvent evaporated under reduced pressure and the residue chromatographed (silica, 98:2 petroleum ether:Et_2O) to afford the 1,4-addition product **4.13** (0.6 g, 56.2%) as a yellow oil in a mixture of isomers - de 31% by ^1H NMR; [Some starting enone **4.4**, was also recovered (eluent: 9:1 petroleum ether:Et_2O; yield: 0.117 g, 11.7%).] R_f (9:1 petroleum ether:Et_2O): 0.4; ν_{max} (film)/cm^{-1}: 3076 (=CH), 2932 (CH), 1739 (C=O), 1640 (C=C); δ_H (270 MHz, $CDCl_3$): 0.83 (Me, major isomer - 65.5%, s), 1.12 (Me, minor isomer - 34.5%, s), 1.25-1.56 (4H, m), 1.59-1.75 (2H, m), 1.94-2.10 (5H, m), 2.14-2.33 (1H, m), 2.35-2.41 (1H, m), 4.95-5.09 (4H, m, H_2C=), 5.72-5.99 (2H, m, H_2C=C*H*CH_2); δ_C (270 MHz, $CDCl_3$): (major isomer) 19.7 (CH_3), 23.3 (CH_2), 29.2 (CH_2), 32.6 (CH_2), 34.2 (CH_2), 34.7 (CH_2), 40.9 (CH_2), 42.3 (quaternary), 58.9 (CH), 114.6 (=CH_2), 115.4 (=CH_2), 137.4 (=CH), 138.7 (=CH), 219.6 (quaternary), (minor isomer) 23.5 (CH_2), 26.2 (CH_3), 28.9 (CH_2), 31.5 (CH_2), 33.3 (CH_2), 34.3 (CH_2), 34.8 (CH_2), 42.0 (quaternary), 61.1 (CH), 114.7 (=CH_2), 115.5 (=CH_2), 137.3 (=CH), 138.4 (=CH);

m/z (EI): 206 (11%, M^+), 191 (6, M^+ - Me), 137 (47, M^+ - pentenyl), 96 (100), ($C_{14}H_{22}O$ requires *M*, 206.1671. Found: M^+, 206.1667).

N-[(4-methylphenyl)sulfonyl]valine 4.21.[107]

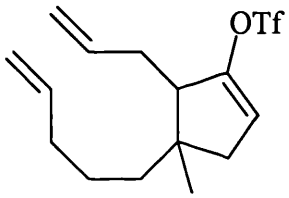


4.21

p-Toluenesulfonyl chloride (1.63 g, 8.5 mmol) in Et_2O (18 mL) was added to a stirred solution of D-valine (1 g, 8.5 mmol) in aqueous NaOH (18 mL of a 1 M solution). The bi-phasic mixture was stirred vigorously at room temperature for 6 h, after which the phases were separated. The aqueous was washed with Et_2O (2 × 50 mL), acidified with 2 M HCl solution to pH 3 and the white suspension extracted with Et_2O (3 × 50 mL). The acidification, extraction process was repeated until no white precipitate formed on addition of acid. The combined organic extracts were dried ($MgSO_4$), solvent evaporated under reduced pressure and the residual white solid recrystallised from the minimum amount (~ 5 mL) of aqueous EtOH (60%) to generate the valine tosylate **4.21** as shiny, white platelets (1.2 g, 52.1%); ν_{max} (KBr)/cm^{-1}: 3292 (amide NH), 2972 (CH), 1705 (C=O), 1331 and 1161 (-SO_2-N); δ_H (270 MHz, $CDCl_3$): 0.85 (3H, d, *J* 6.8 Hz, *i*-Pr), 0.94 (3H, d, *J* 6.8 Hz, *i*-Pr), 2.03-2.17 (1H, m, -CHC*H*(CH_3)$_2$), 2.4 (3H, s, CH_3-Ph), 3.77 (1H, dd, *J* 4.7 and 9.9 Hz, NHC*H*(*i*-Pr)(CO_2H), 5.38 (1H, d, *J* 9.7 Hz, NH), 7.28 (2H, d, *J* 8.1 Hz, aryl), 7.71 (2H, d, *J* 8.4 Hz, aryl), 8.85 (1H, broad s, OH); δ_C (270 MHz, $CDCl_3$): 17.1 (CH_3, *i*-

Pr), 18.9 (CH_3, *i*-Pr), 21.4 (CH, *i*-Pr), 31.3 (CH_3, Me-Ph), 60.6 (CH), 127.2 (CH, aryl), 129.5 (CH, aryl), 136.5 (quaternary, aryl), 143.8 (quaternary, aryl), 176.3 (quaternary, C=O); *m/z* (FAB): 543 (12%, $2M^+ + H$), 294 (42, $M^+ + Na$), 272 (99, $M^+ + H$), 226 (100, $M^+ - CO_2H$), ($C_{12}H_{17}NO_4S$ requires *M* + *H*, 272.0957. Found: $M^+ + H$, 272.0955); ($C_{12}H_{17}NO_4S$ requires C, 53.1; H, 6.3; N, 5.2%. Found: C, 52.9; H, 6.4; N, 5.3%).

5-Allyl-4-methyl-4-(4-pentenyl)-1-cyclopenten-1-yl trifluoromethanesulfonate, 4.22.[64]

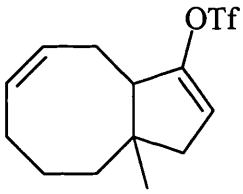


4.22

A cold (-78 °C) solution of ketone **4.13** (0.3 g, 1.45 mmol) in THF (3.0 mL plus 0.2 mL for rinses) was transferred via cannula into a reaction flask containing LDA (0.79 mL of a 2.0 M solution in hexane and THF, 1.6 mmol) in THF (3.2 mL) under nitrogen at -78 °C. After stirring for 1.5 h, a cold (-20 °C) solution of N-phenyltrifluoromethanesulfonimide (0.57 g, 1.6 mmol) in THF (3.0 mL plus 0.2 mL for rinses) was added to the mixture. This was allowed to warm up slowly to room temperature and stirred overnight. The reaction mixture was then directly pre-adsorbed onto silica and chromatographed (silica basified with Et_3N, petroleum ether) to afford the vinyl triflate **4.22** as a colourless oil (0.33 g, 66.4%) as mixture of isomers with a de of 41% by ^1H NMR spectrum. [Some ketone **4.13**, was also recovered (eluent: 99:1 petroleum ether:Et_2O; yield: 96 mg, 32%).] R_f (98:2

petroleum ether:Et_2O): 0.25; ν_{max} (film)/cm^{-1}: 3079 (=CH), 2932 (CH), 1421 and 1210 (-SO_2-O-); δ_H (270 MHz, $CDCl_3$): 1.02 (Me, major, s), 1.10 (Me, minor, s), 1.31-1.50 (4H, m), 1.95-2.08 (3H, m), 2.17-2.34 (3H, m), 2.37-2.44 (m) and 2.55-2.63 (m) (1H, ratio of 2:1), 4.94-5.13 (4H, m, 2 × H_2C=CHCH_2), 5.57-5.59 (1H, m, C*H*=C(OTf)), 5.72-5.87 (2H, m, 2 × H_2C=C*H*CH_2); δ_C (400 MHz, $CDCl_3$): (major isomer) 22.3 (CH_3), 24.1 (CH_2), 32.7 (CH_2), 34.6 (CH_2), 41.1 (CH_2), 42.3 (CH_2), 43.9 (quaternary), 51.6 (CH), 114.8 (=CH_2), 115.7 (CH, TfOC=CH) 116.9 (=CH_2), 136.3 (=CH), 138.8 (=CH), 150.6 (quaternary); (minor isomer) 24.5 (CH_2), 27.7 (CH_3), 33.4 (CH_2), 34.8 (CH_2), 36.6 (CH_2), 40.4 (CH_2), 43.5 (quaternary), 53.8 (CH), 114.9 (=CH_2), 116.1 (CH, TfOC=CH), 117.1 (=CH_2), 135.9 (=CH), 138.7 (=CH), 151.8 (quaternary); δ_F (400 MHz, $CDCl_3$), -74.0 (CF_3, major isomer), -73.9 (CF_3, minor isomer); *m/z* (EI): 338 (25%, M^+), 323 (14, M^+ - Me), 297 (65, M^+ - allyl), 269 (100, M^+ - pentenyl), ($C_{15}H_{21}F_3O_3S$ requires *M*, 338.1164. Found: M^+, 338.1155).

Bicyclic vinyl triflate 4.7.[64]

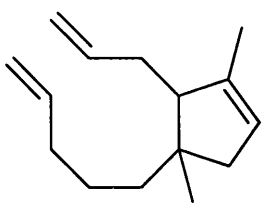


4.7

A cold (-78 °C) solution of ketone **4.6** (64 mg, 0.36 mmol) in THF (0.7 mL plus 0.2 mL for rinses) was transferred via cannula into a reaction flask containing LDA (0.56 mL of a 1.6 M solution in hexane and THF, 0.89 mmol) in THF (1.6 mL) under nitrogen at -78 °C. After stirring for 30 min, DMPU (0.14 mL, 1.07 mmol) was

added, the mixture stirred for a further 15 min and a cold (-20 °C) solution of N-phenyltrifluoromethanesulfonimide (0.64 g, 1.79 mmol) in THF (3.0 mL plus 0.2 mL for rinses) was introduced. The reaction mixture was allowed to warm up slowly to room temperature, stir overnight and then directly pre-adsorbed onto silica and chromatographed (silica basified with Et_3N, petroleum ether) to afford the vinyl triflate **4.7** as a colourless oil (64 mg, 57.5%, de: 78% from ^1H NMR spectrum). [Further elution of the column with 99.5:0.5 petroleum ether:Et_2O, isolated a UV active impurity, and with 99:1 petroleum ether:Et_2O gave the unreacted ketone (10 mg, 15.6%, de: 30% ^1H NMR spectrum).] R_f (98:2 petroleum ether:Et_2O): 0.5, ν_{max} (film)/cm^{-1}: 3012 (=CH), 2936 (CH), 1661 (C=C), 1422 and 1209 (-SO_2-O-), 1142 (s); δ_H (400 MHz, $CDCl_3$): 1.06 (Me, minor, s), 1.17 (Me, major, s), 1.35-1.48 (2H, m), 1.71-1.91 (2H, m), 1.96 (2H, dd, *J* 3.2 and 16.1 Hz), 2.06 (1H, dd, *J* 12.1 and 18.3 Hz), 2.20-2.32 (2H, m), 2.43 (1H, d, *J* 18.2 Hz), 2.75 (1H, dt, *J* 2.3 and 12.0 Hz), 5.51 (1H, t, *J* 2.6 Hz, C(OTf)=C*H*), 5.55-5.58 (2H, m, C*H*=C*H*); δ_C (400 MHz, $CDCl_3$): 24.1 (CH_2), 25.7 (CH_2), 26.3 (CH_3), 26.7 (CH_3), 30.8 (CH_2), 33.4 (CH_2), 42.5 (CH_2), 43.9 (quaternary), 52.3 (CH), 114.4 (C(OTf)=*C*H), 127.0 (=CH), 129.1 (=CH), 152.9 (quaternary); δ_F (400 MHz, $CDCl_3$): -74.1 (CF_3, minor), -74.0 (CF_3, major); *m/z* (EI): 310 (14%, M^+), 160 (53, M^+ - CF_3SO_3H), 55 (100), ($C_{13}H_{17}F_3O_3S$ requires *M*, 310.0851. Found: M^+, 310.0843).

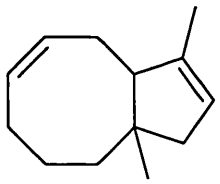
5-Allyl-1,4-dimethyl-4-(4-pentenyl)-2-cyclopentene, 4.23.



4.23

A solution of vinyl triflate **4.22** (34 mg, 0.1 mmol) and $Pd(PPh_3)_4$ (11 mg, 0.01 mmol) in THF (1 mL) was stirred for 5 min at room temperature under nitrogen. MeMgBr (0.12 mL of a 2.5 M solution in Et_2O, 0.3 mmol) was introduced and the mixture refluxed for 1 h. The mixture was cooled and pre-adsorbed directly on to silica. The pre-adsorbed material was chromatographed (silica, petroleum ether) to afford the coupled product **4.23** as a colourless oil (17 mg, 83.3%) in a mixture of isomers - 38% de by ^1H NMR spectrum. R_f (petroleum ether): 0.78; ν_{max} (film)/cm^{-1}: 3075 (=CH), 2929 (CH), 1639 (C=C), 908 (s); δ_H (270 MHz, $CDCl_3$): 0.92 (Me, major, s), 0.98 (Me, minor, s), 1.25-1.38 (4H, m), 1.65 (3H, broad s, =CMe), 1.8-2.09 (4H, m), 2.08-2.21 (3H, m), 4.91-5.06 (4H, m, 2 × H_2C=CHCH$_2$), 5.24 (1H, s, C*H*=CMeCH), 5.76-5.89 (2H, m, 2 × H_2C=C*H*CH$_2$); δ_C (270 MHz, $CDCl_3$): (major isomer) 16.1 (CH_3), 21.8 (=CCH_3), 24.4 (CH_2), 33.2 (CH_2), 34.6 (CH_2), 42.4 (CH_2), 44.9 (CH_2), 45.0 or 45.2 (quaternary), 55.5 (=CH), 114.1 (=CH_2), 114.93 (=CH_2), 123.3 (=CH, CH=CMe), 139.0 (=CH, CH=CH_2), 139.2 (=CH, CH=CH_2), 141.9 (quaternary), (minor isomer) 16.4 (CH_3), 24.8 (CH_2), 27.6 (=CCH_3), 33.4 (CH_2), 34.8 (CH_2), 36.5 (CH_2), 44.3 (CH_2), 45.0 or 45.2 (quaternary), 57.6 (CH), 114.2 (=CH_2), 114.9 (=CH_2), 123.1 (=CH, CH=CMe), 139.2 (=CH, CH=CH_2), 139.4 (=CH, CH=CH_2), 142.6 (quaternary); *m/z* (EI): 204 (6%, M^+), 163 (100, M^+ - allyl), 135 (36, M^+ - pentenyl), ($C_{15}H_{24}$ requires *M*, 204.1878. Found: M^+, 204.1858).

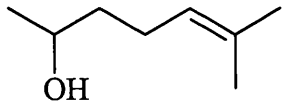
Methyl-coupled bicycle 4.24.



4.24

A solution of vinyl triflate **4.7** (14 mg, 0.045 mmol) and $Pd(PPh_3)_4$ (5 mg, 4.5 μmol) in THF (1 mL) was stirred for 5 min at room temperature under nitrogen. MeMgBr (52 μL of a 2.6 M solution in Et_2O, 0.13 mmol) was introduced and the mixture refluxed for 2 h. The mixture was cooled and pre-adsorbed directly on to silica. The pre-adsorbed material was chromatographed (silica, pentane) to afford the coupled product **4.24** as a colourless oil (5 mg, 63%; de: 57% by ^1H NMR spectrum and 52% by chiral GC) [Some starting vinyl triflate was also recovered (1 mg, 7%).] R_f (pentane): 0.82; ν_{max} (film)/cm^{-1}: 3003 (=CH), 2929 (CH), 1659 (C=C), 1453; δ_H (400 MHz, $CDCl_3$): 0.96 (Me, minor, s), 1.03 (Me, major, s), 1.34-1.46 (2H, m), 1.62 (=CMe, minor, s), 1.67 (=CMe, major, s), 1.69-1.96 (4H, m), 2.00-2.37 (3H, m), 2.4 (2H, d, *J* 11.7 Hz), 5.15 (1H, s, C*H*=CMe, major), 5.22 (1H, s, C*H*=CMe, minor), 5.47-5.61 (2H, m, C*H*=C*H*); δ_C (270 MHz, $CDCl_3$): 15.6 (CH_3, minor), 15.8 (CH_3, major), 23.9 (CH_2), 25.7 (CH_2), 26.5 (=CCH_3, minor), 29.7 (CH_2), 32.8 (CH_2), 34.1 (=CCH_3, major), 45.4 (quaternary), 46.8 (CH_2), 55.9 (CH), 121.4 (=CH), 126.1 (=CH), 131.0 (=CH), 144.7 (quaternary); *m/z* (EI): 176 (48%, M^+), 161 (64, M^+ - Me), 107 (100), ($C_{13}H_{20}$ requires *M*, 176.1565. Found: M^+, 176.1562); GC (120 °C, 2 mg/mL in CH_2Cl_2): retention time (% area), 37.01 (2.238), 37.89 (2.230), 47.41 (0.688), 49.8 (0.689).

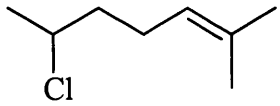
6-Methyl-5-hepten-2-ol, 4.26.



4.26

Sodium borohydride (2.25 g, 59.4 mmol) was added in portions to a cooled (cold water bath), stirred solution of 6-methyl-5-hepten-2-one (5 g, 39.6 mmol) in methanol (80 mL). After the addition was complete, the cooling bath was removed and the mixture stirred at room temperature for 1 h. The white suspension was carefully neutralised and taken to pH 2 with 2 M HCl solution. Most of the solvent was removed under reduced pressure and the concentrated suspension partitioned between water (150 mL) and CH_2Cl_2 (75 mL). The phases were separated, the aqueous re-extracted with CH_2Cl_2 (3 × 200 mL), the combined extracts dried ($MgSO_4$) and solvent evaporated under reduced pressure. The residue was chromatographed (silica, 9:1 petroleum ether:Et_2O) to afford the alcohol **4.26** as a sweet smelling, pale yellow oil (4.6 g, 91.8%). R_f (8:2 petroleum ether:Et_2O): 0.14; ν_{max} (film)/cm^{-1}: 3348 (strong OH), 2923 (CH), 1672 (C=C), 1450 (s), 1175 (s), 1127 (s), 1070 (s); δ_H (270 MHz, $CDCl_3$): 1.18 (3H, d, *J* 6.2 Hz, CH_3CH(OH)), 1.43-1.52 (2H, m, $CH_3CH(OH)CH_2$), 1.62 (3H, s, $(CH_3)_2C$=C), 1.69 (3H, d, *J* 1.2 Hz, $(CH_3)_2C$=C), 1.88 (1H, broad s, OH), 2.04-2.08 (2H, m, $(CH_3)_2C$=$CHCH_2$), 3.74-3.86 (1H, apparent sextet, *J* 6.2 Hz, CH_3CH(OH)), 5.13 (1H, split t, *J* 5.9 Hz, $(CH_3)_2C$=$CHCH_2$); δ_C (270 MHz, $CDCl_3$): 17.5 (CH_3), 23.3 (=CCH_3), 24.4 (CH_2), 25.6 (=CCH_3), 39.1 (CH_2), 67.7 (CH), 124.0 (=CH), 131.8 (quaternary); *m/z* (EI): 128 (10%, M^+), 110 (37, M^+ - H_2O), 95 (100) ($C_8H_{16}O$ requires *M*, 128.1201. Found: M^+, 128.1202).

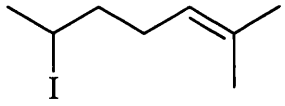
6-Chloro-2-methylhept-2-ene, 4.27.[112]



4.27

Triphenylphosphine (15.9 g, 60.8 mmol) was added to a stirred solution of the heptenol **4.26** (2.5 g, 20.2 mmol) in anhydrous THF (200 mL), at room temperature under nitrogen. When dissolution was complete, anhydrous zinc chloride (3.3 g, 24.3 mmol) was added in one portion, followed by diethyl azodicarboxylate (9.5 mL, 60.8 mmol) and the mixture was stirred overnight at room temperature. Et_2O (wet, 50 mL) was then added to the resulting suspension, stirred for a further 0.5 h and the solids filtered by passing through celite which was washed several times with more Et_2O. The combined filtrate was concentrated, the residue pre-adsorbed onto silica and chromatographed (silica, pentane) to yield the heptenyl chloride **4.27** as a colourless, volatile oil (2.25 g, 76%). R_f (pentane): 0.6; ν_{max} (film)/cm^{-1}: 2969 and 2928 (CH), 1673 (C=C), 1445 (s), 1378 (s); δ_H (270 MHz, $CDCl_3$): 1.50 (3H, d, *J* 6.6 Hz, $CH_3CH(Cl)$), 1.63 (3H, s, $(CH_3)_2C=C$), 1.69 (3H, d, *J* 1.1 Hz, $(CH_3)_2C=C$), 1.67-1.77 (2H, m, $CH_3CH(Cl)CH_2$), 2.11-2.19 (2H, m, $(CH_3)_2C=CHCH_2$), 3.95-4.08 (1H, apparent sextet, *J* 6.6 Hz,, $CH_3CH(Cl)$), 5.07 (1H, split t, *J* 5.9 Hz, $(CH_3)_2C=CHCH_2$); δ_C (270 MHz, $CDCl_3$): 17.6 (CH_3), 25.2 (CH_2), 25.3 ($=CCH_3$), 25.7 ($=CCH_3$), 40.3 (CH_2), 58.3 (CH), 122.9 (=CH), 132.6 (quaternary); *m/z* (EI): 148 (9%, M^+, ^{37}Cl), 146 (27%, M^+,^{35}Cl), 110 (14, M^+ - HCl), 69 (100, $(CH_3)_2C=CHCH_2$), ($C_8H_{15}{}^{35}Cl$ requires *M*, 146.0862. Found: M^+, 146.0857), ($C_8H_{15}{}^{37}Cl$ requires *M*, 148.0833. Found: M^+, 148.0829).

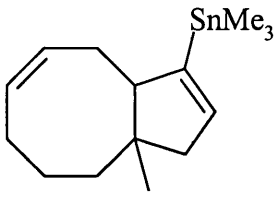
6-Iodo-2-methylhept-2-ene, 4.29.[112]



4.29

The similar protocol to the one in the preceding synthesis of heptenyl chloride **4.27** was followed. Triphenylphosphine (2.4 g, 9.36 mmol), heptenol **4.26** (0.4 g, 3.12 mmol), anhydrous zinc iodide (1.2 g, 3.74 mmol) and diethyl azodicarboxylate (1.47 mL - from a very old reagent bottle, 9.36 mmol) in anhydrous THF (30 mL) were reacted to afford the hetenyl iodide **4.29** as a colourless oil (67 mg, 9.0%). The starting alcohol, **4.26** was also recovered (287 mg, 71.8%). Heptenyl iodide: R_f (pentane): 0.7; ν_{max} (film)/cm^{-1}: 3384 (w), 2964 and 2914 (CH), 1673 (=CH), 1444 (s), 1376 (s); δ_H (400 MHz, $CDCl_3$): 1.55-1.63 (1H, m, $CH_3CH(I)CHH$), 1.64 (3H, s, $(CH_3)_2C=C$), 1.68 (3H, s, $(CH_3)_2C=C$), 1.83-1.90 (1H, m, $CH_3CH(I)CHH$), 1.92 (3H, d, *J* 6.6 Hz, $CH_3CH(I)$), 2.02-2.18 (2H, m, $(CH_3)_2C=CHCH_2$), 4.14-4.20 (1H, m, $CH_3CH(I)CH_2$), 5.06 (1H, split t, *J* 7.2 Hz, $(CH_3)_2C=CHCH_2$); δ_C (400 MHz, $CDCl_3$): 18.3 (CH_3), 26.1 ($=CCH_3$), 28.6 (CH_2), 29.3 ($=CCH_3$), 30.7 (CH), 43.3 (CH_2), 122.7 (=CH), 133.0 (quaternary); *m/z* (EI): 238 (44%, M^+), 111 (32, M^+ - I), 69 (100, $(CH_3)_2C=CHCH_2$), ($C_8H_{15}I$ requires *M*, 238.0219. Found: M^+, 238.0213).

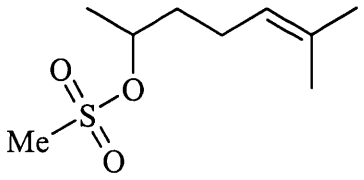
Vinyl stannane 4.30.[115]



4.30

A mixture of vinyl triflate **4.7** (12 mg, 0.038 mmol), lithium chloride (10.4 mg, 2.46 mmol), $Pd(PPh_3)_4$ (1 mg, 0.7 μmol), hexamethylditin (11.5 mg, 0.035 mmol) and THF (1.2 mL) was deoxygenated for 10 min by bubbling nitrogen through and then heated at 60 °C overnight. The brown suspension was filtered through a small pad of celite and the residue washed several times with ether (4 × 10 mL). The filtrate was washed (brine, 2 × 10 mL), dried (Na_2SO_4) and solvent evaporated under reduced pressure. The residue was pre-adsorbed onto florisil (0.5 mg) and chromatographed (florisil column: 1 × 9 cm, elution with pentane, collecting small fractions) to afford the vinyl stannane **4.30** as a colourless oil (11 mg, 89.1%; de: 74% by ^1H NMR spectrum). Some vinyl triflate **4.7** was also recovered (1 mg, 8.3%; R_f (silica TLC plates, pentane, PMA stain): 0.34). Vinyl stannane, R_f (silica TLC plates, pentane, PMA stain): 0.86; ν_{max} (film)/cm^{-1}: 3012 (=CH), 2929 (CH), 1658 (C=C), 766 (strong, s), 526 (strong, s); δ_H (270 MHz, $CDCl_3$): 0.13 (9H, s, $SnMe_3$), 0.95 (Me, minor, s), 1.10 (Me, major, s), 1.36-1.51 (2H, m), 1.69-2.09 (6H, m), 2.36 (1H, d, *J* 16.1 Hz), 2.35-2.5 (1H, m), 2.82 (1H, d, *J* 11.9 Hz), 5.45-5.61 (2H, m, C*H*=C*H*), 5.72-5.74 (1H, m, CH=CSnMe_3); δ_C (270 MHz, $CDCl_3$): (major isomer): -9.7 (CH_3, $SnMe_3$), 24.1 (CH_2), 25.6 (CH_2), 26.5 (CH_3), 32.7 (CH_2), 33.5 (CH_2), 44.8 (quaternary), 49.0 (CH_2), 57.6 (CH), 126.0 (=CH), 130.9 (=CH), 138.2 (=CH), 150.8 (quaternary), (some peaks of minor isomer observed): 20.9 (CH_3), 26.0 (CH_2), 29.6 (CH_2), 43.4 (CH_2), 45.8, (quaternary), 49.4 (CH_2), 54.8 (CH_2), 57.1 (CH), 128.2 (=CH), 130.4 (=CH); *m/z* (EI): 325 (37%, M^+), 311 (98, M^+ - CH_2), 161 (100, M^+ - $SnMe_3$), (accurate mass was unobtainable).

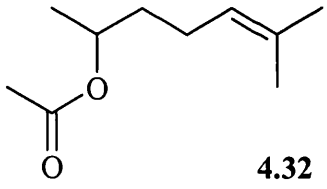
1,5-Dimethyl-4-hexenylmethanesulfonate, 4.31.



4.31

A cold (ice-bath) solution of heptenol **4.26** (0.2 g, 1.5 mmol) in CH_2Cl_2 (4.5 mL) was treated sequentially with the dropwise addition of triethylamine (0.26 mL, 1.87 mmol) and methanesulfonyl chloride (0.15 mL, 1.87 mmol). The cooling bath was removed, the mixture stirred overnight at room temperature, poured into sodium hydrogen carbonate solution (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were dried (Na_2SO_4), solvent evaporated under reduced pressure and residue chromatographed (9:1 petroleum ether:Et_2O) to isolate the mesylate **4.31** as a colourless oil (0.308 g, 99.5%); R_f (8:2 petroleum ether:Et_2O): 0.26; ν_{max} (film)/cm^{-1}: 3386 (weak, -O-), 2934 (CH), 1672 (C=C), 1450 (s), 1352 (s), 1174 (s), 916 (s); δ_H (400 MHz, $CDCl_3$): 1.40 (3H, d, *J* 6.4 Hz, CH_3CH(OMs)), 1.55-1.64 (1H, m, CH_3CH(OMs)C*H*H), 1.59 (3H, s, $(CH_3)_2$C=C), 1.67 (3H,d, *J* 1.2 Hz, $(CH_3)_2$C=C), 1.71-1.79 (1H, m, CH_3CH(OMs)CH*H*), 2.01-2.03 (2H, m, $(CH_3)_2$C=CHCH_2), 2.79 (3H, s, -SO_2-CH_3), 4.74-4.79 (1H, m, CH_3C*H*(OMs)), 5.07 (1H, split t, *J* 7.0 Hz, $(CH_3)_2$C=C*H*CH_2); δ_C (400 MHz, $CDCl_3$): 18.1 (CH_3), 21.6 (=CCH_3), 24.1 (CH_2), 26.0 (=CCH_3), 37.0 (CH_2), 38.9 (-SO_2-CH_3), 80.3 (CH), 122.8 (=CH), 132.9 (quaternary); *m/z* (EI): 206 (20%, M^+), 110 (39, M^+ - $MeSO_3H$), 95 (100, $MeSO_3$-), ($C_9H_{18}O_3S$ requires *M*, 206.0977. Found: M^+, 206.0979).

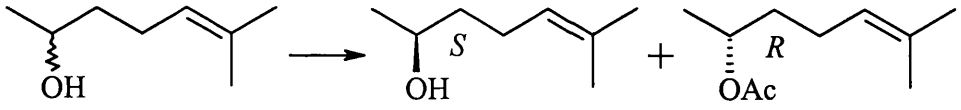
1,5-Dimethyl-4-hexenylacetate 4.32.



4.32

Triethylamine (0.12 mL, 0.93 mmol), DMAP (0.5 mg, 3.9 μmol) and acetic anhydride (0.081 mL, 0.85 mmol) were added sequentially to a stirred solution of heptenol **4.26** (0.1 g, 0.78 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C under nitrogen. The mixture was allowed to warm to room temperature, stirred for a further 4 h and washed with saturated ammonium chloride solution (3 × 5 mL), sodium hydrogencarbonate solution (2 × 5 mL) and brine (2 × 5 mL). The organic phase was dried (Na_2SO_4), solvent removed under reduced pressure and used without any further purification. The acetate **4.32** was generated cleanly as a colourless oil (0.13 g, 97.9%); R_f (9:1 petroleum ether:Et_2O): 0.6; ν_{max} (film)/cm^{-1}: 3449 (w), 2973 and 2931 (CH), 1738 (CO), 1449 (s), 1372 (s), 1242 (s); δ_H (400 MHz, $CDCl_3$): 1.2 (3H, dd, *J* 0.9 and 6.2 Hz, CH_3CH(OAc)), 1.48 (1H, ddd, *J* 5.2, 7.6 and 15.2 Hz, $CH_3CH(OAc)CHH$), 1.57 (3H, s, $(CH_3)_2C=C$), 1.62 (1H, dd, *J* 7.6 and 13.5 Hz, $CH_3CH(OAc)CHH$), 1.67 (3H, s, $(CH_3)_2C=C$), 1.95-2.0 (2H, m, $(CH_3)_2C=CHCH_2$), 2.02 (3H, s, -O-CO-CH_3), 4.87 (1H, apparent sextet, *J* 6.4 Hz, CH_3CH(OAc)), 5.06 (1H, split t, *J* 6.6 Hz, $(CH_3)_2C=CHCH_2$); δ_C (400 MHz, $CDCl_3$): 18.0 (CH_3), 20.4 (CH_3), 21.8 (CH_3), 24.4 (CH_2), 26.1 (CH_3), 36.3 (CH_2), 70.9 (CH), 123.6 (=CH), 132.2 (quaternary), 170.8 (quaternary); *m/z* (EI): 110 (52%, M^+ - CH_3CO_2H), 95 (100), 69 (17, $((CH_3)_2C=CHCH_2)^+$), 55 (100,$((CH_3)_2C=CH)^+$); *m/z* (FAB): 171 (40%, $M^+ + H$), 111 (100, M^+ - CH_3CO_2), (accurate mass unobtainable).

Enzymatic resolution of racemic heptenol 4.26.

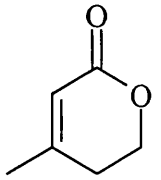


4.26 **4.32**

Racemic heptenol (25 mg), vinyl acetate (1.25 mL) and the enzyme ***Candida antarctica lipase***, immoblized on resin, were stirred in a closed glass vial at 38 °C for 40 min. The suspension was filtered through celite, the solid washed several times with CH_2Cl_2 and the filtrate concentrated by evaporation under reduced pressure. The residue (29 mg) was analysed by ^1H NMR and GC for % conversion and ee respectively. δ_H (270 MHz, $CDCl_3$): 1.9 (3H, d, *J* 4.9 Hz, $CH_3CH(OR)$), 1.21 (3H, d, *J* 4.9 Hz, $CH_3CH(OR)$), 1.42-1.58 (4H, m, $CH_3CH(OR)CH_2$), 1.58 (3H, s, $(CH_3)_2C=C$), 1.62 (3H, s, $(CH_3)_2C=C$), 1.68 (3H, s, $(CH_3)_2C=C$), 1.69 (3H, s, $(CH_3)_2C=C$), 1.96-2.14 (4H, m, $(CH_3)_2C=CHCH_2$), 2.03 (3H, s, -O-CO-CH_3), 3.81 (1H, apparent sextet, *J* 6.4 Hz, $CH_3CH(OH)$), 4.88 (1H, apparent sextet, *J* 6.4 Hz, $CH_3CH(OAc)$), 5.05-5.16 (2H, m, $(CH_3)_2C=CHCH_2$) (ratio of proton $CH_3CH(OR)$ from alcohol and acetate 1:1, therefore, 50% conversion); GC (105 °C, 2 mg/mL in CH_2Cl_2): retention time (% area), (equimolar solution of alcohol and acetate) alcohol: 17.71 (1.831), 18.23 (2.263), acetate: 21.59 (3.053), 23.44 (3.062); (reaction mixture) alcohol: 17.39 (3.081), acetate: 21.50 (0.049), 23.15 (3.984), therefore alcohol, >99% ee (the other isomer was not observed by chiral GC) and acetate, 98.7% ee.

7.3 EXPERIMENTAL CHAPTER 5

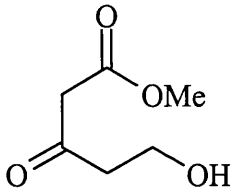
4-Methyl-5,6-dihydro-2H-pyran-2-one, 5.1.



5.1

Phosphazene base ((tetrahydropyrrole)$_3$P=N*t*-Bu) (16.4 μL, 0.053 mmol) was added to a cooled (ice-bath), stirred solution of the non-conjugated lactone **3.1** (60 mg, 0.54 mmol) in acetonitrile (2 mL). The cooling bath was removed, the mixture stirred at room temperature for 2 days, poured into brine (5 mL) and extracted with EtOAc (3 × 5 mL). The combined extracts were dried ($MgSO_4$) and solvent evaporated under reduced pressure. The residue was chromatographed (silica, 85:15 petroleum ether:EtOAc) to yield the conjugated lactone **5.1** as a brown oil (46 mg, 76.7%). R_f (6:4 petroleum ether:EtOAc): 0.43; ν_{max} (film)/cm^{-1}: 3588 (w), 2360 (CH), 1720 (CO); δ_H (270 MHz, $CDCl_3$): 2.01 (3H, s, MeC=), 2.39 (2H, t, *J* 6.4 Hz, HC=CMeC*H*$_2$), 4.38 (2H, t, *J* 6.4 Hz, HC=CMeCH$_2$C*H*$_2$O), 5.83 (1H, q, *J* 1.5 Hz, COC*H*=CMe); δ_C (400 MHz, $CDCl_3$): 23.0 (CH_3), 29.1 (CH_2), 65.9 (CH_2), 116.6 (=CH), 158.1 (quaternary), 164.9 (quaternary); *m/z* (EI): 112 (39%, M^+), 82 (100), ($C_6H_8O_2$ requires *M*, 112.0524. Found: M^+, 112.0525)

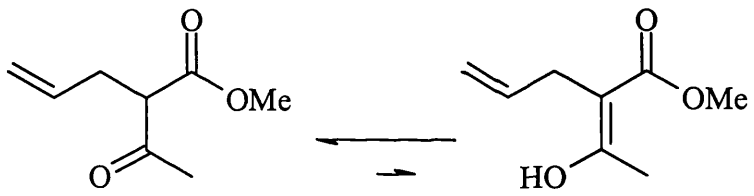
Methyl 5-hydroxy-3-oxopentanoate, 5.9.



5.9

R_f (9:1 CH_2Cl_2:MeOH): 0.61; δ_H (270 MHz, $CDCl_3$): 2.41 (1H, broad s, OH), 2.78 (2H, t, *J* 5.4 Hz, $HOCH_2CH_2CO$), 3.49 (2H, s, $COCH_2CO$), 3.72 (3H, s, COOMe), 3.83 (2H, t, *J* 5.4 Hz, $HOCH_2CH_2$-CO); δ_C (270 MHz, $CDCl_3$): 44.9 (CH_2), 49.3 (CH_2), 52.3 (CH_3), 57.4 (CH_2), 167.3 (quaternary), 203.1 (quaternary).

Methyl 2-acetyl-4-pentenoate, 5.10.



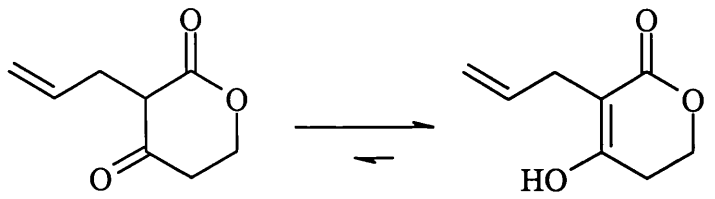
5.10

Sodium hydride (60% dispersion in oil, 3.3 g, 82.5 mmol) in a reaction flask equipped with a nitrogen line and a bubbler, was washed with two portions of dry hexane (20 mL). THF (150 mL) was added and the stirred suspension cooled with an ice-bath. Methylacetoacetate (8.7 mL, 75 mmol) was then added dropwise, the reaction mixture stirred for 20 min and quenched with allyl bromide (7.2 mL, 82.5 mmol). It was then slowly warmed to room temperature, stirred for a further 4 h, water (10 mL) was carefully added and solvent removed under reduced pressure. The

residue was partitioned between Et_2O (100 mL) and brine (300 mL). The phases were separated, the aqueous extracted with Et_2O (3 × 100 mL), the combined extracts dried ($MgSO_4$) and solvent evaporated *in vacuo*. The residue was chromatographed (silica, 95:5 petroleum ether:EtOAc) to afford the allylated product as a yellow brown oil (7.08 g, 60.5%). R_f (85:15 petroleum ether:EtOAc): 0.39; ν_{max} (film)/cm^{-1}: 3640 (w), 3079 (=CH), 2955 (CH), 1741 (CO), 1720 (CO), 1643 (C=C); δ_H (270 MHz, $CDCl_3$): 2.19 (3H, s, MeCO), 2.46-2.63 (2H, m, CH_2=CHC*H*$_2$-CH), 3.50 (1H, t, *J* 7.3 Hz, COC*H*(allyl)CO), 3.69 (3H, s, COOMe), 4.98-5.09 (2H, m, C*H*$_2$=CHCH$_2$-C), 5.69 (1H, ddt, *J* 6.9, 10.2 and 16.8 Hz, CH_2=C*H*CH_2-C), (2 % enolized form): 1.94 (3H, s, Me(OH)C=), 2.88 (2H, d, *J* 5.8 Hz, CH_2=CHC*H*$_2$C=), 12.7 (1H, s, =COH)); δ_C (270 MHz, $CDCl_3$): 29.1 (CH_3), 32.1 (CH_2), 52.3 (CH), 58.9 (OCH_3), 117.3 (=CH_2), 134.1 (=CH), 169.6 (quaternary), 202.3 (quaternary), (enol form): 117.3 (quaternary), 132.6 (quaternary); *m/z* (EI): 156 (36%, M^+), 113 (59), 43 (100), ($C_8H_{12}O_3$ requires *M*, 156.0786. Found: M^+, 156.0787).

Some bis-allylated methylacetoacetate was also isolated (5.16 g, 34.8%). R_f (85:15 petroleum ether:EtOAc): 0.51; δ_H (270 MHz, $CDCl_3$): 2.09 (3H, s, MeCO), 2.58 (4H, m, CH_2=CHC*H*$_2$-C), 3.69 (3H, s, COOMe), 5.03-5.10 (4H, m, C*H*$_2$=CHCH$_2$-C), 5.54 (2H, ddt, *J* 7.3, 9.7 and 17.6 Hz, 2 × CH_2=C*H*CH_2-C).

3-Allyl-4-hydroxy-5,6-dihydro-2H-pyran-2-one, 5.12.

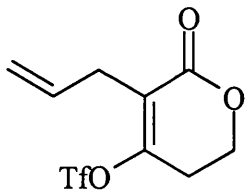


5.12

Allylated methylacetoacetate **5.10** (2.0 g, 12.8 mmol), was added dropwise to a stirred suspension of sodium hydride (60% dispersion in oil, 0.56 g, 14.08 mmol) in THF (75 mL) under nitrogen at -20 °C, sustaining a gentle effervescence. After the addition was complete, the mixture was stirred for 20 min and *n*-BuLi (6.7 mL of a 2.0 M solution in hexane, 13.4 mmol) was added dropwise. The resulting yellow solution was stirred at -20 °C for a further 20 min. Meanwhile paraformaldehyde was cracked.[119] A heterogeneous suspension of paraformaldehyde (1.54 g, 51.2 mmol) and *p*-toluenesulfonic anhydride (0.25 g, 0.76 mmol) in THF (60 mL) was heated and slow distillation of solvent maintained. The distillate was collected under a weak flow of nitrogen, in a flask submerged in a cooling bath at -78 °C. After distillation was complete, the flask containing the cracked paraformaldehyde was sealed with a rubber septum and stored under nitrogen at -78 °C. Formaldehyde was then introduced via a cannula into the reaction flask containing di-anion of **5.10** via cannula. Initially, just under a quarter of the formaldehyde solution was transferred and the reaction followed by TLC (8:2 petroleum ether:EtOAc for starting acyclic compound and 8:2 CH_2Cl_2:MeOH for cyclised product). After 15 min, some starting material was still present. A very small volume (~5 drops) of formaldehyde solution was added to the reaction mixture which was stirred for 15 min and the reaction

checked by TLC. The process was repeated until only a trace amount of starting reagent **5.10** was still present. The reaction mixture was warmed to room temperature, stirred for 1 h and quenched with water (2.3 mL). The mixture was then stirred at room temperature overnight, solvent removed under reduced pressure and residue pre-adsorbed onto silica. Chromatography (silica, 9:1 CH_2Cl_2:MeOH) of the pre-adsorbed material isolated the cyclised lactone **5.12** as cream powder (1.39 g, 70.5%). Some starting acyclic compound was also recovered (eluent: CH_2Cl_2, yield: 0.2 g, 10%). Lactone **5.12**: R_f (8:2 CH_2Cl_2:MeOH): 0.63; ν_{max} (nujol)/cm^{-1}: 1713 (CO), 1592 (s), 1460 (s), 1377 (s); δ_H (400 MHz, $CDCl_3$): (enolised form) 2.60 (2H, t, *J* 6.4 Hz, =C(OH)C*H*$_2$), 3.1 (2H, d, *J* 5.8 Hz, CH_2=CHC*H*$_2$-C), 4.28 (2H, t, *J* 6.4 Hz, CH_2C*H*$_2$-OCO), 4.95-5.94 (2H, m, C*H*$_2$=CHCH$_2$-C), 5.88 (1H, ddt, *J* 6.6, 10.7 and 16.5 Hz, CH_2=C*H*CH$_2$-C), 9.76 (1H, broad s, =C(OH)); δ_C (400 MHz, $CDCl_3$): 27.4 (CH_2), 28.2 (CH_2), 63.5 (OCH_2), 101.8 (quaternary, C=*C*(allyl)CO), 114.4 (=CH_2), 136.0 (=CH), 166.4 (quaternary), 168 (quaternary), (non-enolised form, 23%): 27.5 (CH_2), 37.6 (CH_2), 57.1 (CH), 62.6 (CH_2), 117.7 (=CH), 134.5 (=CH_2), 200.4 (CO); *m/z* (FAB): 155 (100%, M^+ + H), ($C_8H_{10}O_3$ requires *M* + *H*, 155.0708. Found: M^+ + H, 155.0713).

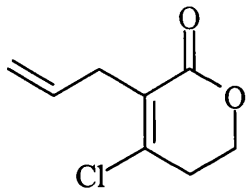
5-Allyl-6-oxo-3,6-dihydro-2H-pyran-4-yl trifluormethanesulfonate, 5.13.[121]



5.13

Diisopropylethylamine (0.42 mL, 2.4 mmol) was added to a stirred suspension of enol lactone **5.12** (0.25 g, 1.6 mmol) in CH_2Cl_2 (2.5 mL) under nitrogen at 0 °C. The solid dissolved on addition of base. Trifluoromethanesulfonic anhydride (0.54 mL, 3.2 mmol) was then added slowly dropwise, the mixture warmed to room temperature, stirred for 5 h and carefully quenched with saturated sodium hydrogencarbonate solution (2 mL). The mixture was poured into more bicarbonate solution (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined extracts were dried (Na_2SO_4) and solvent evaporated under reduced pressure. The residue was chromatographed (silica basified with triethylamine, 65:35 petroleum ether:CH_2Cl_2) to afford vinyl triflate **5.13** as a brown oil (0.29, 63.3%). R_f (8:2 petroleum ether:CH_2Cl_2): 0.48; ν_{max} (film)/cm^{-1}: 3085 (=CH), 2917 (CH), 1733 (CO), 1678 (C=C), 1424 and 1219 (-O-SO_2-); δ_H (400 MHz, $CDCl_3$): 2.91 (2H, t, *J* 6.3 Hz, C=C(OTf)C$H_2$$CH_2$), 3.20 (2H, d, *J* 6.4 Hz, CH_2=CHCH_2-C), 4.44 (2H, t, *J* 6.3 Hz, C(OTf)CH_2CH_2-O), 5.09-5.17 (2H, m, CH_2=CHCH_2-C), 5.80 (1H, ddt, *J* 6.4, 10.2 and 16.9 Hz, CH_2=C*H*CH_2-C); δ_C (400 MHz, $CDCl_3$): 27.2 (CH_2), 29.0 (CH_2), 63.8 (CH_2-O), 117.6 (=CH_2), 118.0 (quaternary, CF_3, q, *J* 319 Hz), 122.6 (quaternary), 132.2 (=CH), 155.8 (quaternary), 163.7 (quaternary); δ_F (400 MHz, $CDCl_3$): -74.4; *m/z* (FAB): 573 (70%, $2M^+$ + H), 287 (100, M^+ + H), 149 (100, M^+ - OSO_2CF_3), ($C_9H_9F_3O_5S$ requires *M* + *H*, 287.0201. Found: M^+ + H, 287.0201); ($C_9H_9F_3O_5S$ requires C, 37.8; H, 3.2%,. Found: C, 38.0; H, 3.3%).

3-Allyl-4-chloro-5,6-dihydro-2H-pyran-2-one, 5.14.[122]

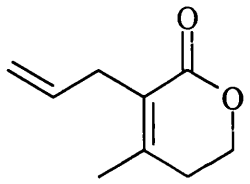


5.14

Oxalyl chloride (1.4 mL, 16.2 mmol) was added to a solution of enol lactone **5.12** (0.25 g, 1.6 mmol) in Et_2O (25 mL) under nitrogen at room temperature. After stirring for 5 h, the mixture was cooled to 0 °C and DMF (1.25 mL, 16.2 mmol) was added dropwise over 15 min. The mixture was stirred for a further 10 min, brought up to room temperature and benzyltriethylammonium chloride (1.82 g, 8.0 mmol) and $BF_3.Et_2O$ (0.2 mL, 1.6 mmol) were introduced sequentially. The reaction mixture was then stirred for 60 h, poured into a cooled (ice-bath) solution of 10% sodium hydrogencarbonate solution (50 mL) and the aqueous extracted with Et_2O (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4), solvent evaporated under reduced pressure and residue chromatographed (silica, 6:4 petroleum ether:CH_2Cl_2) to yield vinyl chloride **5.14** as a pale yellow oil (0.16 g, 57.2%). R_f (3:7 petroleum ether:CH_2Cl_2): 0.18; ν_{max} (film)/cm^{-1}: 3079 (=CH), 2912 (CH), 1720 (CO), 1638 (C=C), 1293 (s), 1131 (s); δ_H (400 MHz, $CDCl_3$): 2.83 (2H, t, *J* 6.3 Hz, C=C(Cl)C*H*$_2$CH$_2$-O), 3.26 (2H, d, *J* 6.4 Hz, CH_2=CHC*H*$_2$-C), 4.40 (2H, t, *J* 6.3 Hz, C(Cl)CH$_2$C*H*$_2$-O), 5.05-5.15 (2H, m, *H*$_2$C=CHCH$_2$-C), 5.82 (1H, ddt, *J* 6.4, 10.0 and 16.5 Hz, CH_2=C*H*CH$_2$-C); δ_C (400 MHz, $CDCl_3$): 32.0 (CH_2), 32.8 (CH_2), 64.6 (CH_2-O), 116.6 (=CH_2), 127.5 (quaternary), 132.9 (=CH), 147.2 (quaternary), 163.0 (quaternary); *m/z* (FAB): 175 (^{37}Cl, 32%, M^+ + H), 173 (^{35}Cl, 81%, M^+ + H), 132

(100), ($C_8H_9{}^{37}ClO_2$ requires *M* + *H*, 175.0340. Found: M^+ + H, 175.0335), ($C_8H_9{}^{35}ClO_2$ requires *M* + *H*, 173.0369. Found: M^+ + *H*, 173.0361).

3-Allyl-4-methyl-5,6-dihydro-2H-pyran-2-one, 5.15.[111]

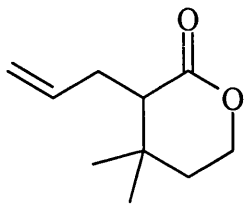


5.15

MeLi (0.64 mL of a 1.5 M solution in Et_2O, 0.96 mmol) was introduced into a reaction flask containing commercially bought (Aldrich) lithium 2-thienylcyanocuprate (3.6 mL of a 0.25 M solution in THF, 0.92 mmol) under nitrogen at -78 °C. After stirring the golden-green cuprate solution for 15 min, vinyl triflate **5.13** (0.25 g, 0.87 mmol) in Et_2O (1 mL) was added, the mixture stirred for a further 15 min, poured into ammonium chloride solution (10 mL) and extracted with Et_2O (3 × 5 mL). The combined extracts were washed (brine), dried ($MgSO_4$), solvent evaporated under reduced pressure and residue chromatographed (silica, 4:6 petroleum ether:CH_2Cl_2) to give the methyl lactone **5.15** as a yellow oil (97 mg, 73.2%). R_f (2:8 petroleum ether:CH_2Cl_2): 0.1; ν_{max} (film)/cm^{-1}: 3076 (=CH), 2920 (CH), 1706 (CO), 1641 (C=C), 1404 (s), 1304 (s), 1137 (s); δ_H (400 MHz, $CDCl_3$): 1.97 (3H, s, MeC=), 2.43 (2H, t, *J* 6.3 Hz, C=C(Me)CH_2), 3.1 (2H, d, *J* 6.1 Hz, CH_2=CHCH_2-C), 4.32 (2H, t, *J* 6.3 Hz, C(Me)CH_2CH_2-O), 4.99-5.09 (2H, m, CH_2=CHCH_2-C), 5.82 (1H, ddt, *J* 6.3, 10.1 and 17.1 Hz, CH_2=C*H*CH_2-C); δ_C (400 MHz, $CDCl_3$): 19.9 (CH_3), 30.5 (CH_2), 30.7 (CH_2), 65.0 (OCH_2), 115.0 (=CH_2), 124.5 (quaternary), 134.9 (=CH), 151.1 (quaternary), 165.1 (quaternary); *m/z* (EI):

152 (26%, M^+), 137 (27, M^+ - Me), 124 (36, M^+ - CO), 79 (100); ($C_9H_{12}O_2$ requires *M*, 152.0837. Found: M^+, 152.0830).

3-Allyl-4,4-dimethyltetrahydro-2H-pyran-2-one, 5.16.[91]



5.16

The same procedure as for 1,4-conjugate of methyl on the monocyclic enone **4.4**, was followed using $CuBrMe_2S$ (14 mg, 68.1 μmol), MeMgBr (0.16 mL of a 2.8 M solution in Et_2O, 0.46 mmol) in THF (1 mL), DMPU (95 μl, 0.78 mmol), a mixture of enone **5.15** (50 mg, 0.32 mmol) and TMSCl (84 μL, 0.65 mmol) in THF (0.3 mL plus 0.1 × 2 mL for rinses) to generate the methyl addition product **5.16** (39 mg, 72.5%) by chromatography (silica, 6:4 petroleum ether:CH_2Cl_2). R_f (2:8 petroleum ether:CH_2Cl_2): 0.2; ν_{max} (film)/cm^{-1}: 3075 (=CH), 2961 (CH), 1741 (CO), 1641 (C=C); δ_H (400 MHz, $CDCl_3$): 0.99 (3H, s, Me), 1.19 (3H, s, Me), 1.76-1.84 (2H, m, $CHC(Me)_2CH_2$), 2.20-2.26 (1H, m, CH_2=CHC*H*H-C), 2.31 (1H, dd, *J* 3.4 and 9.3 Hz, (allyl)C*H*CO-O), 2.50-2.59 (1H, m, CH_2=CHCH*H*-C), 4.33 (2H, dd, *J* 4.9 and 6.8 Hz, $C(Me)_2CH_2CH_2$-O), 5.04 (1H, dd, *J* 1.0 and 10.3 Hz, CH_2=$CHCH_2$-C), 5.12 (1H, dd, *J* 1.5 and 17.1 Hz, CH_2=$CHCH_2$-C), 5.90-6.03 ((1H, m, CH_2=C*H*CH_2-C); δ_C (400 MHz, $CDCl_3$): 24.8 (CH_3), 29.0 (CH_3), 29.8 (CH_2), 33.2 (quaternary), 38.2 (CH_2), 51.0 (CH), 65.0 (CH_2), 115.8 (=CH_2), 137.4 (=CH), 174.1 (quaternary); *m/z*

(EI): 168 (28%, M^+), 153 (45, M^+ - Me), 70 (100); ($C_{10}H_{16}O_2$ requires *M*, 168.1150. Found: M^+, 168.1153).

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