An approach to the synthesis of ingenane diterpenes

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A THESIS

entitled

An Approach to the Synthesis of Ingenane Diterpenes

submitted by

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-Memorandum-

The work described in this thesis was carried out in the University of Durham and Merck Sharp and Dohme laboratories between September 1996 and August 1999. This thesis is the work of the author, except where acknowledged by reference and has not been submitted for any other degree in this of any other University.

-Abbreviations-

2D	:two dimensional
Bz	:benzoyl
ch	:cyclohexyl
CI	:chemical ionisation
COSY	:COrrelated SpectroscopY
cpn	:cyclopentyl
cpr	:cyclopropyl
d	:doublet
dd	:doublet of doublets
DCC	:dicyclohexylcarbodiimide
DCE	:dichloroethane
DCM	:dichloromethane
DEPT	:Distortionless Enhancement through Polarisation Transfer
DIBAL-H/DIBAL	:diisobutylaluminium hydride
DMAP	:4-dimethylaminopyridine
DME	:1,2-dimethoxyethane
DMF	:N,N dimethylformamide
DMSO	:dimethyl sulphoxide
EDA	:ethyl diazoacetate
EI	:electron impact
eq	:equivalent/equivalents
ESI	:electrospray ionisation
ether	:diethyl ether
FAB	:fast atom bombardment
FCC	:flash column chromatography
FGI	:functional group interconversion
GC	:gas chromatography
h	:hour/s
HMDS	:1,1,1,3,3,3-hexamethyldisilazane
HMPA	:hexamethylphosphoramide

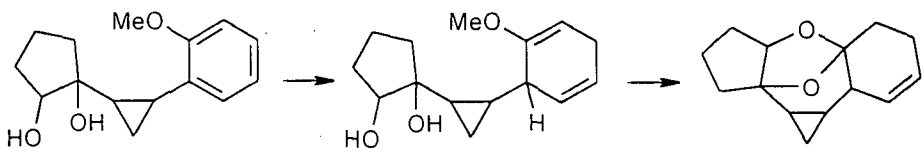
HRMS	:high resolution mass spectrometry
IR	:infra red
LHMDS	:lithium hexamethyldisilazide
m	:multiplet
m-CPBA	:*meta*-chloro peroxybenzoic acid
min	:minute/s
mpt.	:melting point
MS	:mass spectroscopy
NBS	:N-bromo succinimide
NIS	:N-iodo succinimide
NMP	:N-methyl-2-pyrrolidinone
NMR	:nuclear magnetic resonance
p	:pentet
PCC	:pyridinium chlorochromate
ppt	:precipitate
q	:quartet
rt	:room temperature
s	:singlet
t	:triplet
TBDMS	:*tert*-butyldimethylsilyl
Tf	:triflate
THF	:tetrahydrofuran
tlc	:thin layer chromatography
TMEDA	:N,N,N′,N′-tetramethylethylenediamine
TMS	:trimethylsilyl
TPAP	:tetrapropylammonium perruthenate
TsOH	:*para*-toluenesulphonic acid

ABSTRACT

An Approach to the Synthesis of Ingenane Diterpenes

Edward M. O. Sumner
Ph.D. 2001

Ingenol is the parent compound of the ingenane diterpenes. Certain C-3 fatty acid derivatives of these compounds are potent tumour promoters. Their mode of action is thought to occur through binding to and activation of the cell regulatory enzyme, protein kinase C. Central to the ingenane skeleton is a bicylo[4.4.1]undecanone-11-one unit which is a rare example of *trans*-intrabridgehead or inside–outside stereochemistry and is very strained. The structures are also highly oxygenated, ingenol itself is host to a *cis*-triol motif. To date ingenol has yet to succumb to total synthesis. Access to this system was envisaged *via* a tandem Birch reduction–divinylcyclopropyl (Cope) rearrangement of a phenylcyclopropane followed by a biomimetic pinacol-pinacolone skeletal shift. A model study in to the Birch reduction chemistry of phenylcyclopropanes is discussed and involves the preparation of phenylcyclopropanes substituted with methoxymethyl, vinyl and carboxylate groups. The reductive cleavage of the cyclopropane ring is observed with any functionality able to stabilise intermediate radical or anionic species or that can act as a leaving group. In the case of methoxymethyl substitution, reductive cleavage can be avoided by using proton sources; thus dihydro derivatives are readily available. The ring opening mechanism associated with vinyl substituted phenylcyclopropanes such as 2-phenyl vinylcyclopropane and 2-methoxymethyl-3-phenyl vinylcyclopropane has been shown to be particularly facile and is probably radical in nature. The possible utility of this methodology in the preparation of indenyl-type structures *via* 5-*exo*-trig cyclisation of radical intermediates has been investigated and led to the synthesis of 3-(2′-vinylcyclopropyl)-N,N, diethyl benzamide by way of Suzuki cross-coupling of the cyclopropyl boronate, ethyl 2-(4,4,5,5-tetramethyl[1,3,2]dioxaborolane)cyclopropanecarboxylate. In this case the presence of benzamide functionality allows a degree of reaction tuning (even in the presence of a vinyl group) so as to provide products of either reductive cyclopropane cleavage or those of aromatic reduction and related Cope rearrangement. The key Birch reduction substrate for ingenol synthesis, 1-(1,′2′-dihydroxycyclopentyl)-2-(2″methoxyphenyl)cyclopropane, was prepared from the *cis*-diene, Z-1-(cyclopent-1-ene)-2-(2′-methoxyphenyl)ethene, by dihydroxylation followed by cyclopropanation. Unfortunately the 2,5 rather than the desired 1,4-regioisomer was obtained from the Birch reduction step. Installation of electron withdrawing functionality such as an amide on the aromatic ring should overcome any such problem in the future. The 2,5 isomer forms an interesting hexacyclo acetal when heated or on contact with protic or Lewis acids.

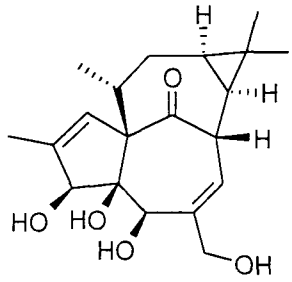


-Contents-

1.0 Introduction

1.1 Introduction

This thesis is concerned with a synthetic approach to the diterpene natural product, ingenol (**1**), and related methodology undertaken to this end. A key step in our approach to this molecule was the Birch reduction of a phenylcyclopropane. A model study was, therefore, conducted to evaluate the feasibility of this step and also investigate the possibility of generating indene-type molecules using this methodology. This will be the subject of chapter two (results and discussion –part 1), whereas chapter three (results and discussion –part 2) details synthetic work towards ingenol itself.



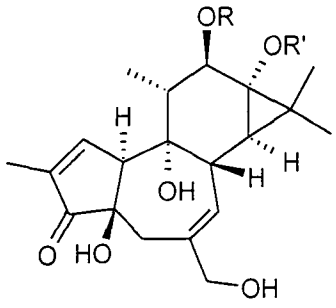
Ingenol (**1**)

Ingenol is the parent compound of the ingenane family of diterpenes which have attracted considerable interest due to their tumour promoting biological activity. This is thought to occur through binding to and activation of the cell regulatory enzyme, protein kinase C. The structure exhibits a highly strained BC ring system, which is a rare example of "inside-outside" or *trans*-intrabridgehead stereochemistry, and contains a high degree of oxygenated functionality including a *cis*-triol. This combination of factors presents the chemist with a formidable synthetic challenge and, as a result, at the time of writing, ingenol has yet to succumb to total synthesis.

1.2 Isolation and Structure of the Ingenanes

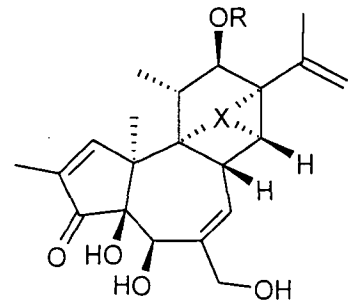
The ingenane diterpenes have been identified as the principal irritants in the genus Euphorbia, the largest genus (ca. 1600 species) of the Euphorbiaceae (spurge) family.[1] This is one of the largest families of flowering plants, comprising nearly 300 genera and approximately 7000 species, which are found in both tropical and temperate areas. Several species are grown commercially including *Hevea brasiliensis* Muell. Arg., the latex of which provides the raw material for rubber manufacture; *Vernicia fordii* Airy Shaw, the seeds of which provide tung oil; whereas *Euphorbia pulcherrima* Willd, *Euphorbia milii* Des Moul and *Euphorbia tirucalli* L. are house plants, the Poinsetta, the Crown of Thorns and the Pencil Tree respectively.

Individual species of Euphorbiaceae have long been known for their toxic effects,[2] which include, among others, skin inflammations, conjunctivitis and purgative properties. Extracts have also been utilised as arrow poisons. As a result, they have historically been adopted by both herbal and traditional medicine as remedies for illnesses as diverse as migraine, parasitic infections, bacterial infections and for use as abortifacients. Due to concerns over toxicity, however, these treatments were slowly phased out up to a point now when only castor oil (from the seeds of *Ricinus communis* L.) is commonly used in western medicine. Nevertheless, the chemical and biochemical interest in the extracts from these plants continued and was rewarded by the isolation and structural elucidation of the biologically active components, namely, esters of the tigliane (e.g., phorbol as tetradecanoyl phorbolacetate – T.P.A)[3], daphnane (e.g., mezerein)[4] and ingenane diterpenes, Figure 1.2.1. The isolation of these compounds is not straightforward, many examples being thermally unstable or susceptible to hydrolysis or transesterification reactions. However, if low temperatures and neutral conditions are maintained throughout, successful separation and purification can be achieved using a series of solvent extractions followed by chromatography.



Tigliane (**2**)

Phorbol: R=R'=H;
T.P.A: R=$CO(CH_2)_{12}CH_3$,
R'=$COCH_3$

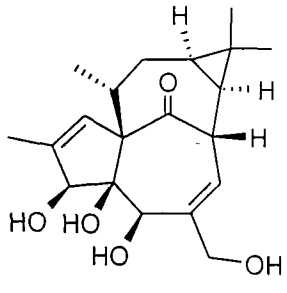


Daphnane (**3**)

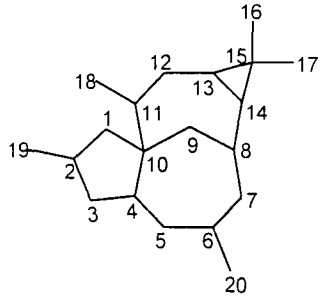
Mezerein: R=$OC(CH=CH)_2C_6H_5$,
X=O_3CPh

Figure 1.2.1

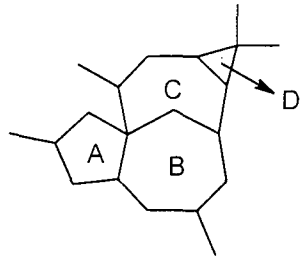
Using the techniques referred to immediately above, the ingenanes have been identified as the principle irritants in the genus Euphorbia. The first ingenane ester was isolated in 1968 from the latex of *Euphorbia ingens* E. meyer and seed oil of *Euphorbia lathyris* L. by Hecker and co-workers.[5] This was ingenol-3-hexadecanoate. However, the absolute configuration was not known until 1970 when Zechmeister *et al*[6] solved the structure by X-ray crystallography. Zechmeister obtained ingenane crystals by firstly subjecting ingenol-3-hexadecanoate to mild base hydrolysis, providing the resinous parent alcohol (ingenol). This in turn was treated with acetic anhydride / pyridine to yield ingenol-3,5,20-triacetate which was recrystalised from ether-petrol.



Ingenol (**1**)



Ingenane numbering



Ring system

Figure 1.2.2

The ingenol structure, as shown in Figure 1.2.2, is a highly functionalised tetracycle. The central bicyclo [4.4.1] undecan-11-one unit, comprising the B and C rings, is a rare example of *trans* intrabridgehead or "inside-outside" stereochemistry and is very strained (see section 1.2.1). The molecule is also highly oxygenated, being host to three contiguous *cis*-hydroxyl groups at C-3, C-4 and C-5, a bridging keto group at C-9 and a primary hydroxyl group at C-20. Many examples of ingenol esters with different oxygenation states at C-3, C-4, C-5, C-12, C-13, C-16 and C-20 have been isolated.[7]

1.2.1 In/Out Stereoisomerism

Bridged bicyclic structures can adopt one of three possible configurations. These are outside-outside (**4**), inside-inside (**5**) or inside-outside (**6**) and refer to the orientation of the bridgehead atoms or groups,[8] Figure 1.2.3.[9]

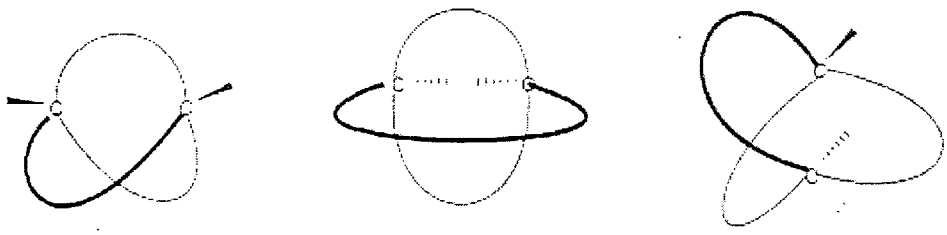
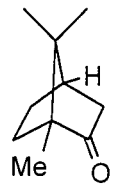


Figure 1.2.3

Which conformation is adopted depends on both the size of the rings and the nature of the bridgehead groups. For example, the cavity created by small rings may not be sufficiently large to avoid massive steric repulsion on housing an "in" bridgehead substituent, therefore, in small ring bicyclics, the most stable configuration is invariably outside-outside. This is the case for bicyclo[1.1.1]pentane (**7**) and camphor (**8**), Figure 1.2.4. In the case of ingenol, the [4.4.1] core is an example of inside-outside geometry. The hydrogen at C-8 being inside and the cyclopentene bond at C-10 being outside; as can be seen from the crystal structure, **9**.[10] In this regard, Funk[11] has calculated isoingenol (the C-8 epimer of ingenol, outside-outside) to be 5.9 kcal mol^{-1} more stable than the natural product.

(7)



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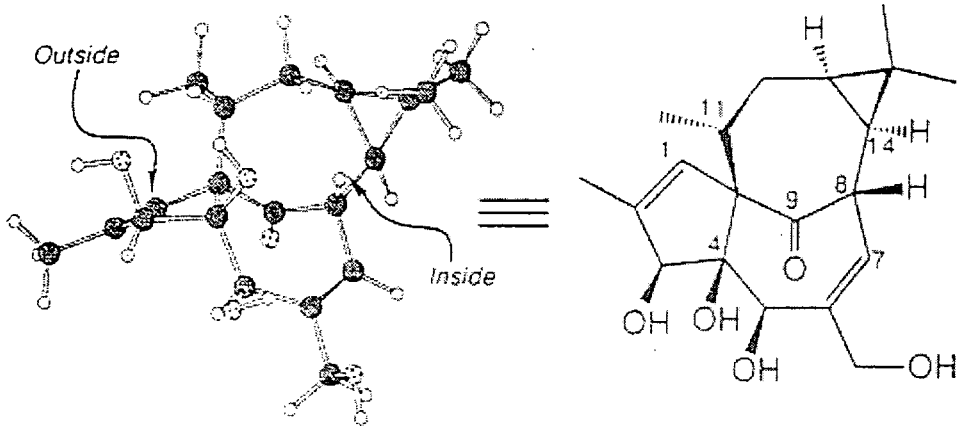


(9)

Figure 1.2.4

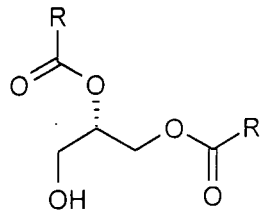
1.3 Biological Activity

The ingenane esters have been shown to exhibit a wide range of biological activity including anti-leukaemia and anti-HIV properties.[12] However, the work of, among others, Berenblum[13] and Roe *et al*[14], has illustrated that they are also potent tumour-promoters. This is to say that these compounds, although not carcinogenic in their own right, activate latent tumour cells which have been formed by previous exposure to an initiating compound. This process is known as cocarcinogenesis.[15]

Their mode of action is thought to occur through binding to and activation of protein kinase C (PKC).[16] PKC is a Ca^{2+} and phospholipid dependent enzyme that is widespread throughout the tissues and organs of mammals and is responsible for

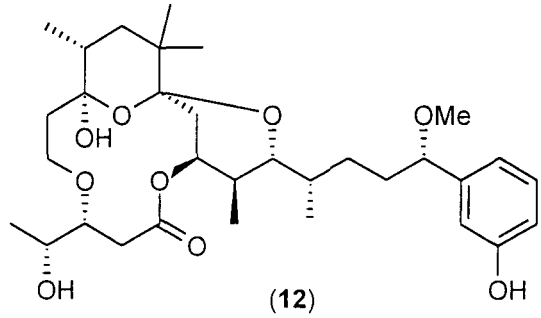
many aspects of cell regulation including proliferation.[17] The endogenous activators of PKC are diacylglycerols (DAG) (**10**), however, the interaction between the two is only transient. Certain ingenane esters are able to substitute for DAG, binding more permanently, dramatically increasing the affinity of the enzyme for Ca^{2+}, and hence, eliciting an exaggerated biological response. Other PKC activators that mimic DAG are teleocidins (**11**), asplysiatoxins (**12**), bryostatins (**13**) and esters of phorbol (**14**), Figure 1.3.1.

It has been shown that for successful binding to occur, ingenane compounds must possess both the correct "inside-outside" ring stereochemistry and also ester functionality attached *via* the hydroxyl group at C-3.[18] In this regard, ingenol itself has been shown to be biologically inactive,[19] so has the isoingenol molecule, **15**, prepared by Paquette *et al* (see section 1.5), which exhibits *cis* BC ring geometry.[20]

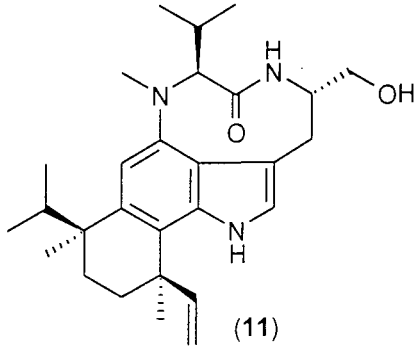


(**10**)

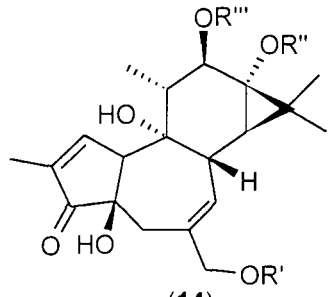
R = fatty acid



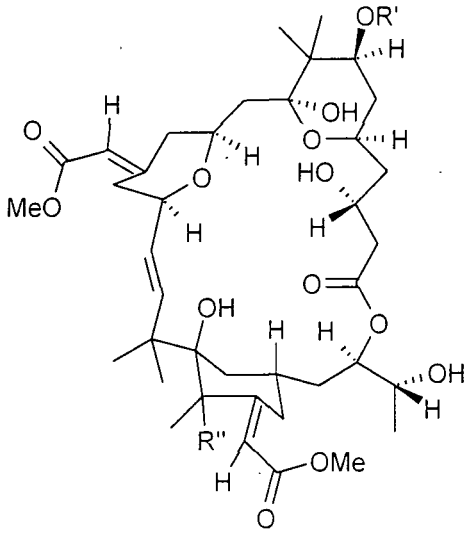
(**12**)



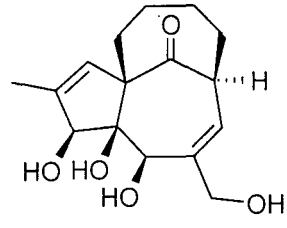
(**11**)



(**14**)



(**13**)

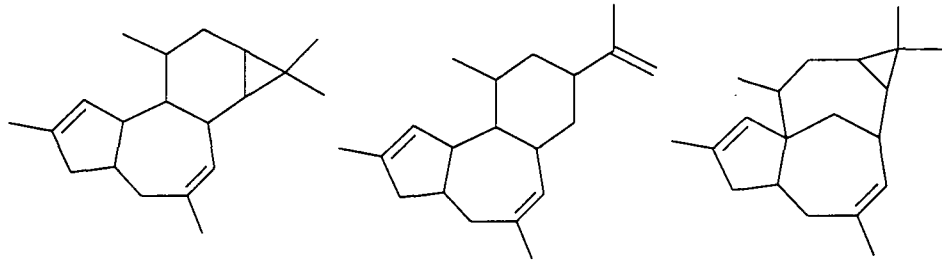


(**15**)

Figure 1.3.1

1.4 Biosynthesis

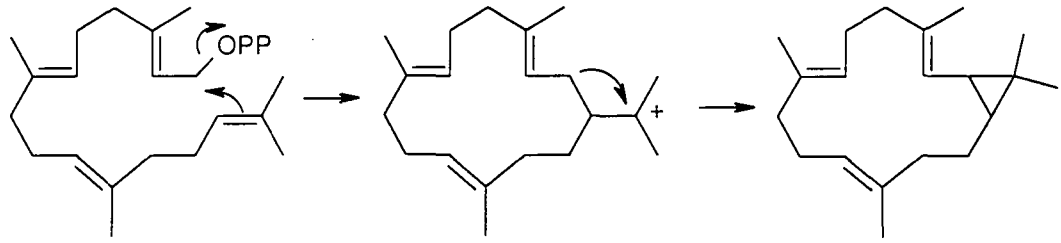
The biosynthesis of the ingenane diterpenes has not been the subject of a detailed biological study. However, Adolf and Hecker[21] have brought together individual pieces of evidence in a proposed biosynthetic pathway that links the ingenanes to the tigliane and daphnane families of diterpenes, Figure 1.4.1. In this, geranyl-geranyl pyrophosphate is postulated as the common precursor to these structurally similar compounds.



Tigliane Daphnane Ingenane

Figure 1.4.1

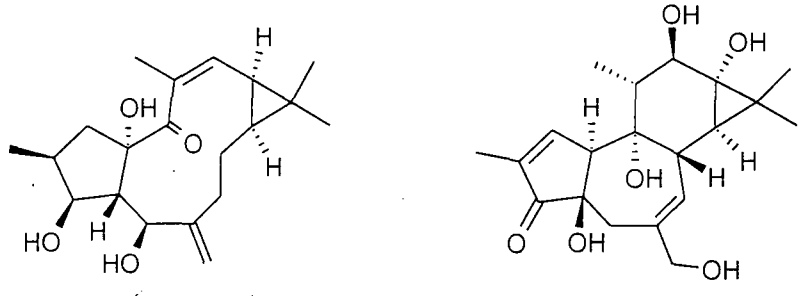
Geranyl-geranyl pyrophosphate has been synonymous with diterpene biosynthesis for some time, however, a so-called "concertina" style cyclisation reaction, giving rise to, among others, the kauranes, pimaranes, beyeranes and trachylobanes was regarded as the principal mechanism involved.[22] Not until the isolation of the 14-membered macrocyclic diterpenes, casbene (**16**)[23] (from the seedlings of the caster oil bean, *Ricinus communis* L., Euphorbiaceae) and cembrene[24] (from various pine trees including *pinus albicaulis* Engelm, Pinaceae) was another alternative mechanism, apparently linking these compounds, thought to exist. In the new mechanism, geranyl-geranyl pyrophosphate appears to undergo a head-to-tail cyclisation reaction resulting in a cembrene cation species (**17**). Subsequent loss of a proton from which results in a cyclopropane and the casbene skeleton (**16**), Scheme 1.4.1.



geranyl-geranyl pyrophophate cembrene cation (**17**) casbene (**16**)

Scheme 1.4.1

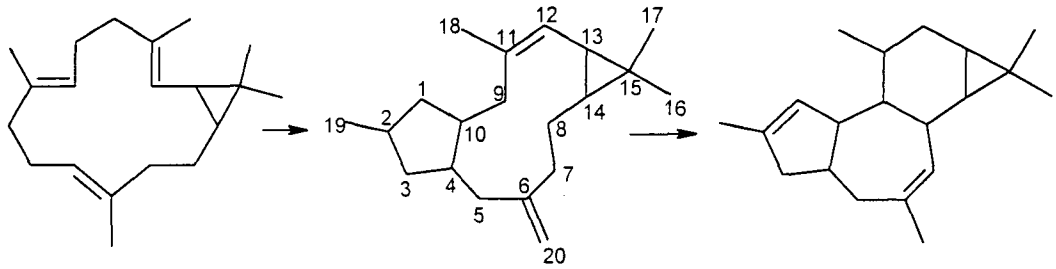
The structure of casbene (**16**) has been unequivocally proved by its total synthesis[25] and is now regarded as the parent compound of many diterpenes that contain a cyclopropane ring. Included in this category are the lathyranes and tiglianes. Many examples of compounds exhibiting these skeletal types have been isolated from species of Euphorbiaceae, including esters of lathyrol (**18**)[26] (caper spurge, *Euphorbia lathyris* L.) and phorbol (**19**)[27] (purging croton, *Croton tiglium* L.), Figure 1.4.2.



Lathyrol (**18**) Phorbol (**19**)

Figure 1.4.2

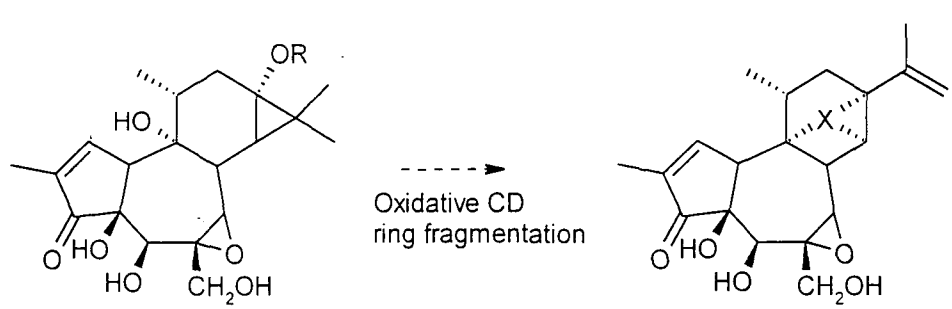
These compounds can be viewed as products of successive cyclisation reactions of casbene (**16**). In the first instance, between C-4 and C-10 providing the *trans* fused five-eleven membered lathyrane bicycle, and secondly, between C-8 and C-9 resulting in the *trans* fused seven-six membered ring system evident in the tiglianes, Scheme 1.4.2.



Casbene (**16**) Lathyrane Tigliane

Scheme 1.4.2

The link between the daphnanes and the tiglianes is also strong. Both families have been found to co-exist in species of Euphorbiaceae[28] and structurally the only difference between the two is the cyclopropane ring; replaced by an *iso*-propenyl group in the daphnanes. Biosynthesis of daphnanes can, therefore, be rationalised in terms of oxidative CD ring fragmentation of tigliane precursors. This mechanism requires the presence of oxygenated functionality at both C-9 and C-13 in the tigliane starting material, providing a triol upon ring opening and ultimately a characteristic ortho-ester in the resultant daphnane structure. In support of this hypothesis, many examples of daphnanes bearing identical functionality to the tigliane-type mancinellin esters (**20**) (from the beech apple, *Hippomane mancinella* L., Euphorbiaceae) have been isolated[29]. For example, daphnetoxin (**21**) (Dwarf laurel, *Daphne mezereum*, Thymelaeaceae), Scheme 1.4.3.

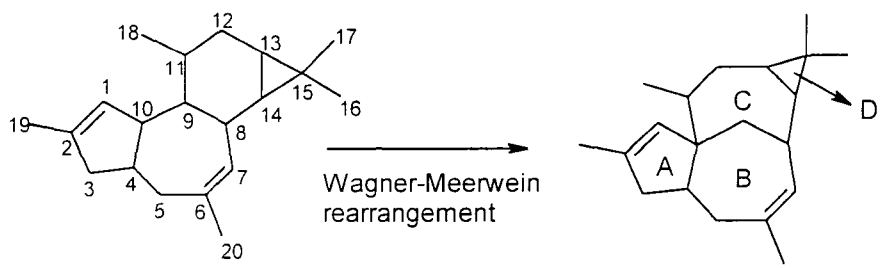


ester of 12-deoxy-5-hrdroxyphorbol-
6α, 7α–oxide (mancinellin ester) (**20**)

daphnetoxin (**21**)
(X=O_3CPh)

Scheme 1.4.3

A close structural relationship also exists between the ingenanes and the tiglianes. In this case, however, formation of the ingenane framework requires a skeletal shift of C-11 from C-9 to C-10, Scheme 1.4.4. This transformation is of particular interest to this thesis (see section 1.6) and may be an example of a Wagner-Meerwein rearrangement. Although this hypothesis is unproven, skeletal shifts of this nature are not uncommon in biosynthesis.[30] Further, Hecker[31] has demonstrated the reverse transformation, that is, the preparation of a tigliane species from ingenane starting material, thus supplying further, strong evidence for its existence.



Tigliane Ingenane

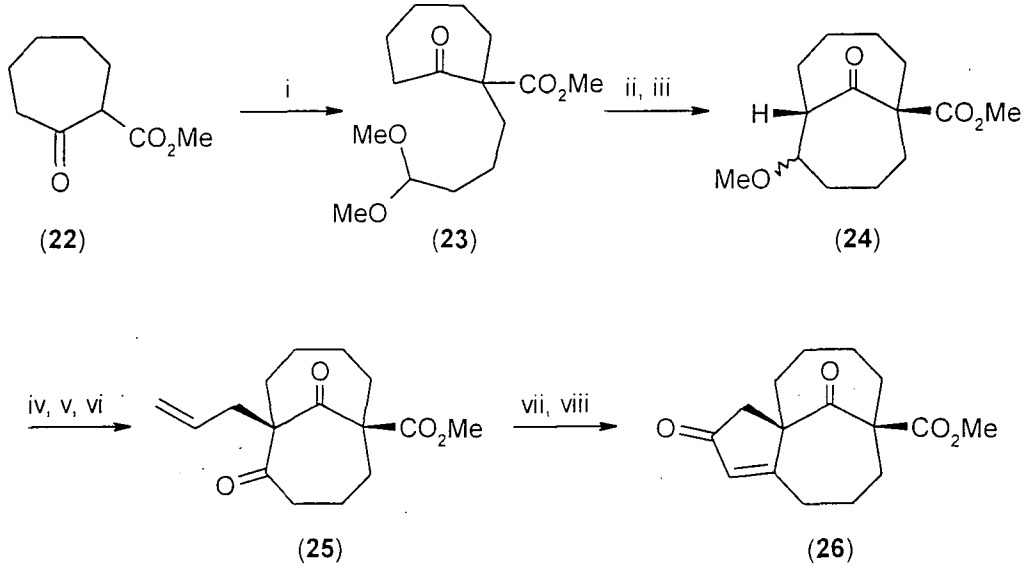
Scheme 1.4.4

1.5 Previous Synthetic Approaches to the Ingenanes

Ingenol (**1**) is the parent compound of the ingenane group of diterpenes which possess a rare and highly strained *trans*-locked [4.4.1] undecanone skeleton. In addition to this "inside-outside" stereochemistry, ingenol exhibits an all *cis* array of hydroxyl groups, which makes the molecule a particularly challenging target. As a result, to date, ingenol has yet to yield to total synthesis.[9]

Many synthetic approaches have been made towards the ingenanes,[32] however, only four have been successful in constructing ingenane frameworks with the correct stereochemistry, namely, those by Funk,[10,11] Rigby,[33] Tanino-Kuwajima[34] and Winkler[18,35] (which will be discussed in the following pages).

Early synthetic approaches tended to concentrate on construction of isoingenol analogues. This is the less strained C-8 epimer of ingenol with *cis* rather than *trans*-intrabridgehead stereochemistry. In this regard, Mehta[36] has demonstrated a simple synthesis of the core structure (**26**) starting from 2-methoxycarbonylcycloheptanone (**22**), which serves as a pre-formed C-ring, Scheme 1.5.1. The β-keto ester (**22**) was firstly alkylated, incorporating a side chain armed with a dimethyl acetal and the ketone was converted to the silyl enol ether. The requisite functionality was now in place to effect closure of the seven-membered B-ring. This was initiated by treatment with $TiCl_4$ in an intramolecular variant of the Mukaiyama reaction. Finally, the resultant methoxy ether was converted to the ketone (**25**) using TMS-Cl followed by PCC and the five-membered A-ring was installed using an alkylation-aldol condensation sequence.

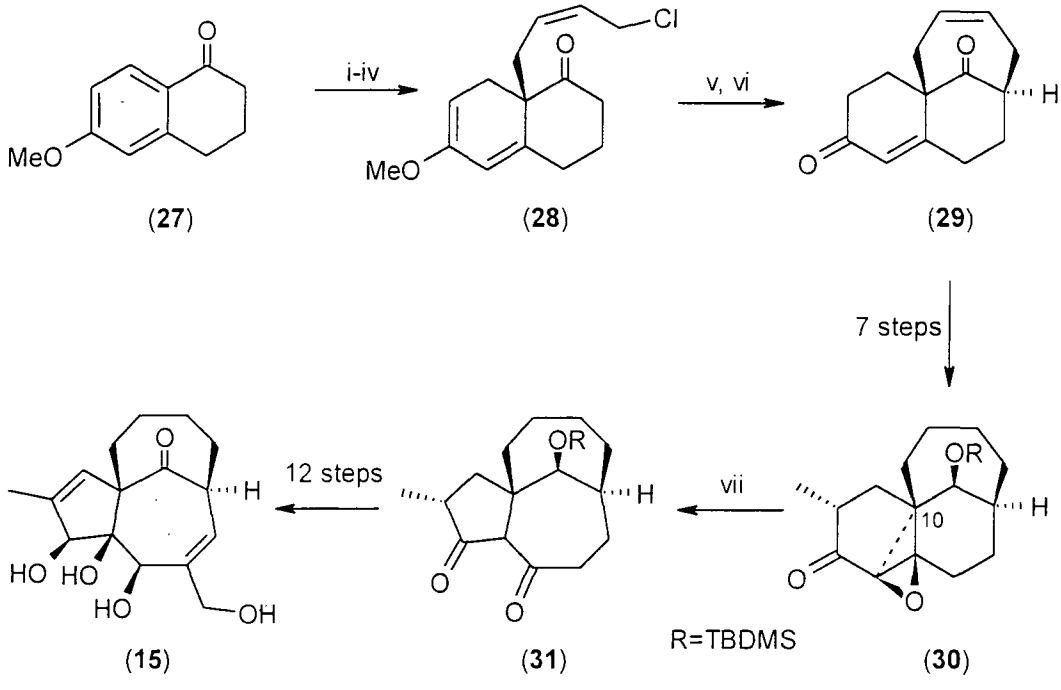


(**22**) (**23**) (**24**) (**25**) (**26**)

Scheme 1.5.1. Reagents: i, NaH, RBr, DMF, 58%; ii, *n*-BuLi, HMDS, THF, TMS-Cl; then iii, $TiCl_4$, DCM, 66% for two steps; iv, TMS-Cl, NaI, MeCN, 92%; v, PCC, 93%; vi, *n*-BuLi, HMDS, HMPA, THF, then allyl-Br, 70%; vii, $PdCl_2$, Cu_2Cl_2, DMF-H_2O, O_2, 83%; viii, NaH, THF, 71%.

The Mehta molecule (**26**), although possessing the basic framework of isoingenol, bears only minimal functionality. Paquette[20,37] has demonstrated the synthesis of a more functionalised isoingenol precursor (**15**). This was also the first ingenane directed synthesis published. In this approach, an α,β-epoxy ketone (**30**) was photo-

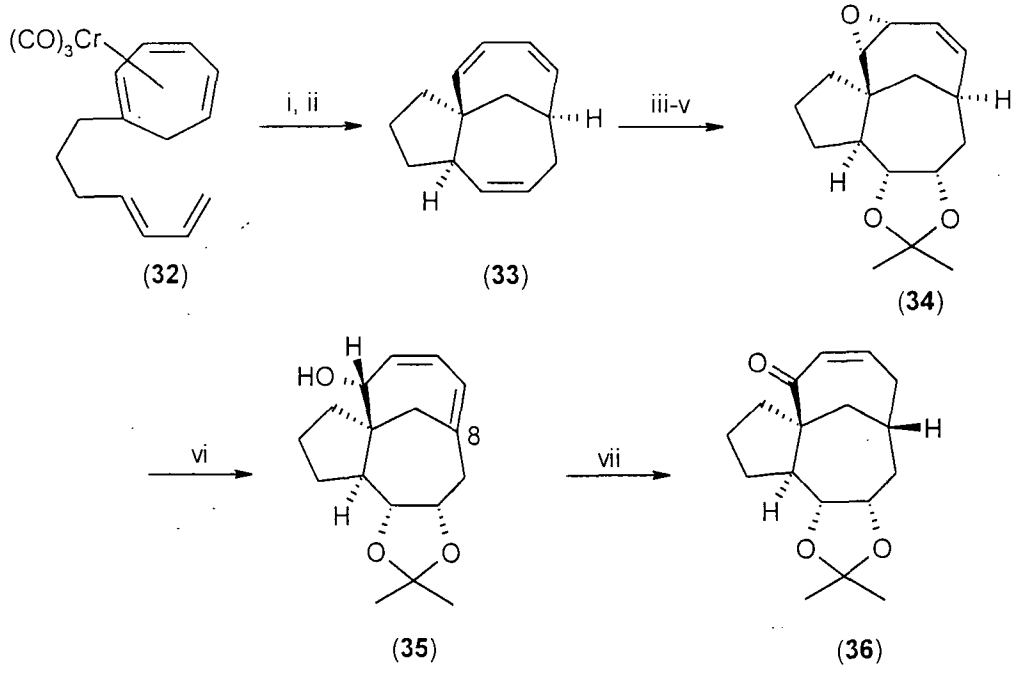
isomerised in the key step to afford the ABC central unit. The required substrate (**30**) was readily prepared from tetralone **27** in a sequence including double alkylation and vanadium catalysed epoxidation. Subsequent irradiation of this molecule induced the predicted isomerisation to afford the 1,3-diketone (**31**) in 65% yield, Scheme 1.5.2. This transformation can be explained by initial C_α-O homolytic bond cleavage followed by C_β migration (in this case C-10 migration) and concurrent ketone formation. The synthesis was completed by functionalisation of the A and B-rings in a 12 step procedure.



Scheme 1.5.2. Reagents: i, Na, NH_3; ii, $(i\text{-PrO})_3Al$, Me_2CO; iii, KNH_2, NH_3; iv, (Z)-1,4-dichloro-2-butene; v, KH, *t*-BuOH, DME; vi, H_3O^+, 32% for six steps; vii, hv 300nm, EtOH, 65%.

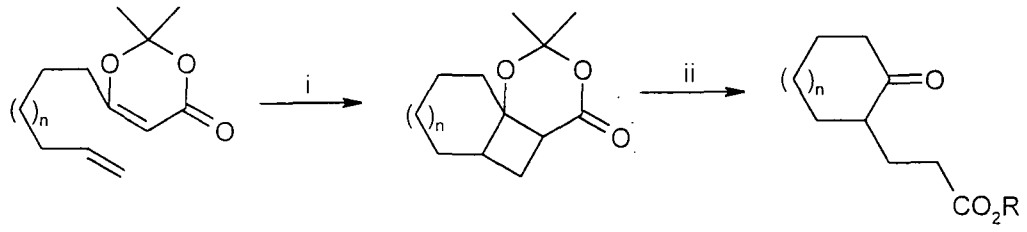
Although the Paquette molecule offers a high degree of functionalisation it has been shown to be completely devoid of biological activity.[20] In explanation, this synthesis, as with Mehta's approach, produced the less strained *cis* intrabridghead stereochemistry. However, it is now accepted that both oxygenated functionality (more specifically C-3 oxygenation) and *trans* ring stereochemistry is required to initiate a biological response (see section 1.3). Thus, existing methodology directed

towards construction of *cis* geometry, although of synthetic interest, is of no biological interest. In this regard, a very interesting procedure has recently been devised by Rigby[33] which uses an isomerisation reaction to convert readily available out-out bicyclo [4.4.1] undecane species (*cis* geometry) to the more strained in-out bridging relationship (*trans* geometry), Scheme 1.5.3. In this methodology, an out-out system was generated from **32** using a chromium promoted intramolecular [6 + 4] cycloaddition. The isolated double bond was then protected as the acetonide and an epoxide was installed at the more hindered position of the diene (30%) from the more accessible *exo*-face of the molecule. Subsequent lithium amide mediated epoxide ring opening of **34**, provided the desired vinylic alcohol with a bridgehead double bond in place at C-8 and the alkoxide hydrogen in a crucial β-orientation. Treatment of this substrate with KH and 18-crown-6 at 0°C in the key step, initiated a [1,5] sigmatropic hydride shift which proceeded in high yield (68%), generating the desired *trans* intrabridgehead stereochemistry evident in **36**. Creation of the *trans* geometry demonstrates the suprafacial nature of this operation.



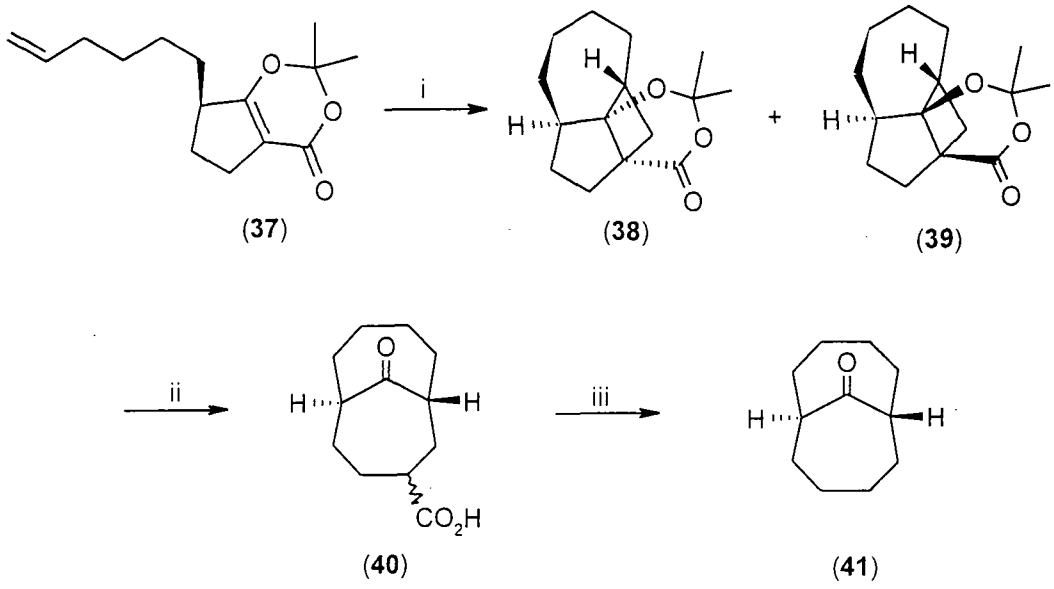
Scheme 1.5.3. Reagents: i, 1,4-dioxane, Δ; ii, hν (pyrex), hexanes, 82% over two steps; iii, OsO_4; iv, DMP, H^+, 76% over two steps; v, *m*-CPBA, 30%; vi, $LiNEt_2$, THF, 86%; vii, KH, 18-cr-6, THF, 0°C, then NH_4Cl, 68%.

The first recorded synthesis of the correct inside-outside [4.4.1] undecane skeleton was demonstrated by Winkler[35] and co-workers in 1987 using a dioxenone photoaddition-retroaldol fragmentation sequence. This strategy is based on a modified de Mayo reaction reported by Baldwin.[38] In this, dioxenone heterocycles undergo [2 + 2] photocycloaddition reactions with alkenes. The resultant cyclobutane intermediates can then be encouraged to ring open in a retro-aldol reaction to yield 1,5-dicarbonyls. Unfortunately, with unsymmetrical alkenes the regiochemistry of the reaction could not be predicted. Winkler[39] circumvented this problem by tethering the alkene in an intramolecular version of the reaction and in doing so prepared six, seven and eight membered ring esters in good yield (74%, 50% and 50% respectively) and with high levels (>50:1) of regiocontrol, Scheme 1.5.4.



Scheme 1.5.4. Reagents: i, hν (pyrex), 0.01M in acetone/acetonitrile, ii, TsOH.

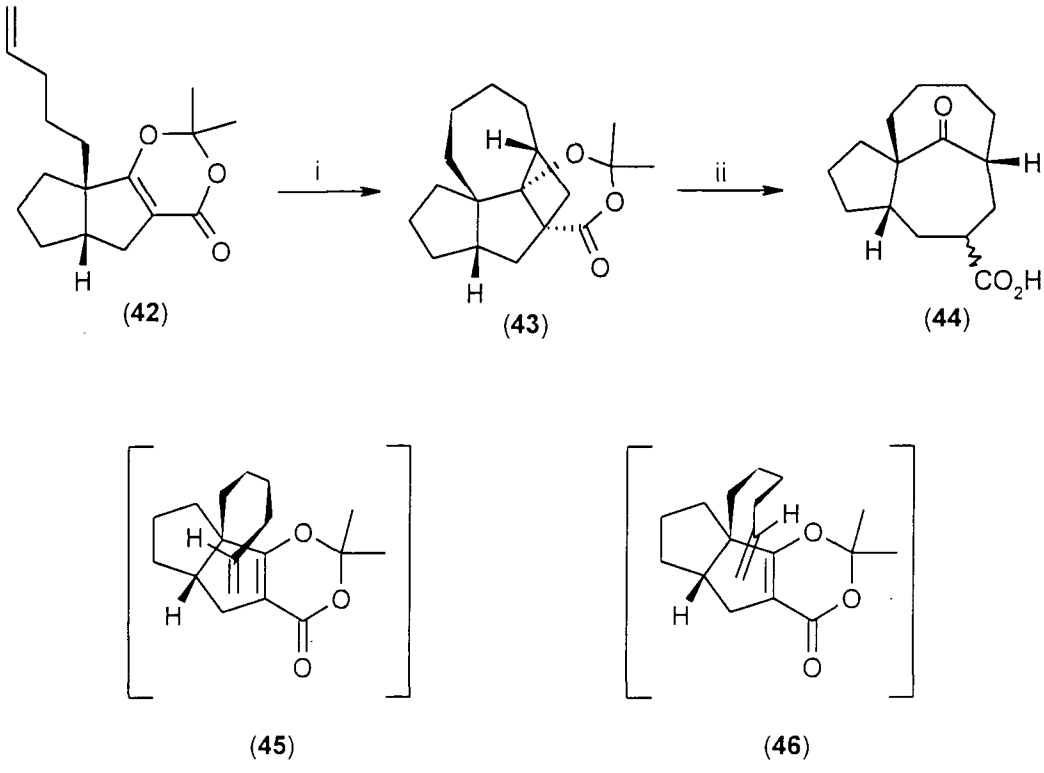
In order to prove the utility of this methodology in the construction of the *trans* intrabridgehead ring system exhibited by the ingenanes the photosubstrate **37** was prepared.[40] However, upon irradiation, the terminal alkene was able to approach from both sides of the molecule which led to the formation of two adducts, **38** and **39** (4.3:1, 30%). Nevertheless, fragmentation of the mixture with KOH followed by Barton decarboxylation[41] provided the [4.4.1] undecanone bicycle **41** as a single enantiomer with the desired "inside-outside" stereochemistry, Scheme 1.5.5.



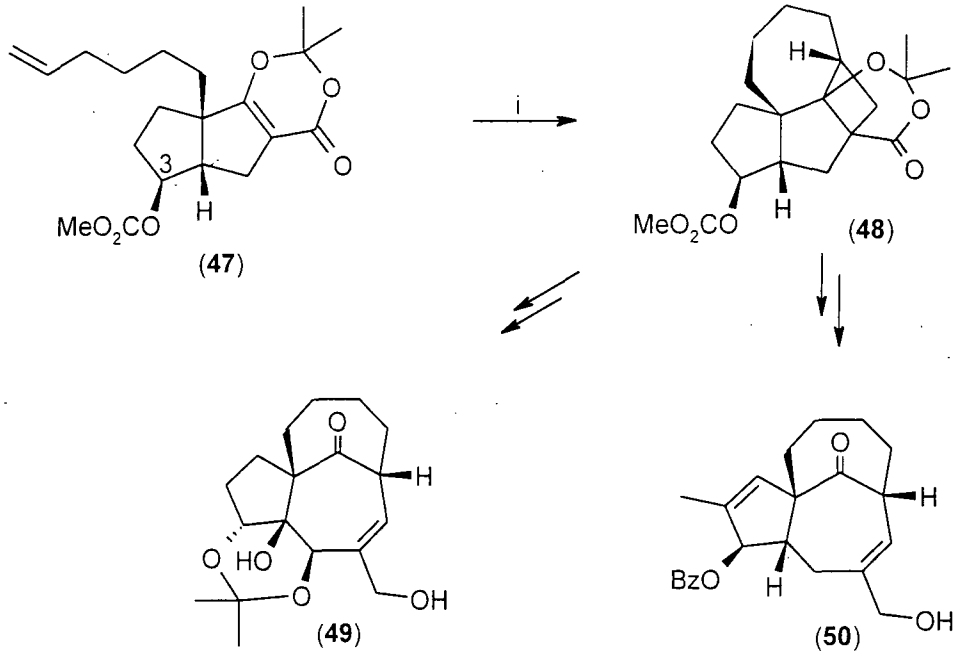
Scheme 1.5.5. Reagents: i, hν (pyrex), 0°C, Me_2CO/MeCN, 30%; ii, KOH, MeOH, 85%; iii, oxalyl chloride, 2-mercaptopyridine-N-oxide (Na salt), DMAP, *t*-BuSH, toluene, THF, 60%.

With a successful annulation reaction now developed, Winkler[35] targeted the ingenol skeleton by preparing the more advanced photosubstrate, **42**, which incorporates the five membered ingenane A-ring, Scheme 1.5.6. In this case, movement of the tethered alkene was restricted to the top face of the molecule, resulting, upon irradiation, in a single photoadduct (**43**) in high yield (85%). Subsequent fragmentation under basic conditions provided the first example of an ingenane skeleton (**44**) with the essential strained stereochemistry at C-8. The exclusive formation of the inside-outside isomer in this strategy is attributable to the transition state adopted during cyclisation. Of the two possible conformations of the nascent seven membered ring the pseudochair form (**45**) is the most favourable; the alternative pseudoboat conformation (**46**) suffering from transannular non-bonding interactions.

Winkler[18] and co-workers have now extended this route using a C-3 oxygenated photosubstrate (**47**) from which the biologically active ingenol analogues, **49** and **50**, have been accessed *via* multi-step procedures, Scheme 1.5.7.

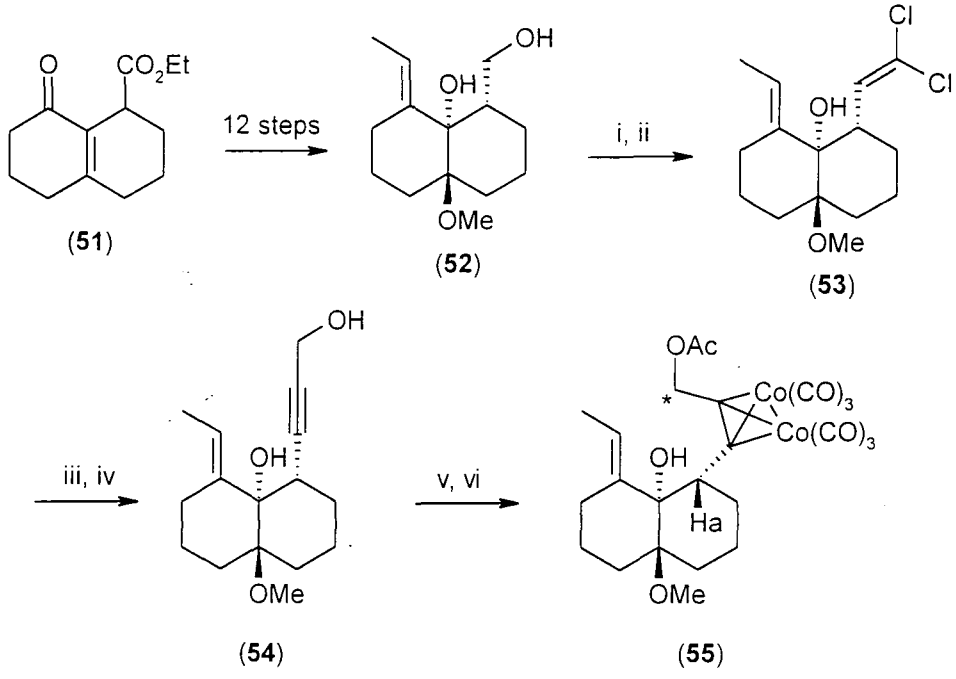


Scheme 1.5.6. Reagents: i, hν (pyrex), Me_2CO/MeCN, 0°C, 85%; ii, KOH, MeOH, 88%.



Scheme 1.5.7. Conditions: i, hν (pyrex), Me_2CO/MeCN, 0°C, 61%.

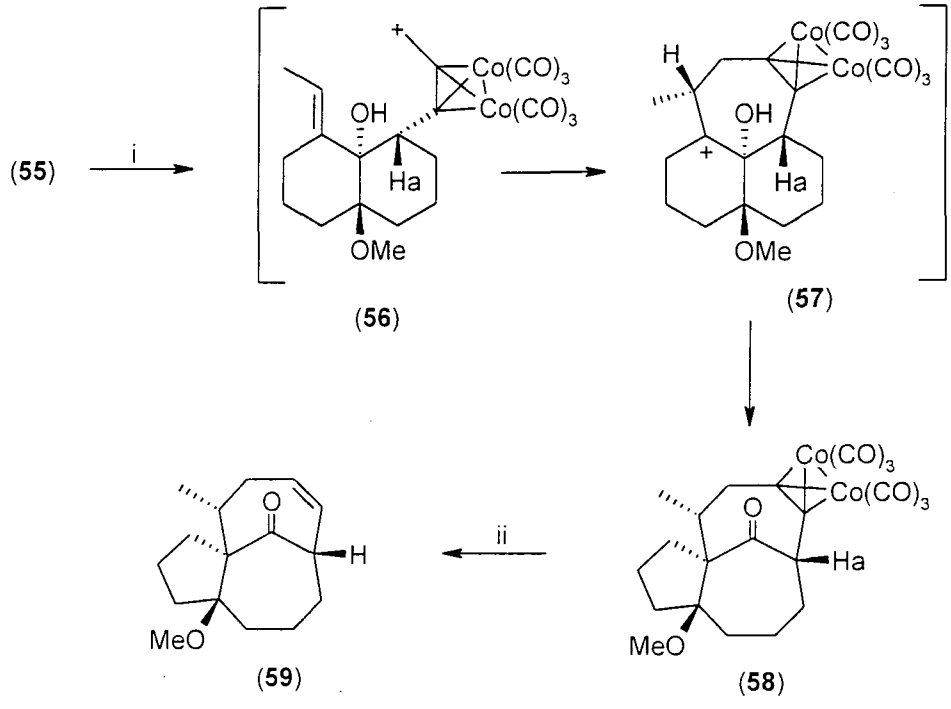
More recently, Tanino-Kuwajima[34] and co-workers have developed some promising new methodology to manipulate the strained stereochemistry at ingenane C-8. This route utilises a tandem cyclisation-rearrangement sequence initiated by the formation of a dicobalt hexacarbonyl stabilised "Nicholas" cation.[42] The starting material here is the keto ester **51**, from which the *trans*-decalinol, **52**, was prepared (12 steps). Conversion of the primary alcohol to the acetylenic ester and subsequent installation of the dicobalt hexacarbonyl moiety then provided the required Nicholas substrate (**55**), Scheme 1.5.8. In this molecule, the proton Ha is placed *trans*-diaxial with respect to the hydroxyl group of the decalinol which equates, ultimately, to a β C-8 proton in the *trans* [4.4.1] ring chemistry of ingenane target. Furthermore, the conformational rigidity of both the decalinol substructure and the dicobalt motif bring the latent cationic centre (*) and the ethylidene carbon within close proximity which necessitates a facile ring closure.



(**51**) (**52**) (**53**) (**54**) (**55**)

Scheme 1.5.8. Reagents: i, DMSO, $(COCl_2)_2$, Et_3N, DCM, 100%; ii, $Cl_3CPO(OEt)_2$, BuLi, THF/Et_2O, 95%; iii, BuLi, THF, then MeOCOCl; iv, DIBAL, toluene, 67% over two steps; v, Ac_2O, Et_3N, DMAP, DCM, 97%; vi, $Co_2(CO)_8$, DCM, 98%.

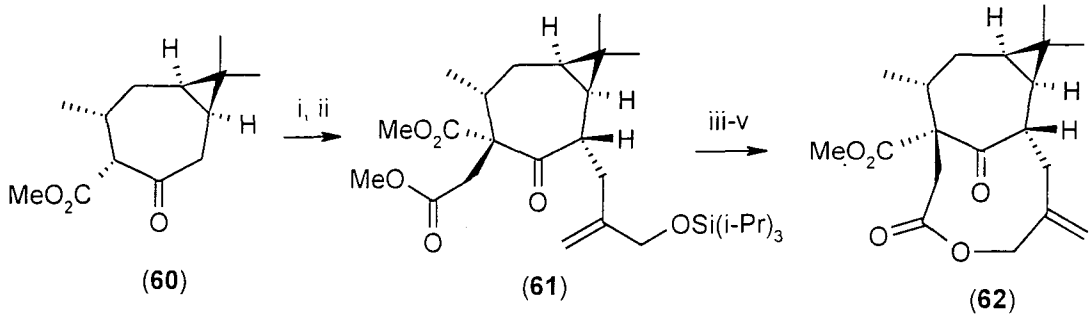
The key ring closing step was initiated by conversion of the free hydroxyl group to an aluminium alkoxide with $CH_3Al(OCOCF_3)OAr$ (where Ar = 2,6-$(CH_3)_2$-4-$(NO_2)C_6H_2$), thus promoting the formation of the dicobalt hexacarbonyl propargyl cation **56**. This underwent the predicted electrophilic addition to the ethylidene carbon forming the seven membered ring intermediate **57**, which spontaneously rearranged to yield the desired tricycle (**58**, 77%). Finally, reductive deprotection (Li/NH_3) provided the ingenane structure (**59**) in 75% yield, Scheme 1.5.9.



Scheme 1.5.9. Reagents: i, $CH_3Al(OCOCF_3)OAr$ (where Ar = 2,6-$(CH_3)_2$-4-$(NO_2)C_6H_2$), DCM, -23°C to rt, 77%; ii, Li, NH_3, -78°C, 75%.

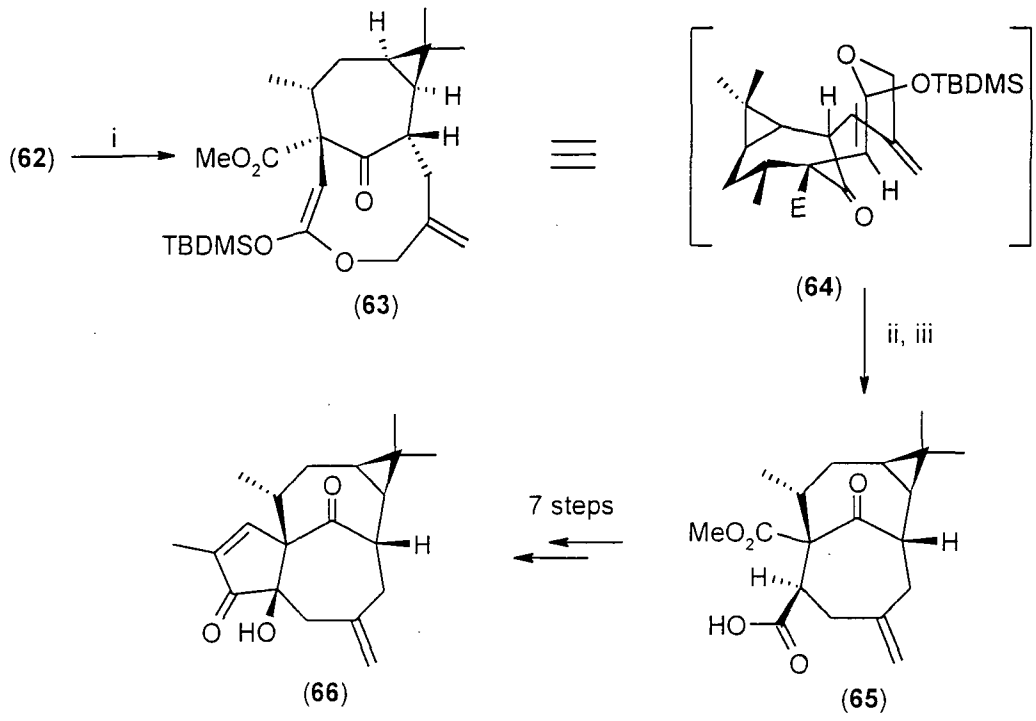
The most complete synthesis of the natural product to date has been made by Funk *et al.*[10,11] In this case, the *trans* [4.4.1] undecanone ingenol ring system was prepared by ring contraction of the lactone **62**. This compound is an excellent substrate in this regard as, although an example of a *trans* bicycle, thus providing the *trans* ingenane bicycle on contraction, it suffers little of the "bending" strain experienced by the ingenane [4.4.1] ring system[43] and hence is easily accessible. Initially, in order to prepare this macrocycle (**62**), the seven membered ketone, **60**, embodying both the C

and D rings of ingenol, was assembled.[11] The configuration of this molecule facilitated stereoselective attachment of two pendant side chains, *trans* to each other, thus setting the correct ring stereochemistry. Subsequent desilylation (HF, 86%) and selective saponification (KOH, 91%) was followed by lactonisation (DCC, DMAP, 62%), which completed the synthesis of the nine membered ring, Scheme 1.5.10.



Scheme 1.5.10. Reagents: i, LDA, HMPA, THF, then $BrCH_2C(CH_2)CH_2OSi(^iPr)_3$, 74%; ii, NaH, DMF, then $BrCH_2CO_2Me$, 85%; iii, HF, MeCN, 86%; iv, KOH, MeOH, 91%; v, DCC, DMAP, DMAP.HCl, DCM, 62%.

The ring contraction reaction took the form of a Claisen rearrangement and was effected by heating the silyl enol ether of **62** in toluene. This compound (**63**) is thought to adopt a boat-like transition state (**64**) during rearrangement and provided, after desilylation, the carboxylic acid **65** (88% over three steps), Scheme 1.5.11. The requisite functionality was now in place to install the five-membered A-ring, which was achieved in a seven-step procedure.



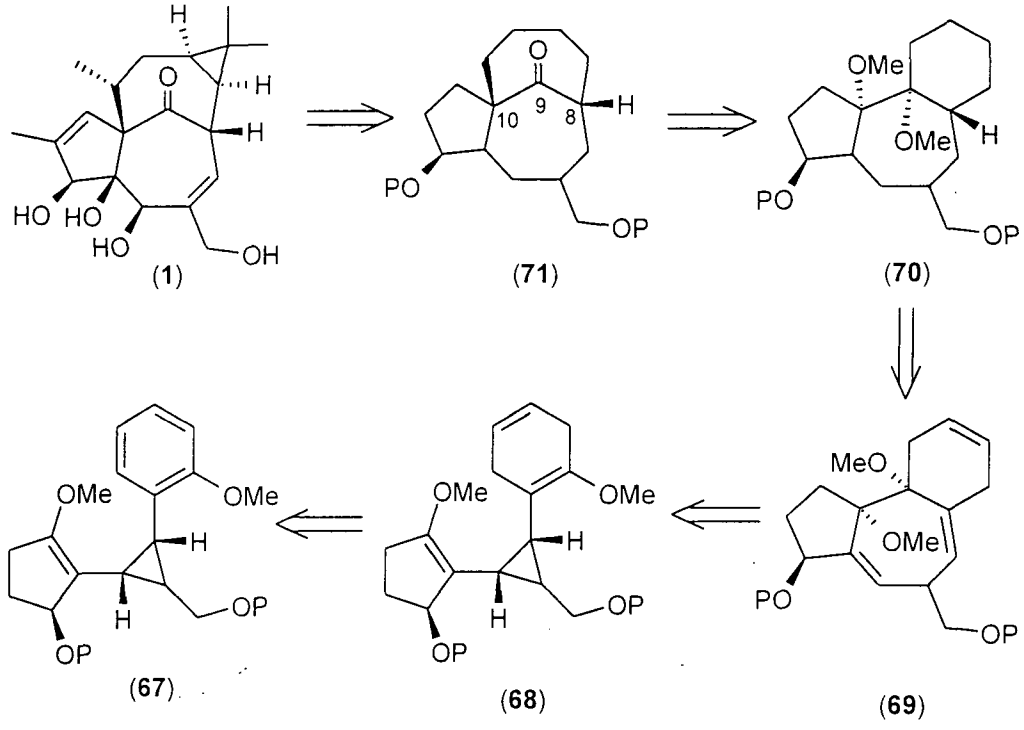
Scheme 1.5.11. Reagents: i, LHMDS, HMPA, TBDMS-Cl, THF; ii, Δ, toluene; iii, HF, MeCN, 88% over three steps.

The final compound (**66**) is the first example of a tetracycle possessing the necessary ring stereochemistry and also exhibits much of the functionality of ingenol, only lacking in C-5 and C-20 oxygenation and the C-6 to C-7 double bond. To date, no publications concerning the biological activity of **66** or its derivatives have been published.

1.6 Proposed Work

It is postulated that the ingenane family of diterpenes has the same biosynthetic origins as the structurally related tigliane and daphnane diterpenes (see section 1.4). That is, cationic cyclisation of a 14-membered macrocycle such as casbene, providing the tigliane framework. Subsequent oxidative CD ring fragmentation of which results in the daphnane skeleton, or alternatively, a Wagner-Meerwein shift of C-11 from C-9 to C-10 generating the ingenane tetracycle. In relation, our proposal

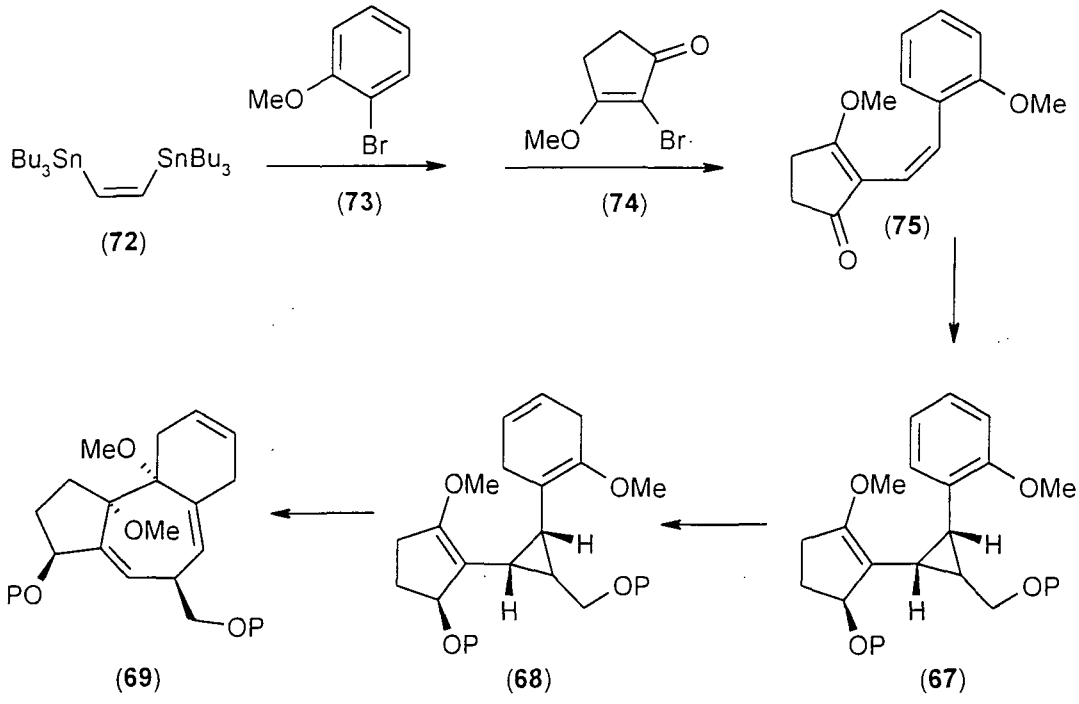
comprises construction of a tigliane skeleton (**70**) equipped with suitable functionality at C-9 and C-10 to initiate a "biomimetic" pinacol-pinacolone skeletal rearrangement. Access to this system by means of a tandem Birch reduction-divinylcyclopropane (Cope) rearrangement of a phenylcyclopropane such as **67** is planned, Scheme 1.6.1. The latter half of this sequence is an established, high yielding method for the preparation of seven membered rings[44] and it has also been shown by Wender[45] to be a potential route to the BC rings of tigliane natural products.



Scheme 1.6.1.

In order to incorporate the necessary functionality at an early stage of the synthetic pathway but also allow for flexibility in the synthesis, a convergent route to the Birch substrate (**67**) was sought. With this in mind, a *cis*-diene such as **75** was targeted as a key intermediate. It is anticipated that assembly of **75** will be possible by two successive palladium cross coupling reactions of the *bis*-stannane **72** with bromoenone **74** and aryl bromide **73**, Scheme 1.6.2. Cyclopropanation of the acyclic double bond of **75** then provides the desired phenylcyclopropane (**67**). The

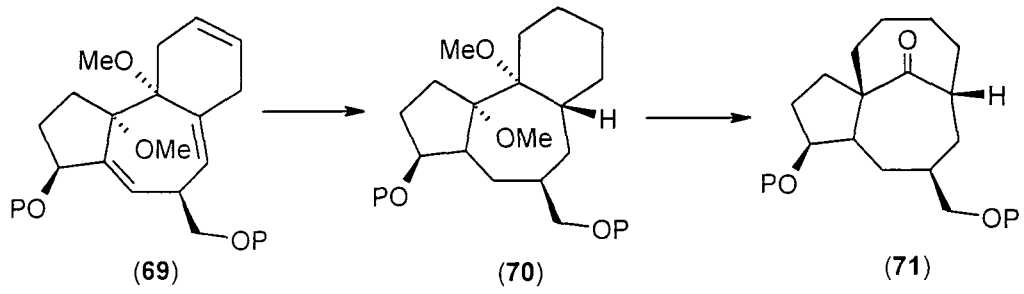
regiospecificity of this reaction is assumed as steric repulsion between the terminal aromatic unit and the cyclopentene ring should render this olefin more strained and thus more reactive to a carbene/carbenoid. Asymmetry can also be incorporated at this stage by use of diazocarbonyl chemistry, either by the use of a chiral ester appendage or a chiral catalyst.[46] Subsequent Birch reduction of **67** is directed by the methoxy group to yield the desired *cis*-divinylcyclopropane (**68**), which in turn undergoes a spontaneous Cope style rearrangement to yield the tigliane skeleton (**69**). This transformation is thought to occur through the normal boat transition-state where the double bonds lie over the cyclopropane ring.[44] The presence of the methoxy groups in the substrate (**68**), although adding steric crowding, is not considered a concern and has been shown, in certain cases, to actually facilitate this type of rearrangement.



Scheme 1.6.2

At this stage the vital stereochemistry at C-8 can be installed by face-selective hydrogenation of **69**. This selectivity is assumed as it creates a *trans* BC ring juncture with the C-ring adopting a preferred chair conformation and places all the alkyl substituents in preferred equatorial positions. In the final step, demethylation

followed by acid treatment initiates the pinacol-pinacolone rearrangement to yield the ingenane ring system, Scheme 1.6.3.



Scheme 1.6.3

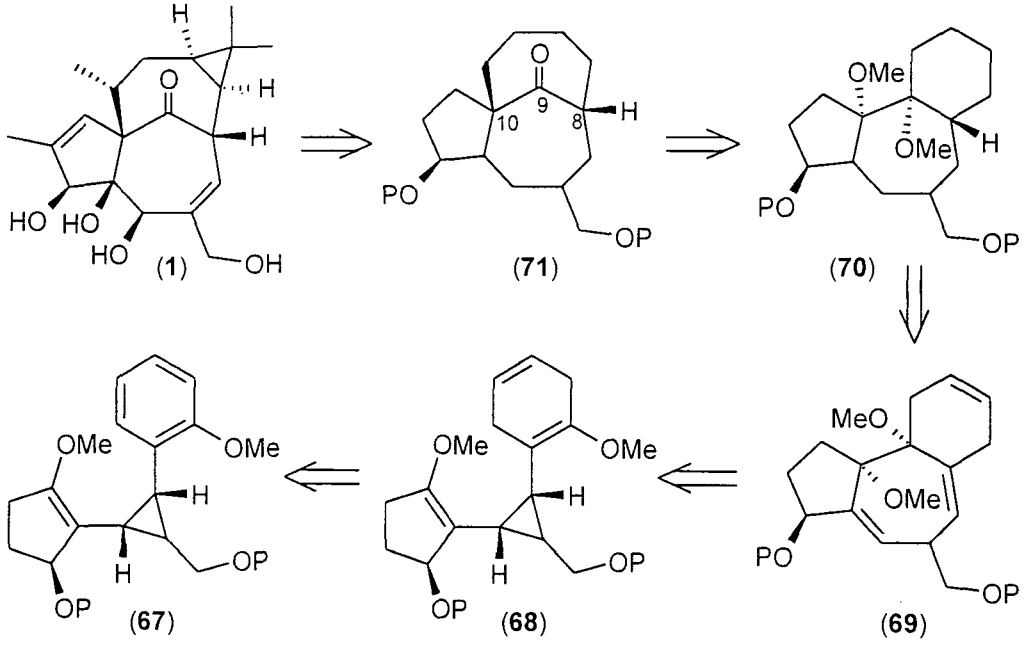
A key step in this strategy is the Birch reduction of a phenylcyclopropane. Reductions on substrates of this type have been relatively underexplored, although the products obtained have been shown to vary according to both the reaction conditions employed and functionality present.[47] A model study has, therefore, been conducted to investigate this step which is discussed in the next chapter.

2.0 Results and Discussion –Part 1

-Birch Reduction Model Study

2.1 Introduction

This project is directed towards the synthesis of the tetracyclic ingenane family of diterpenes and more specifically the parent tetra-ol, ingenol (**1**), which has eluded total synthesis thus far. A synthetic pathway to this class of molecules has been devised and is outlined in scheme 1.6.1. The key steps in this approach are the tandem Birch reduction-divinylcyclopropyl (Cope) rearrangement of a substrate such as **67** (i.e. a phenylcyclopropane) and the pinacol-pinacolone rearrangement of the resultant tigliane-type compound, **70**. The latter transformation can be considered biomimetic as the ingenanes are believed to be the product of a similar alkyl shift in nature (see section 1.4). In order to test this strategy it was necessary, firstly, to investigate the Birch reduction of phenylcyclopropanes which may also provide rapid access to indene-type products. Therefore, a model study was conducted in which a number of phenylcyclopropanes have been synthesised and their Birch reduction chemistry evaluated.

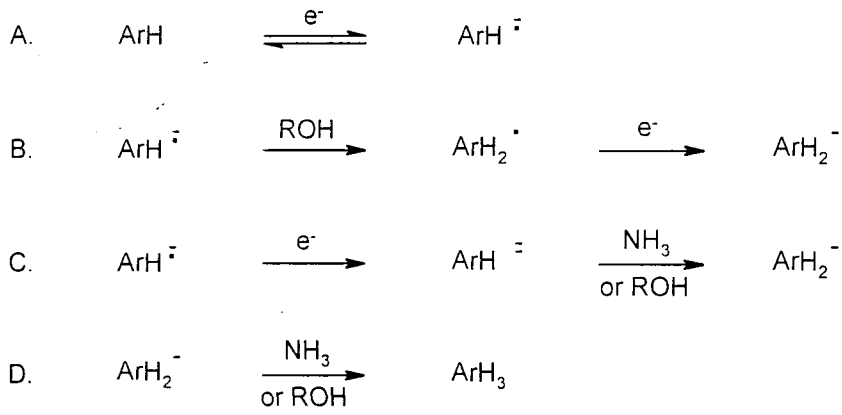


Scheme 1.6.1

2.2 The Birch Reduction

The reduction of aromatic compounds to their dihydro derivatives by alkali metal/ammonia solutions is a powerful synthetic procedure.[48] The metals show a high solubility in liquid ammonia and provide electron rich solutions which are excellent reducing mediums. These solutions, sometimes referred to as "bronz" or "metallic" phases, are generally deep blue in colour and can be used in conjunction with inert co-solvents such as ether or THF (to aid substrate solubility) and weak acids (e.g. alcohols) which act as proton sources.

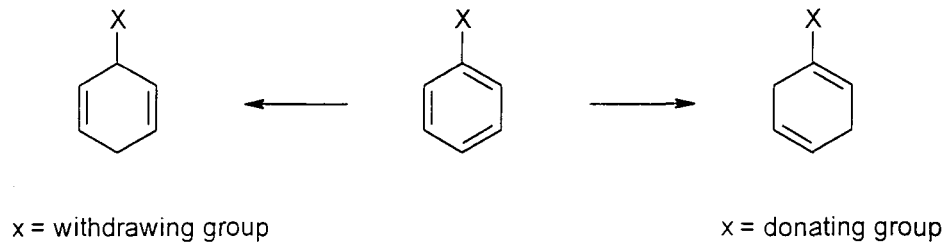
The first step in the mechanism proceeds by the reversible acceptance of an electron by the substrate yielding a radical-anion (Eq. A, Scheme 2.2.1). If the substrate has a high electron affinity it can be further reduced to a dianion (Eq. C). Two subsequent protonation steps then yields the reduced species. In these cases, no proton source is required as protonation occurs readily by ammonia. In less reactive systems (where radical-anion concentration is low) the radical-anion is firstly protonated by alcohol to yield a radical (Eq B) which then accepts another electron and proton (from alcohol or ammonia) providing the reduced species.



Scheme 2.2.1

Substrates for Birch reduction, therefore, can be classified into two categories (relative to benzene), namely, activated or unactivated. Activated aromatics (e.g. polyaromatics, aromatics containing electron withdrawing groups) have high electron

affinities and are able to stabilise anionic intermediates. Unactivated substrates have the opposite properties and include alkylbenzenes, aryl ethers and aminobenzenes. As well as determining reactivity, substituents also control the regioselectivity of the reaction. In this, "electron donating groups direct reduction so that the major product has a maximum number of such groups attached to the residual double bonds, and a minimum number attached to allylic sites"[49] -The Birch Rule. The opposite is true of electron withdrawing groups, Scheme 2.2.2.



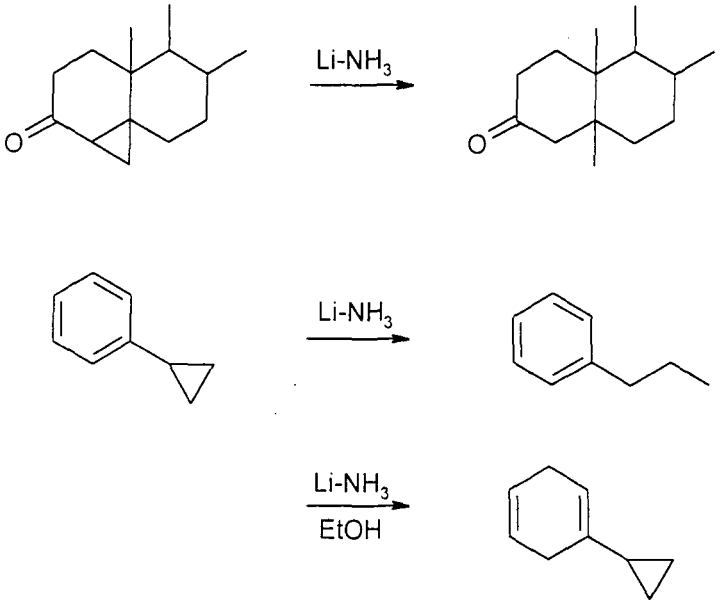
Scheme 2.2.2

The metals most commonly used in the Birch reduction are lithium, sodium and potassium, although calcium has also been successfully employed.[50] The metals vary in reduction potential (Li>K>Na>Ca), having standard electrode potentials in liquid ammonia (at -50°C) of -2.99, -2.73, -2.59 and -2.39V respectively.[51] The choice of metal is, therefore, important and has been shown to affect the outcome of reactions, although this may be in part related to aggregation or co-ordination of anionic intermediates with the metal cation. Other considerations include the use of proton sources, which with activated systems can lead to over reduction, and both temperature[52] and electron concentration[53] can moderate the reaction pathway.

2.3 The Birch Reduction of Phenylcyclopropanes

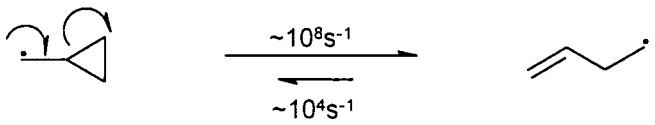
Most classes of aromatic compound have had their Birch reduction chemistry thoroughly reviewed and the technique has become an established laboratory procedure (see section 2.2). In contrast, relatively little work has been conducted on

the Birch reduction of phenylcyclopropanes. It has been demonstrated, however, that cyclopropane rings in conjugation with either a carbonyl[54] or a phenyl[55] group may undergo reductive cleavage under Birch conditions (scheme 2.3.1), although, this is not always the case and there appears to be a fine balance between cleavage and normal aromatic reduction. In this regard, phenylcyclopropane has been shown to undergo cleavage[56] with lithium/ammonia and reduction[57] with lithium/ammonia/ethanol (proton source), Scheme 2.3.1. This has also been demonstrated by Rabideau *et al*[58] in a related system where the ratio between the two has been altered by the choice of metal, solvent and temperature.



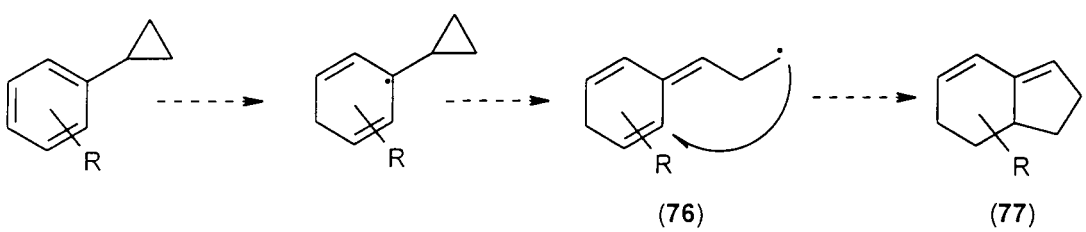
Scheme 2.3.1

In the cleavage mechanism proposed by Walborsky and Pierce for phenylcyclopropanes, the first step is analogous to normal aromatic reduction, that is, acceptance of an electron by the aryl moiety generating a radical-anion.[55b] One canonical form of these species contains a cyclopropylradical. These units are known to undergo rapid ring opening,[59] driven by a release of strain, producing an acyclic butenyl radical, Scheme 2.3.2. In the case of phenylcyclopropanes, this generates hexenyl radical-anion intermediates, subsequent protonation and re-aromatisation of which yields the cleaved products,[60] Scheme 2.3.4.



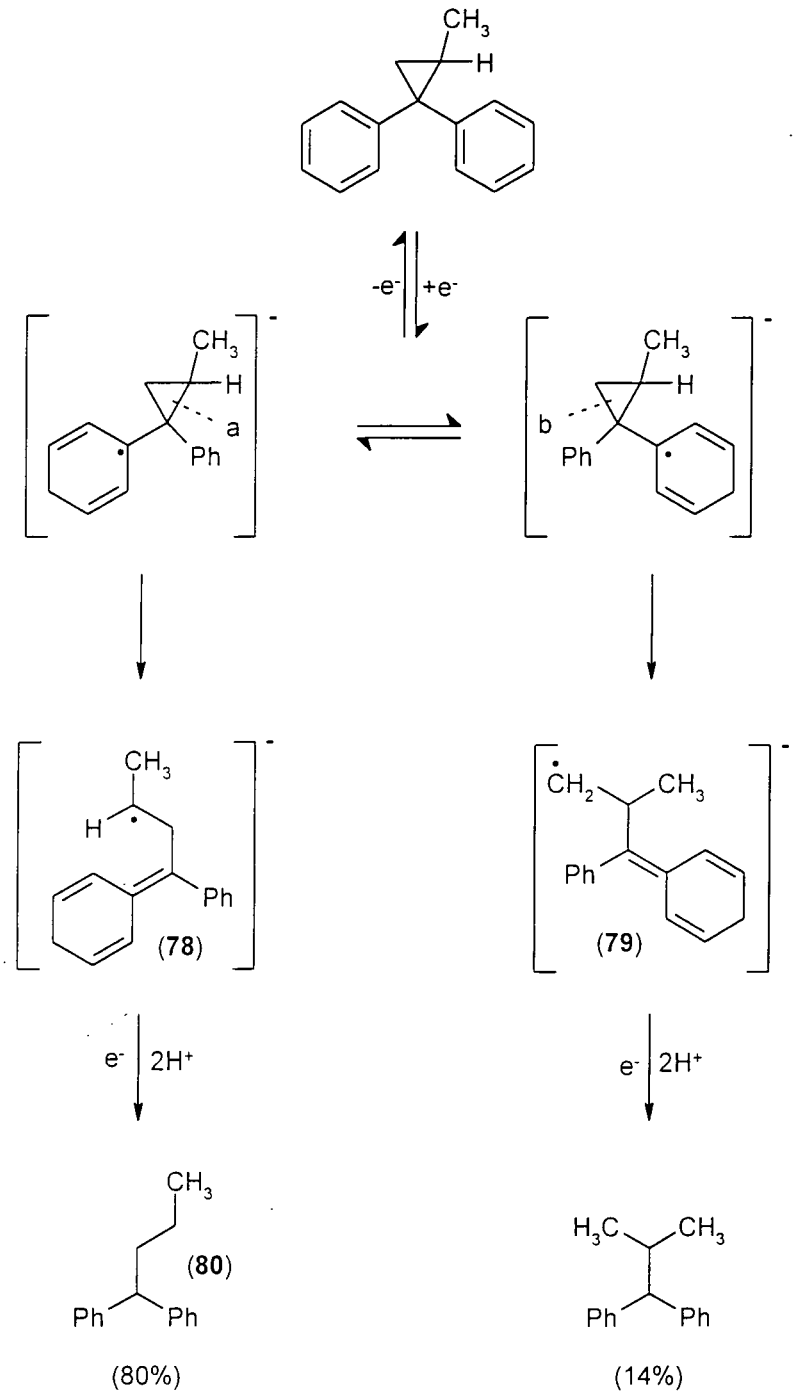
Scheme 2.3.2

Alternatively, in theory, it may be possible for a hexenyl radical (**76**) generated during the reaction to undergo a 5-*exo*-trig cyclisation providing a functionalised indene (**77**), Scheme 2.3.3. This is viable only if the ratio of cyclopropane cleavage to normal aromatic reduction is high. Further, the hexenyl radical (**76**) must also have a sufficiently long lifetime to enable ring closure. Appropriate functionalisation of the cyclopropane with a radical-stabilising group and the phenyl ring with an electron withdrawing group may facilitate this process allowing simple access to this common structural unit.



Scheme 2.3.3

If the substrate contains two non-equivalent cyclopropane bonds, the cleavage mechanism also introduces the possibility of regioselectivity. In this regard, the authors have attributed the regioselectivity observed in scheme 2.3.4 to the stability of the ring-opened intermediates **78** and **79** resulting from the cleavage of bonds a and b respectively. The more stable radical-anion, **78**, giving rise to the major product (**80**). Although there is strong evidence for this hypothesis, other researchers have suggested that regioselectivity can be dictated by steric and electronic effects,[55d] use of solvents[55c] and/or the degree of cyclopropane orbital overlap with the adjacent π system,[54b,60b] that is, the bond possessing maximal overlap being cleaved preferentially.



Scheme 2.3.4

2.4 Phenylcyclopropane Preparation

2.4.1 Introduction

In this model study we wished to evaluate the effect (e.g. mesomeric, inductive) of various functional groups about the cyclopropane ring during Birch reduction and in doing so assess the possible utility of this methodology in the synthesis of ingenol and/or the construction of indene-type molecules (see section 2.3). With these points in mind, our targets were cyclopropanes **81** to **88**, the tri-substituted cyclopropane, **88**, serving as an excellent model compound (cf. structure **67**, scheme 1.6.1) for ingenol synthesis, Figure 2.4.1.

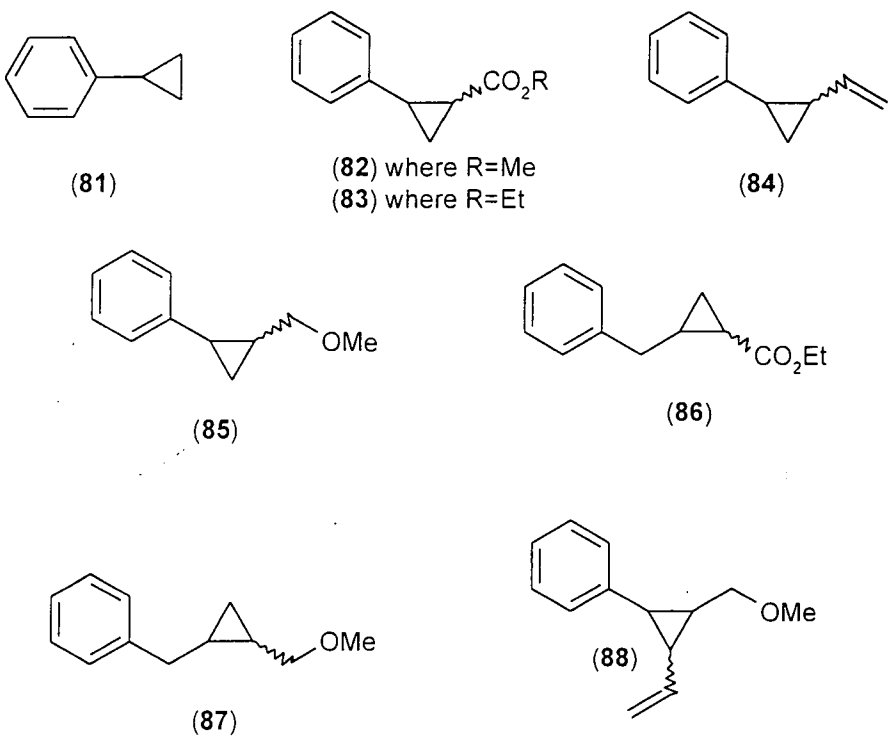
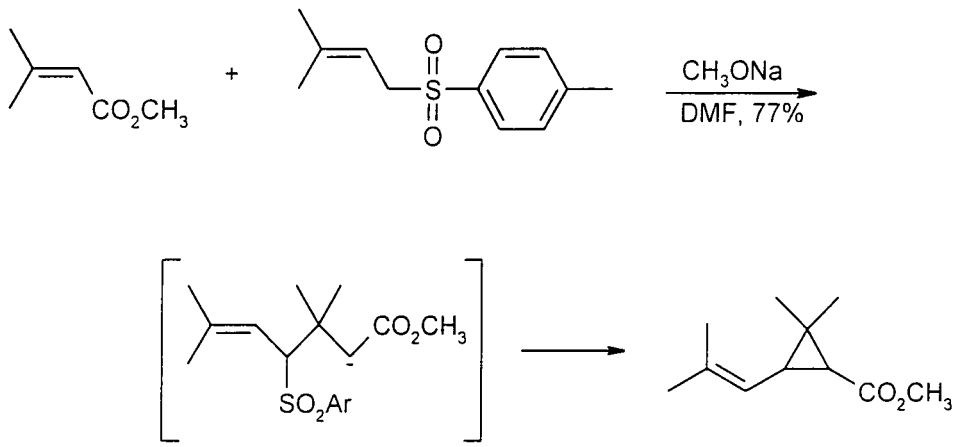


Figure 2.4.1

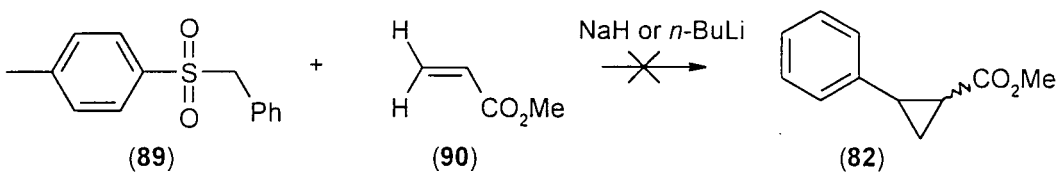
2.4.2 Synthesis of Cyclopropanes 81 to 88

The use of sulfone chemistry in the construction of cyclopropanes has been well documented. An example of which is the synthesis of chrysanthemic esters demonstrated by Schatz,[61] Scheme 2.4.1.



Scheme 2.4.1

Following this precedent, attempts were made to prepare methyl 2-phenylcyclopropanecarboxylate (**82**) by generation of the sulfur ylide of benzyl-*p*-toluene sulfone (**89**) and subsequent reaction with methyl acrylate (**90**). Unfortunately, the use of both NaH and *n*-BuLi as bases failed to result in an effective reaction, starting materials only being recovered, Scheme 2.4.2.

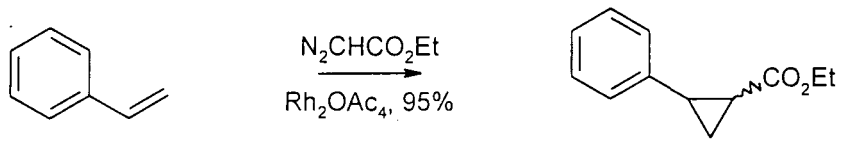


(**89**) (**90**) (**82**)

Scheme 2.4.2

An alternative method of cyclopropyl ester synthesis involves the decomposition of diazo esters in olefins.[62] These reactions are effectively catalysed by several transition metal salts that contain an open co-ordination site which include, among

others, compounds of palladium, copper and rhodium. In the mechanism, the diazo compound undergoes electrophilic addition to the catalyst followed by extrusion of nitrogen. This forms a reactive carbenoid species, which inserts into the double bond providing the cyclopropane.[63] Using this technique, Nozaki[64] and co-workers have synthesised ethyl 2-phenyl-cyclopropanecarboxylate (**83**) from the reaction between styrene (**91**) and EDA using dirhodium tetraacetate as the catalyst. Following this procedure, **83** was obtained in 95% yield as a mixture of *cis* and *trans* isomers (4:6), as ascertained by ^{1}H NMR analysis. The *cis* isomer was distinguished from the *trans* by the large (9Hz) $^3J_{HH}$ coupling constant observed; those associated with *trans* cyclopropanes tend to be of a lower magnitude (4-9.5Hz).[65] The predominance of the *trans* isomer was predicted and is a result of steric effects of the phenyl ring. A molecular ion peak at *m/z* 190 in the mass spectrum confirmed the preparation of the product, as did the presence of a characteristic ester carbonyl stretch (1725cm^{-1}) in the IR spectrum, Scheme 2.4.3.

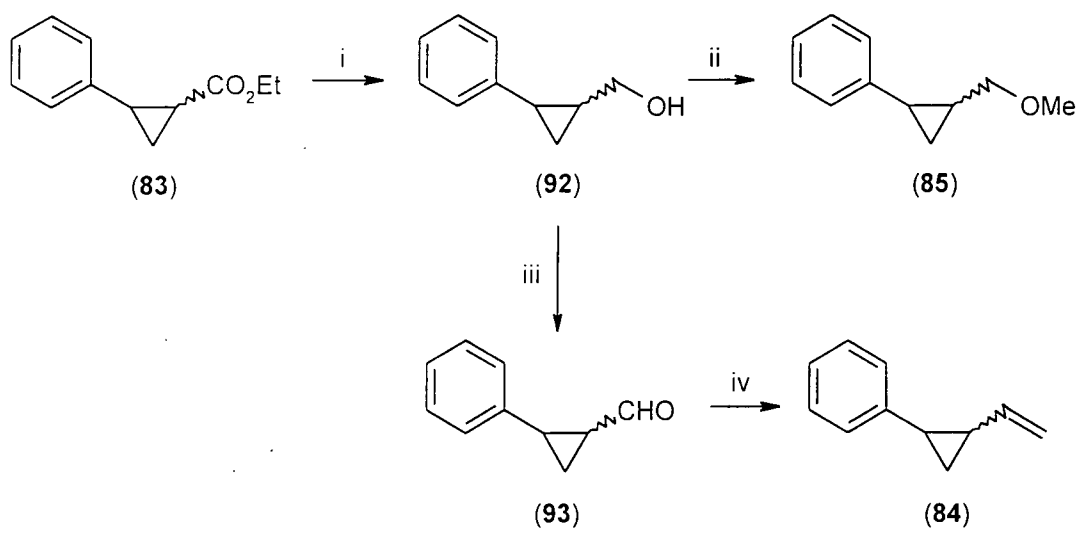


(**91**) (**83**)

Scheme 2.4.3

With **83** in hand, the methoxyl and vinyl substituted cyclopropanes, **85** and **84**, were readily available, Scheme 2.4.4. The ester, **83**, being handled as a mixture of diastereoisomers, was firstly reduced by treatment with $LiAlH_4$, the resultant alcohol (**92**) was obtained in 89% yield. The transformation was accompanied by the appearance of a distinctive broad OH stretch in the IR spectrum (3125-3550cm^{-1}) and the loss of all ethoxyl signals in the ^{1}H NMR whilst EI-MS provided a molecular ion at *m/z* 148. In the next step, conversion to the methoxy ether (**85**) was achieved under the standard conditions of MeI and KOH in 90% yield. **85** was obtained after FCC as a 1:2 mixture of diastereoisomers (^{1}H NMR). The formation of this product was confirmed by characteristic methoxy singlets between δ3.28 and δ3.60 in the ^{1}H NMR and the correct $M+NH_4^+$ peak at *m/z* 180 by CI-MS. Oxidation of the alcohol **92** to the corresponding aldehyde (**93**) was effected with PCC/alumina. Using PCC

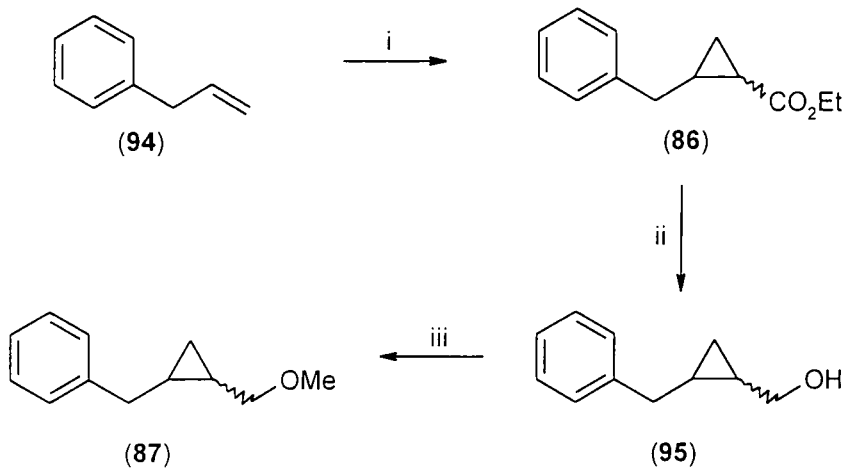
in this manner avoids troublesome chromium deposits during work-up and the crude product was isolated by a simple filtration on completion of the reaction.[66] The product (**93**) was obtained in 76% yield after FCC and the structure was confirmed by the appearance of aldehyde doublets at δ8.76 and δ9.42 in the ^{1}H NMR corresponding to two diastereoisomers. The IR spectrum was also very distinctive, containing an aldehyde carbonyl stretch at 1703cm^{-1} and two aldehyde proton stretches at 2732 and 2835cm^{-1} respectively. In the final step, conversion of aldehyde **93** to the vinyl substituted cyclopropane (**84**) was achieved by reaction with the Wittig reagent generated from methyl triphenylphosphonium iodide and *n*-BuLi, the product being obtained in 74% yield as a 1:1 mixture of diastereoisomers (^{1}H NMR). The ^{1}H NMR spectrum for this product also showed terminal olefin signals between δ4.82 and δ5.65 and CI-MS gave *m/z* 145 ($M+1^+$) as the base peak.



Scheme 2.4.4. Reagents: i, $LiAlH_4$, 89%; ii, MeI, KOH, 90%; iii, PCC/alumina, 76%; iv, Ph_3PCH_2I, *n*-BuLi, 74%.

The ester, **86**, was accessed using an analogous method to that described for the preparation of ethyl 2-phenyl-cyclopropanecarboxylate (**83**), that is, rhodium catalysed decomposition of EDA in alkene, Scheme 2.4.5. However, in this case, allyl benzene (**94**) replaced styrene and **86** was prepared in 59% yield as a 2:1 mixture of diastereoisomers (^{1}H NMR). In the preparation of **83**, comparison of the cyclopropane coupling constants in the ^{1}H NMR identified the *trans* isomer as the major product. In this case, the cluttered nature of the ^{1}H NMR spectrum prevented

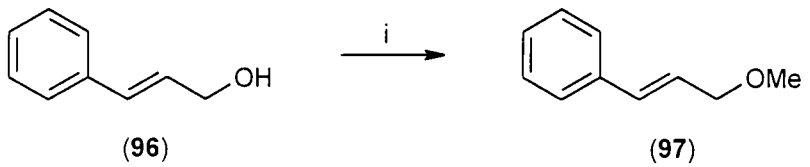
such analysis, however, it is assumed that the *trans* isomer again predominates. Confirmation of the structure was provided by characteristic quartet (δ4.10-δ4.35) and triplet (δ1.20-δ1.36) ethyl ester signals in the ^{1}H NMR as well as the presence of four "doublet of doublets" at δ2.58, δ2.76, δ2.85 and δ2.94 which correspond to the extra methylene group in this homologue. A strong molecular ion peak (21%) at *m/z* 204 was also observed by EI-MS.



Scheme 2.4.5. Reagents: i, EDA, $Rh_2(OAc)_4$, 59%; ii, $LiAlH_4$, 83%; iii, MeI, KOH, 72%.

As in the previous synthesis, ester reduction of **86** was effected by treatment with $LiAlH_4$ (83%) and protection of the resultant primary alcohol (**95**) provided the methyl ether (**87**) which was isolated (72%) as a 2:1 mixture of diastereoisomers. The preparation of **95** was confirmed by a broad OH stretch in the IR spectrum (3100-3500cm^{-1}) and a molecular ion peak at *m/z* 162 was evident in the mass spectrum (EI-MS). The preparation of **87** was accompanied by the appearance of two methoxy singlets in the ^{1}H NMR between δ3.16 and δ3.50 whilst a strong (100%) $M+NH_3^+$ peak (*m/z* 194) was observed by CI-MS.

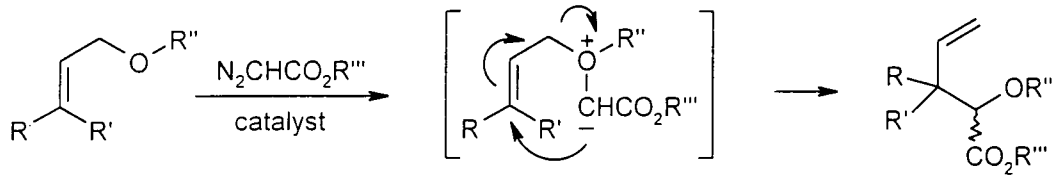
The tri-substituted cyclopropane (**88**) has been accessed by a five-step procedure. In the first step, *trans*-cinnamyl alcohol (**96**) was protected as its methyl ether (**97**) by treatment with MeI and KOH. **97** was isolated after distillation in 89% yield. A molecular ion was observed (*m/z* 148) by EI-MS and a methoxy singlet was apparent in the ^{1}H NMR spectrum at δ3.51, Scheme 2.4.6.



(96) (97)

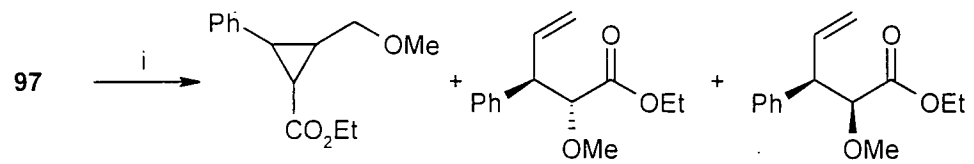
Scheme 2.4.6. Reagents: i, KOH, MeI, 89%.

In the next step, it was necessary to cyclopropanate this allylic ether with EDA. However, the reaction between allylic ethers and diazocarbonyl compounds is sometimes complicated by the formation of oxonium ylides.[67] This provides a framework for [2,3] sigmatropic rearrangements as depicted in scheme 2.4.7.



Scheme 2.4.7

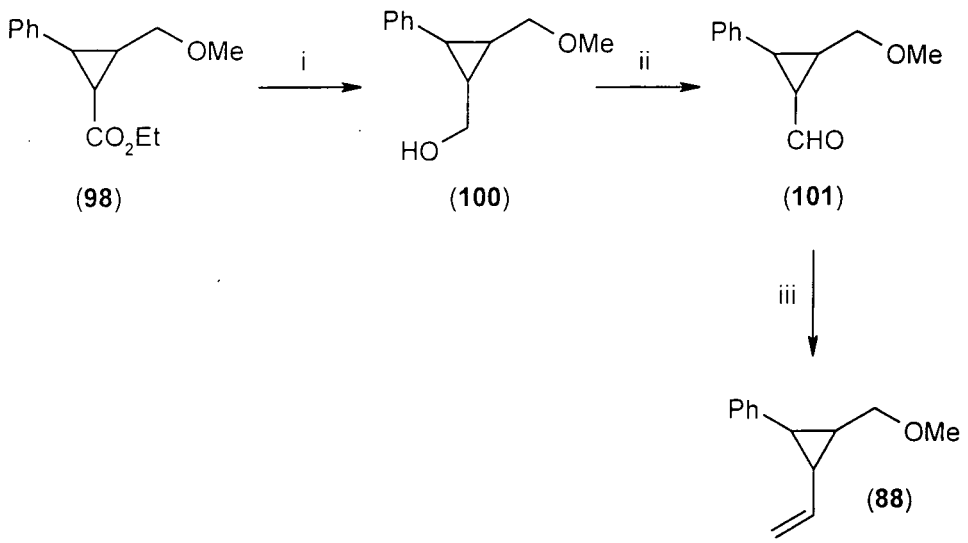
In the event, a complicated mixture of products was indeed isolated (93% mass recovery) which proved difficult to separate by FCC. Nevertheless, repeated chromatography did enable the separation, albeit in low yield (4%), of the desired cyclopropane (**98**) as a single diastereoisomer together with a quantity (8%) of the rearrangement product **99** (as a mixture of two diastereoisomers), Scheme 2.4.8.



(98, 4%) (99, 8%)

Scheme 2.4.8. Reagents: i, EDA, $Rh_2(OAc)_4$.

The structure of **98** was confirmed by the presence of an ethoxyl quartet (δ4.28) and triplet (δ1.38) in the ^{1}H NMR together with three high field cyclopropane protons at δ2.10, δ2.22 and δ2.69. The signal at δ2.69 corresponds to the cyclopropane proton adjacent to the phenyl ring and appears as a triplet with a coupling constant of 5.8Hz. Coupling constants of this magnitude are characteristic of *trans* cyclopropanes (as discussed earlier, p33).[65] The diastereoisomer isolated, therefore, has a *trans* relationship between the phenyl ring and both the ether (a result of the all-*trans* starting material) and the ester functionality. The structures of **99** were confirmed by comparison of ^{1}H NMR spectral data with that obtained by Doyle and co-workers[67] who have also reported this reaction and are consistent with the configurations shown. To complete the synthesis of **88**, the ester functionality was manipulated in a similar sequence to that previously described for the preparation of **84** (page 34). That is, $LiAlH_4$ reduction to the primary alcohol (**100**) (70%), Swern oxidation (82%) to the aldehyde, **101**, and finally, installation of the vinyl group by Wittig reaction (43%), Scheme 2.4.9.

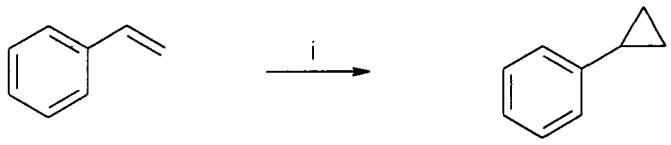


Scheme 2.4.9. Reagents: i, $LiAlH_4$, 70%; ii, $(COCl)_2$, DMSO, **100** then NEt_3, 82%; iii, Ph_3PCH_2I, *n*-BuLi, 43%.

Verification of successful reduction of the ester (**98**) was obtained from the IR spectrum, which contained a prominent OH stretch (3100-3600cm^{-1}). An accurate mass was also obtained (192.1149), which matched the calculated value (192.1150).

The formation of the aldehyde (**101**) coincided with the appearance of a typical aldehyde peak (δ9.71) in the ^{1}H NMR and the IR spectrum contained a characteristic aldehyde carbonyl stretch (1701cm^{-1}). Whereas the disappearance of such signals in the spectra recorded for **88**, indicated that the terminal olefin unit had been introduced.

Phenylcyclopropane (**81**) was prepared from styrene following a modified Simmons-Smith procedure.[68] In this, a diethyl zinc/methylene iodide combination replaces the classical Zn-Cu couple/methylene iodide system to effect carbene generation, Scheme 2.4.10. In many cases increased product yields have been reported under these conditions. However, in the event, even with excess reagents (3eq. $ZnEt_2$ and 4eq. CH_2I_2) and extended reaction times (38 hours), low conversion to **81** was observed (29%). Product purification also proved troublesome, excess styrene was removed by Spaltrohr distillation but removal of residual methylene iodide could not be effected by either distillation or chromatography. As a result, this product was subsequently handled as a mixture. Corroboration of the structure was obtained from the ^{1}H NMR spectrum, which contained the correct number (five) of high-field cyclopropane signals (δ0.75-δ1.92), and from EI-MS, which provided a strong (58%) molecular ion peak (*m/z* 118).



(**91**) (**81**)

Scheme 2.4.10. Reagents: i, Et_2Zn, I_2CH_2, 29%.

2.5 Lithium Reductions with the Absence of H^+ (Series 1)

2.5.1 Introduction

This first series of reductions was designed to evaluate the propensity of the phenylcyclopropanes under study to reductively cleave, better understand the nature of the mechanisms at work (e.g. ionic, radical) and thus, ultimately, control or moderate the ratio of aromatic reduction to cyclopropane cleavage. The cyclopropanes, **81** and **83** to **87** are unactivated and were, therefore, reduced under a standard set of conditions recommended for the reduction of such aryls.[69] These were 10eq lithium, 200ml of $l.NH_3$ per 1g of lithium, an ether co-solvent and at a temperature of –78°C. The reactions were quenched with ethanol 2 hours after the achievement of the characteristic deep blue colour associated with the Birch reduction. Ammonia was then evaporated and, after the addition of water, extractive isolation (ether) provided the products.

2.5.2 Series One Reductions –Results

The reduction of phenylcyclopropane (**81**) provided a mixture (0.22g) of two products (GC). Attempts to separate these compounds by both distillation and chromatography proved fruitless, however, it was possible by ^1H NMR analysis to identify the components as unreacted starting material and the dihydro product (**102**) in the ratio 1:2.5 respectively (equating to 15% of **102**), Scheme 2.5.1. The three vinyl protons for this product appeared between δ5.45 and δ5.72 and the GC EI-MS spectrum showed a strong molecular ion (19%) at *m/z* 120 whereas the base peak (*m/z* 70) corresponded to the loss of the cyclopropyl unit (C_3H_5). The residual methylene iodide contaminant present in the starting material was not evident in the crude product (^1H NMR) and may have been converted to the amine salt during the reaction; thus being consigned to the aqueous layer during work-up. This side reaction appeared not to effect the reduction process although the product yield was notably low.

(**81**) (**102**, 15%)

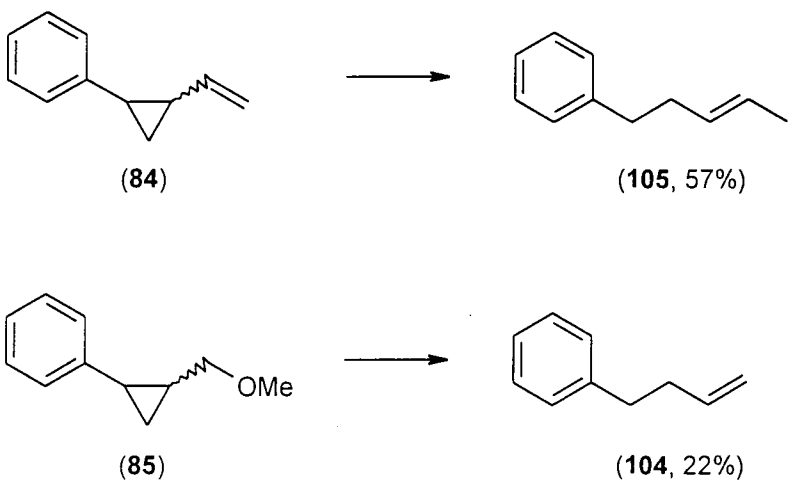
Scheme 2.5.1

The reduction of **83** resulted in a complicated mixture of "decomposition" products, the only discernible compound being the ring opened product, 4-phenylbutanoate (**103**), which was isolated by FCC in 26% yield, Scheme 2.5.2. Ester groups are known to undergo direct reduction under dissolving metal conditions, for example, the Bouveault-Blanc procedure,[70] and a reaction of this type may be responsible for the low yield observed here. **103** was identified by ethoxyl signals in the ^{1}H NMR at δ1.26 (3H triplet) and δ4.12 (2H quartet) and a prominent ester carbonyl at 1731cm^{-1} in the IR spectrum. A molecular ion was also observed by EI-MS (*m/z* 192).

(**83**) (**103**, 26%)

Scheme 2.5.2

Ring opened products also resulted from the reduction of **84** and **85**, Scheme 2.5.3. In the case of **85**, 1-phenyl-but-3-ene (**104**). This compound was isolated after FCC in 22% yield and showed distinctive terminal alkene proton signals at δ5.13-δ5.25 (2H) and δ6.02 (1H) in the ^{1}H NMR spectrum and a molecular ion at *m/z* 132 by EI-MS. 2-phenyl-vinylcyclopropane (**84**) provided the alkene **105** in a more respectable yield of 57%. GC-MS analysis of the crude product in this case indicated the presence of a small quantity of an isomeric material; presumably the *cis* alkene, however, attempts to isolate this compound by FCC failed. The ^{1}H NMR again provided conclusive evidence for the formation of this compound, having vinyl signals at δ5.63 (2H) and aromatic signals between δ7.20 and δ7.40 (5H). The mass spectrum corroborated this, containing a molecular ion at *m/z* 146 and a tropylium ion (*m/z* 91) as the base peak.

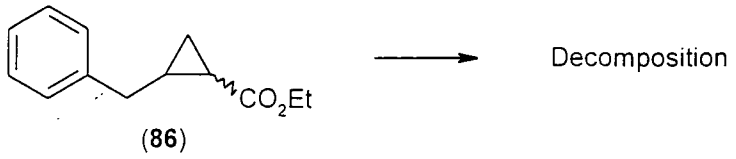


(**84**) (**105**, 57%)

(**85**) (**104**, 22%)

Scheme 2.5.3

A substantial amount of fragmentation occurred on reduction of the ester homologue, **86**. The major products of which proved to be unstable on silica. As a result, satisfactory isolation and characterisation of individual products was not possible, Scheme 2.5.4. This is most probably a result of competitive ester reduction (as seen previously with **83**).



(**86**)

Scheme 2.5.4

In the case of **87,** the cyclopropane ring remained intact during reduction, providing the product of aromatic reduction, the dihydro derivative **106**, Scheme 2.5.5. This product was isolated (20% after FCC) as a mixture of diastereoisomers in the same ratio as the starting material (1:2, *cis*:*trans*). The process of aromatic reduction was not very efficient, however, and a substantial amount of starting material was also obtained (26%). **106** was identified by characteristic cyclohexadiene CH_2 group signals in the ^1H NMR (δ2.55-δ2.80) and a molecular ion (*m/z* 178) by EI-MS. An

accurate mass was also obtained (178.1358), which corresponded with the calculated value (178.1358).

(**87**) (**106**, 20%)

Scheme 2.5.5

2.6 Lithium Reductions in the Presence of H^+ (Series 2)

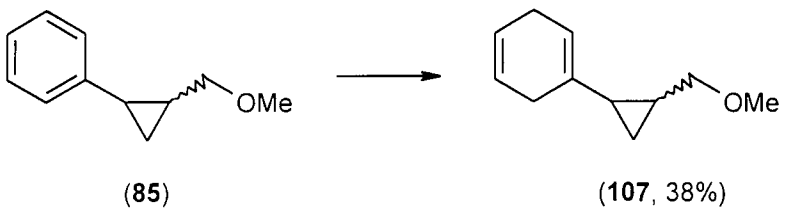
2.6.1 Introduction

In the first series of reductions cyclopropane ring cleavage was observed if the cyclopropane was conjugated with the aromatic ring and was also substituted with methoxymethyl, vinyl or ester functionality. Reductive cleavage was not observed if an extra methylene group was inserted between the aromatic ring and the cyclopropane. This second series of reductions was designed to see if the tendency of the cyclopropane to cleave would be effected in the presence of a proton source (e.g. alcohol). The substrates **84**, **85** and **88** were, therefore, reacted under identical conditions to those described previously (series 1, section 2.5) except ethanol (3eq.) was used as a proton source. Additionally, **84** was subjected to reduction using 10 equivalents of ethanol. The use of a proton source can alter the reaction time as the alkali metal is slowly destroyed by the acid resulting in "self-quenching" of the reaction. This was the case for the tri-substituted cyclopropane, **88**, and the reaction of **84** using 10eq of ethanol, in which the deep blue colour persisted for 45 minutes and one hour respectively.

2.6.2 Series Two Reductions –Results

Contrary to the previous result, the reduction of **85** in the presence of ethanol resulted in aromatic reduction only, the dihydro product **107** being isolated in 38% yield as an

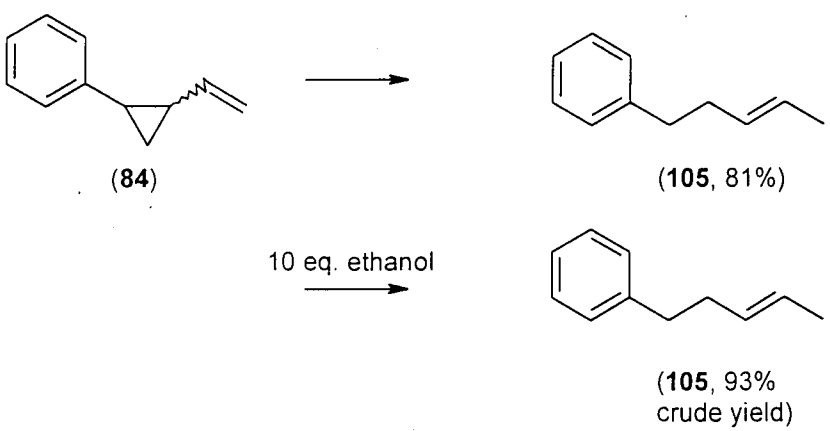
inseparable mixture of diastereoisomers (1:1), Scheme 2.6.1. The structure shown is consistent with all the analytical data obtained, including the ^{1}H NMR, which was devoid of aromatic protons but contained CH_2 cyclohexadiene signals between δ2.45 and δ2.75. An MH^+ peak (*m/z* 165) was also observed by CI-MS.



(**85**) (**107**, 38%)

Scheme 2.6.1

The reduction of 2-phenyl-vinylcyclopropane (**84**) again resulted in the ring opened alkene, **105**, although in the higher yield of 81%. Repeating the reaction using 10 equivalents of ethanol had no effect other than to increase this further to 93%, Scheme 2.6.2.



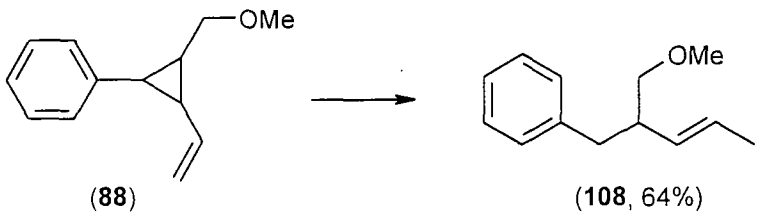
(**84**) (**105**, 81%)

(**105**, 93% crude yield)

Scheme 2.6.2

Considering the above result, it was unsurprising to isolate **108** (64%) from the reaction of tri-substituted cyclopropane **88**, Scheme 2.6.3. The ^{1}H NMR spectrum of **108** contained a 3H doublet centred at δ1.64 corresponding to the terminal methyl group and the ^{13}C NMR contained six signals in the aromatic/olefinic region of the spectrum ranging from δ125.7 to δ140.2 which is correct for the structure as shown.

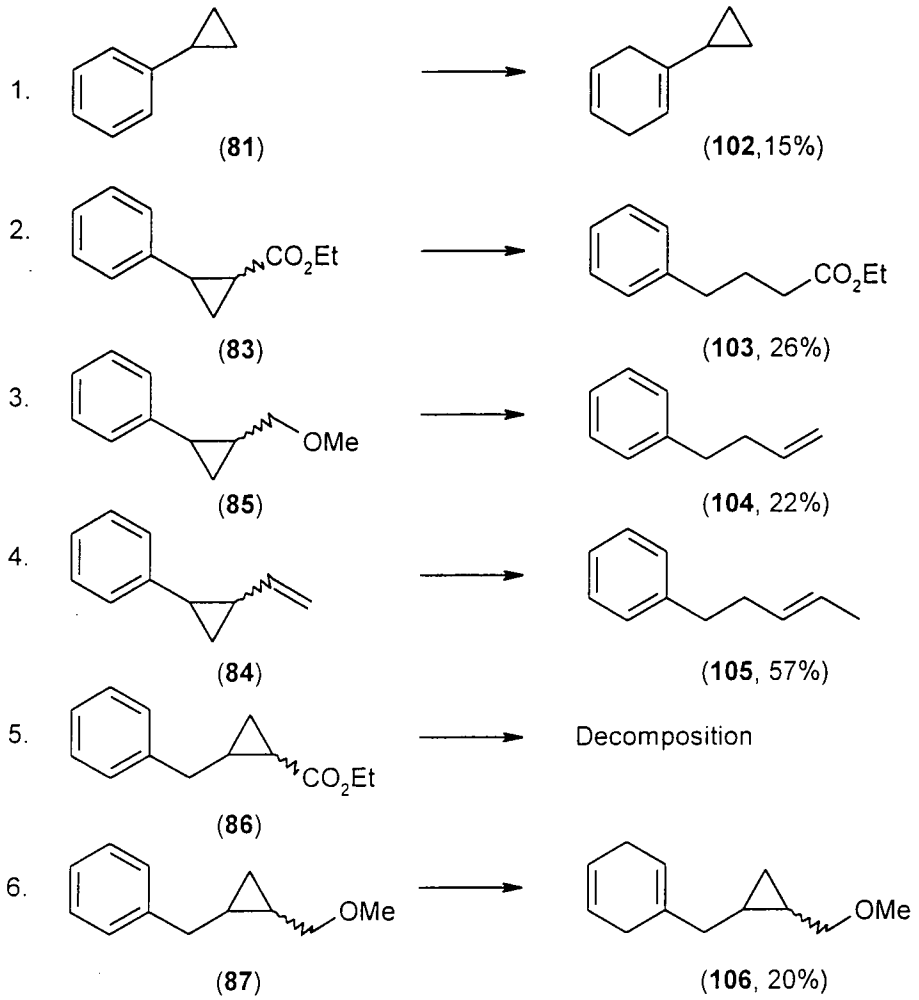
Further evidence was obtained from the mass spectrum (EI-MS), which contained a molecular ion at *m/z* 190 and a tropylium ion (*m/z* 91) as the base peak.



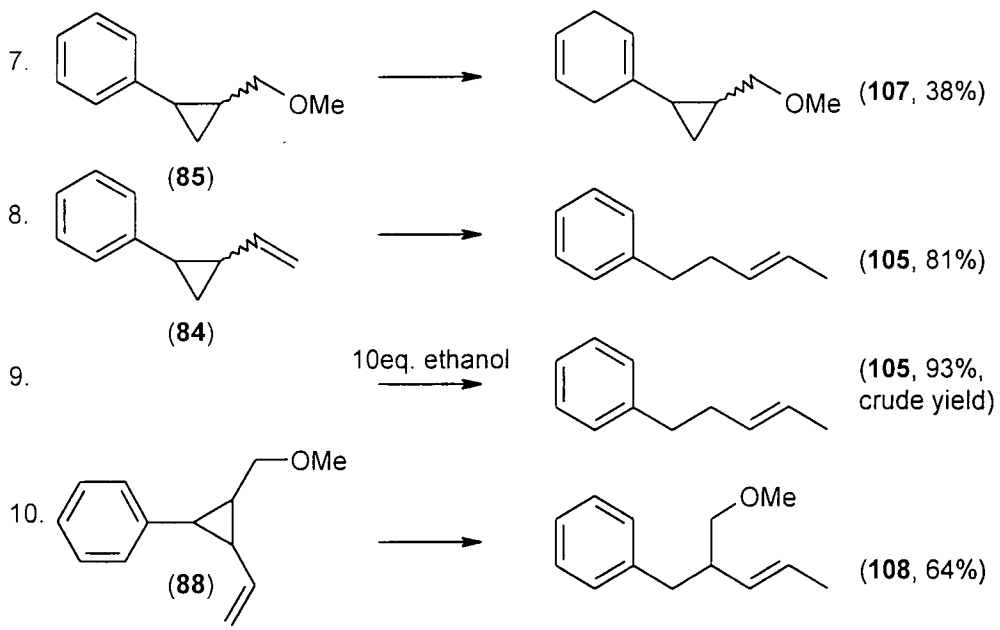
(**88**) (**108**, 64%)

Scheme 2.6.3

2.7 Summary of Series 1 Reductions



2.8 Summary of Series 2 Reductions



2.9 Conclusions -Series One and Two

In the first series of reductions, substituting the cyclopropane with an ester, methoxymethyl or vinyl group resulted in reductive cyclopropane ring fragmentation (entries 2, 3 and 4, section 2.7). The ring opening was also shown to occur in a regiospecific manner. In this, of the two cyclopropane bonds available, only products resulting from the cleavage of bond A (figure 2.9.1) were observed. These observations support the mechanism proposed by Walborsky and Pierce (see page 30) in which the cyclopropane ring is encouraged to open (as a radical-anion) in the direction of an appropriately substituted β-carbon.[55b] Such a substituent (in our case an ester or vinyl group) acts to stabilise the resultant ring-opened intermediate. We have demonstrated that a leaving group (in our case a methoxy group) also encourages this behaviour, Scheme 2.9.1.

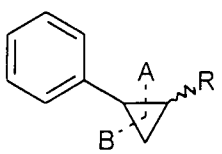
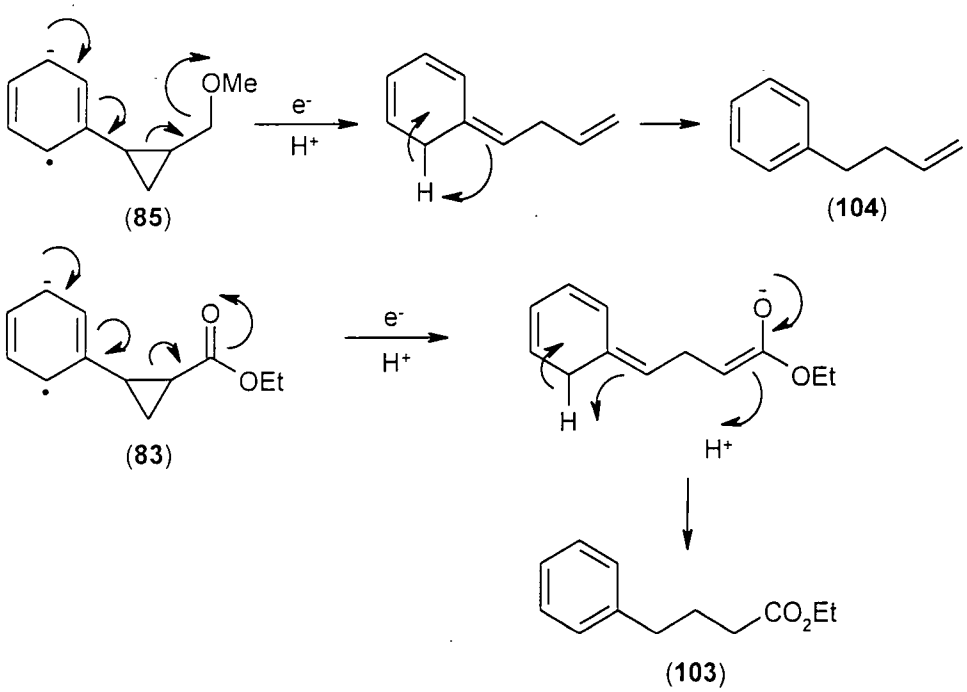


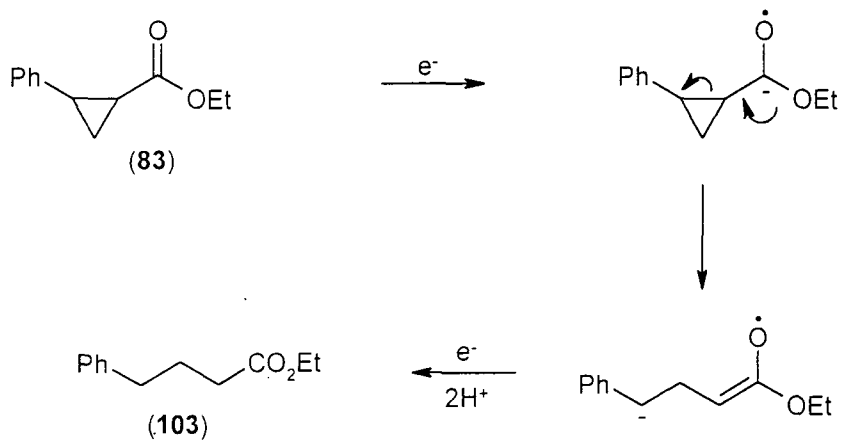
Figure 2.9.1



Scheme 2.9.1

This mechanism is substantiated by both entries 1 and 6 (section 2.7). In the former, phenylcyclopropane (**81**) contains no stabilising functionality, and in the latter, the flow of electrons from the aryl moiety is prevented by the incorporation of methylene spacer. In both cases, normal aromatic reduction results. The result for phenylcyclopropane is also contrary to the literature, which suggests that a proton source is necessary to avoid cyclopropane ring cleavage[56] (see Scheme 2.3.1).

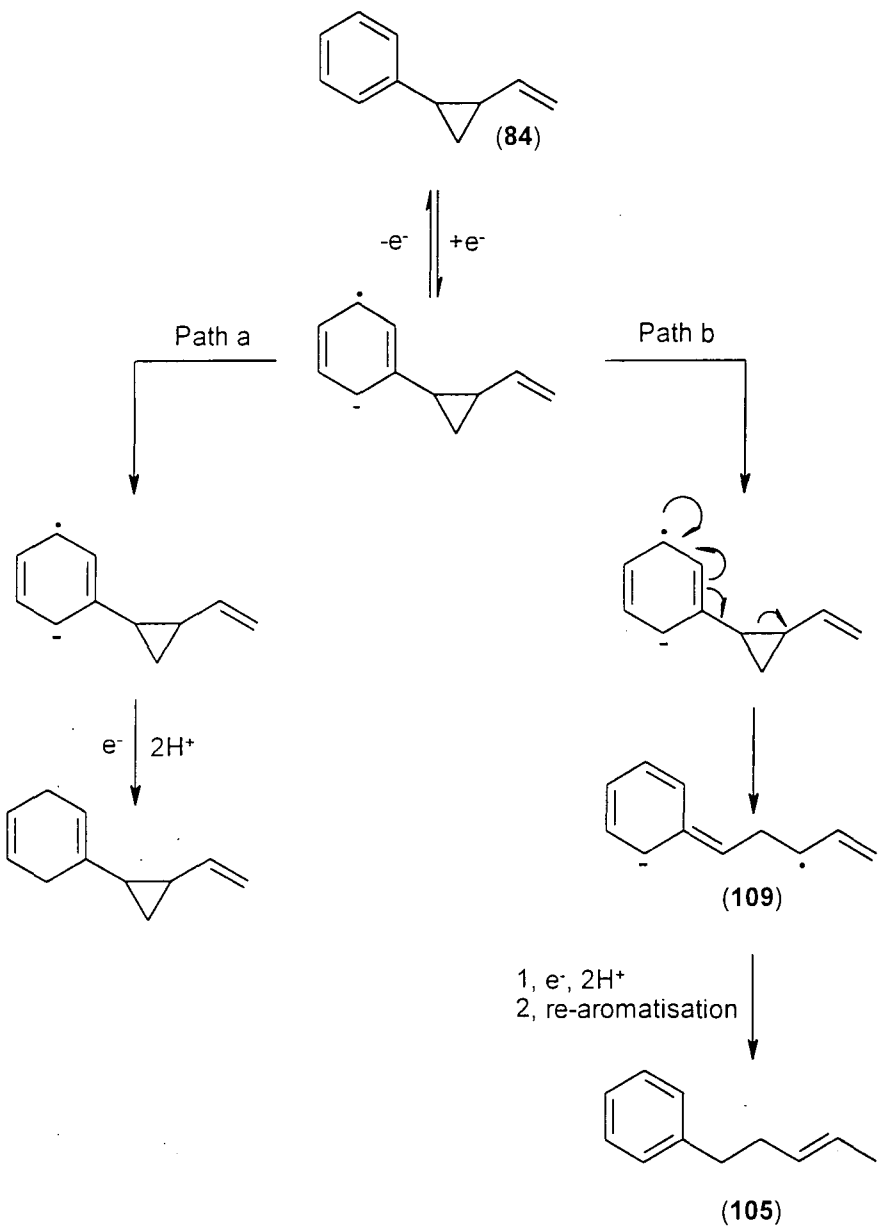
It should be noted that although the product obtained from the reduction of ethyl-2-phenylcyclopropanecarboxylate (**83**), that is, the ester **103**, is consistent with the mechanism proposed earlier (scheme 2.9.1), cyclopropane rings conjugated only with a carboxylate group can also undergo cleavage.[71] Therefore, another alternative mechanism involving initial electron attack of the ester functionality may also be possible with this substrate, Scheme 2.9.2.



Scheme 2.9.2

In the second series of reductions, the presence of a proton source in the reducing medium appeared to promote the ring cleavage of 2-phenyl-vinylcyclopropane (**84**), the alkene **105** being isolated in excellent yield (entries 8 and 9, section 2.8). As the starting material in these reactions was a 1:1 mixture of *cis* and *trans* isomers, the high yields (i.e. >50%) of cleaved product also demonstrates the process to be indiscriminate of cyclopropane geometry. In the case of **85**, this process was seen to be halted (entry 7, section 2.8), the reaction yielding the product of normal aromatic reduction only (**107**). We believe this is a result of protonation of ionic intermediates, thus precluding the cyclopropane ring opening mechanism shown in

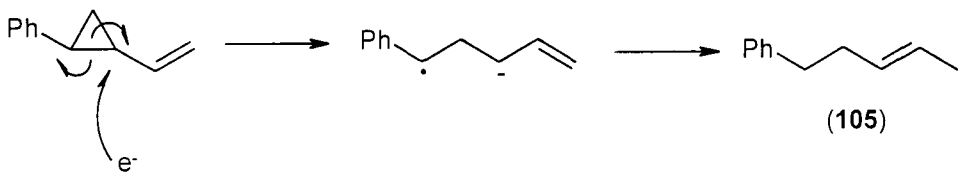
Scheme 2.9.1. This observation also suggests a radical process associated with vinyl substitution, which is not hindered by proton sources. A possible mechanism is shown in Scheme 2.9.3. The ring opening pathway (path b), resulting in the stabilised radical intermediate, **109**, occurring faster than further aryl reduction (path a).



Scheme 2.9.3

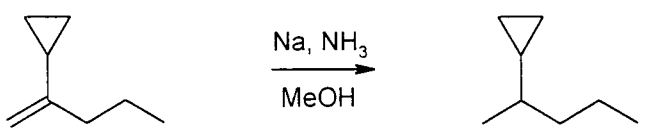
The preference for vinyl assisted ring opening under these conditions was once again highlighted in the reduction of the tri-substituted cyclopropane, **88**, which provided the acyclic product **108** in good yield (entry 10, section 2.8). This substrate served as an excellent model compound for the synthesis of ingenol and the implications of this result are discussed in more detail later (section 3.2.1).

The results from series one and two reductions, although firm, do not entirely rule out the possibility of an alternative mechanism for vinyl assisted cyclopropane cleavage. In this, the vinylcyclopropyl unit maybe attacked directly as illustrated below, Scheme 2.9.4.



Scheme 2.9.4

However, this mechanism above seems unlikely as it has been demonstrated elsewhere that double bond reduction is the usual product in this situation,[72] Scheme 2.9.5. Further, the dihydro derivative (**107**) produced from **85** (entry 7, section 2.8) also contains a vinylcyclopropyl unit which failed to undergo cleavage.

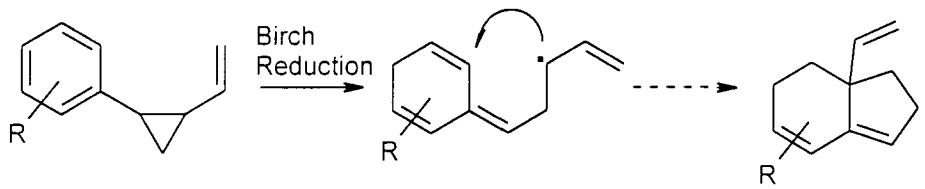


Scheme 2.9.5

2.10 Approaches to Vinyl Substituted Phenylcyclopropanes

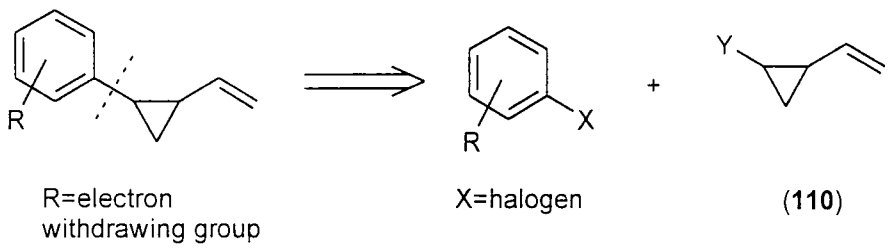
2.10.1 Introduction

A primary objective of our study into the Birch reduction chemistry of phenylcyclopropanes was to generate indene-type molecules. No such compounds were isolated in our initial investigations (see sections 2.7 and 2.8), however, the results from these studies suggest that vinyl substituted phenylcyclopropanes undergo a facile radical ring cleavage under Birch reduction conditions. In order to prepare an indene, the radical intermediate formed in these reactions must undergo a 5-*exo*-trig cyclisation reaction as outlined in scheme 2.10.1.



Scheme 2.10.1

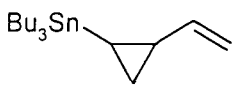
For this to occur, the radical must ring-close at a faster rate than simple quenching. Believing that substitution of the phenyl ring with an electron-withdrawing group may encourage this process, access to a range of such 1-phenyl-2-vinylcyclopropanes was required. It was anticipated that this could be achieved through the preparation of a common intermediate (**110**), which could undergo transition metal mediated cross-coupling with a number of substituted halo-aromatics, Scheme 2.10.2. Three approaches to compounds of this type have been made and are discussed in the following sections.



Scheme 2.10.2

2.10.2 Preparation of Cyclopropyltin Compounds

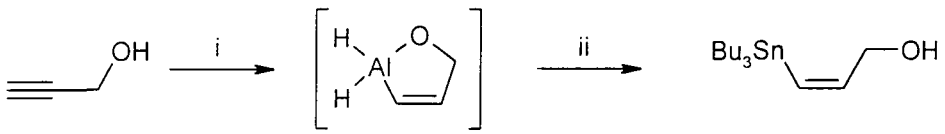
The palladium catalysed cross-coupling reaction of organotin reagents with organic halides, pioneered by Stille, is a versatile method of generating carbon-carbon bonds.[73] Aryl halides are competent partners in this reaction and have been shown to undergo successful coupling with a wide range of organotin compounds including alkylnyl, alkenyl and alkyl tins. The cyclopropyl tin species, **111**, previously prepared by Corey *et al*,[74] was therefore targeted, Figure 2.10.1.



(111)

Figure 2.10.1

Following the Corey procedure, propargyl alcohol (**112**) was firstly subjected to *trans* hydroalumination by reaction with $LiAlH_4$; this led to the formation of the Z-3-alumino-2-propene-1-oxide species (**113**). Subsequent treatment with tri-*n*-butyltin triflate then provided the vinyl stannane (**114**). This compound proved to be unstable on silica (ascertained by 2D tlc) but rapid FCC did allow partial purification, the semi-pure oil being isolated in 73% yield, Scheme 2.10.3.

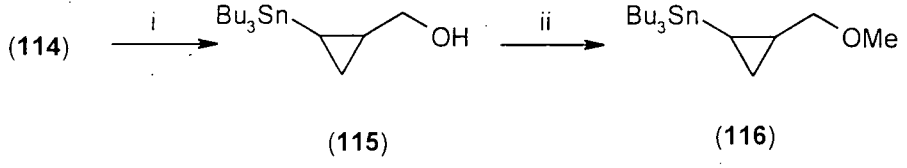


(112) **(113)** **(114)**

Scheme 2.10.3. Reagents: i, $LiAlH_4$, then ii, Bu_3SnOTf, 73% (2 steps).

The formation of **114** was verified by the presence of characteristic tri-*n*-butyl groups in the ^1H NMR spectrum (δ0.71-δ1.71) and a broad OH stretch in the IR spectrum (3100-3600cm^{-1}). The mass spectrum (EI-MS) also contained tin isotope patterns and a peak at *m/z* 291 corresponding to the loss of an *n*-butyl group (both CI-MS and FAB-MS failed to obtain a molecular ion peak). Cyclopropanation of **114** was

effected utilising the standard Simmons-Smith procedure, namely, Zn/Cu couple in combination with methylene iodide, Scheme 2.10.4. As organotin compounds can show a degree of acid sensitivity, diisopropylethylamine was used to complex the zinc iodide produced during the reaction and thus lower the Lewis acidity. **115** was obtained in 45% yield and was identified by the appearance of prominent cyclopropane signals in the ^{13}C NMR spectrum (δ1.5, δ7.1 and δ17.4) and the disappearance of vinyl signals in the ^{1}H NMR spectrum. On this occasion CI-MS provided further evidence in the form of a peak at *m/z* 72 (100%) which corresponds to the loss of the $SnBu_3$ unit from MH^+. At this point in the synthesis, although it was possible to convert the primary alcohol of **115** to a vinyl group as described by Corey and thus complete the synthesis of **111**, it was decided to simply protect this unit in order to test the Stille cross-coupling reaction. To this effect, **115** was treated with MeI and KOH, the methoxy ether, **116**, being obtained in 66% yield. The formation of **116** coincided with the appearance of a methoxy singlet in the ^{1}H NMR spectrum (δ3.29) and a C-O stretching band at 1107cm^{-1} in the IR spectrum. As previously, it was not possible by either CI-MS or FAB-MS to obtain a molecular ion in the mass spectrum, however, a peak at *m/z* 319 (100%) arising form the loss of an *n*-butyl group from the molecular ion was evident by EI-MS.

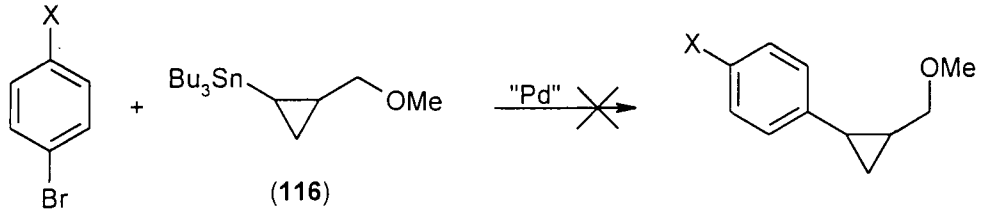


Scheme 2.10.4. Reagents: i, Zn/Cu, I_2CH_2, *i*-Pr_2NEt, 45%; ii, MeI, KOH, 66%.

2.10.3 Attempted Stille Coupling of Cyclopropyltin (116)

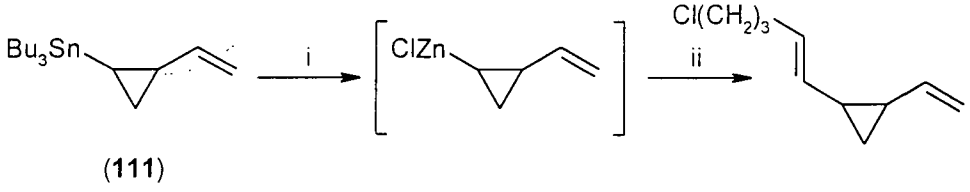
Aryl bromides have been reported to undergo efficient coupling with a wide range of organotin compounds.[73] Catalysts such $PdCl_2(PPh_3)_2$, $PdCl_2(MeCN)_2$ or $Pd(PPh_3)_4$ are the most widely used and the solvents of choice are DMF or THF which are polar and thus able to dissolve both the catalyst and the organotin component. Attempts

were made to couple the stannane cyclopropane **116** with both 4-bromobenzoic acid and 4-bromoanisole using a variety of palladium catalysts in both THF and DMF and at temperatures ranging from 20°C to 100°C. Unfortunately no coupled products were observed, starting materials only being recovered, Scheme 2.10.5.



Scheme 2.10.5

Although cyclopropanes in many cases exhibit substantial double bond character,[75] it appears that cyclopropyl-tins are not amenable to direct Stille coupling, as are vinyl tins. Examples in the literature indicate that for successful coupling to occur, conversion to the organozinc[76] or organomagnesium[77] reagent is required, for example, Scheme 2.10.6. This type of coupling, although promising, was not investigated in this thesis.

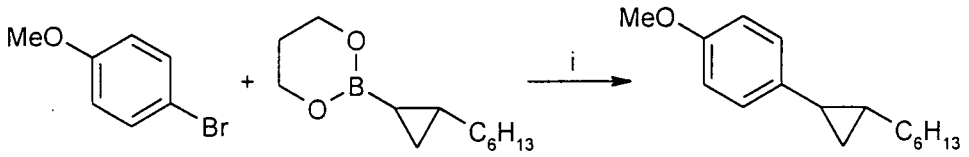


Scheme 2.10.6. Reagents: i, *n*-BuLi, THF, then $ZnCl_2$; ii, $Pd(PPh_3)_4$, $ICH{=}CH(CH_2)_3Cl$, 67% (2steps).

2.10.4 The Synthesis of Cyclopropylboronate Esters

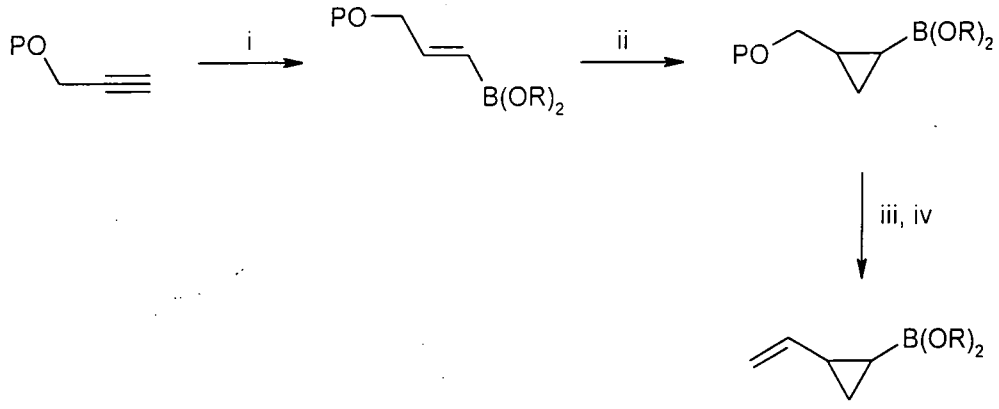
With the failure of the cyclopropyl stannane, **116**, to undergo successful Stille coupling (section 2.10.3), we sought a new cyclopropyl cross-coupling species of the type described earlier (**110**, Scheme 2.10.2). Cyclopropyl boronate esters and acids

have recently become popular Suzuki cross-coupling partners, reacting readily with aryl halides to provide phenyl-substituted cyclopropanes in high yield. Many examples of this type now abound the literature,[78] for example, Scheme 2.10.7.[79]



Scheme 2.10.7. Reagents: i, $Pd(PPh_3)_4$, *t*-BuOK, 1,2 DME, 80%.

Cyclopropyl boronates are commonly prepared by hydroboration of the corresponding alkyne[80] with catecholborane[81] followed by cyclopropanation of the resultant vinylboronate.[82] A scheme targeting the required vinyl substituted cyclopropylboronate ester/acid was subsequently devised which utilises a protected propargyl alcohol as a cheap and readily available starting material, Scheme 2.10.8.



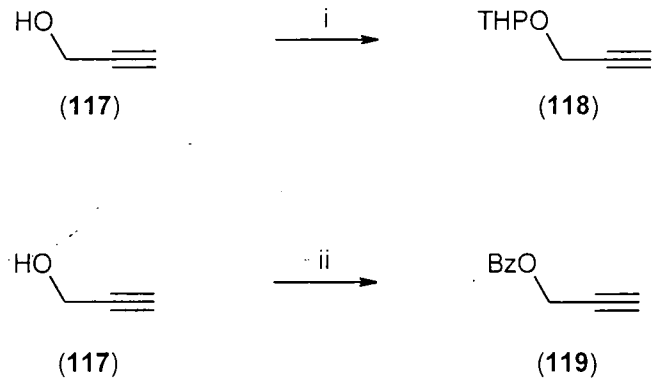
Scheme 2.10.8. Transformations: i, hydroboration; ii, cyclopropanation; iii, deprotection; iv, F.G.I.

It was decided to investigate the use of both THP and benzoyl protecting groups in the above sequence. This allows the freedom to remove the group under either mildly acidic or basic conditions, thus not interfering with the boron functionality (boron-carbon bond cleavage generally requires strongly oxidising conditions, e.g. alkaline H_2O_2, or hot acid treatment, e.g. acetic acid, 100°C).[80a] Additionally, both

ether (THP) and ester (Bz) groups show resistance to catecholborane attack,[81b] therefore, allowing the hydroboration step to proceed un-hindered.

2.10.5 Preparation of 118 and 119

Conversion of propargyl alcohol (**117**) to its THP-ether (**118**) was achieved with dihydropyran in combination with TsOH. The protected alcohol, **118**, was isolated in 55% yield after distillation. Formation of this compound was corroborated by the IR spectrum, which contained an alkyne CH stretch at 3290cm^{-1} but no alcohol stretch. Further, the mass spectrum (EI-MS) contained a peak at *m/z* 140 (1%), corresponding to the molecular ion. The benzyl protected compound (**119**) was prepared in 74% yield by treatment of propargyl alcohol (**117**) with a combination of benzoyl chloride, DMAP and triethylamine. The elemental analysis values obtained for this ester (C, 74.88; H, 4.99%) were consistent with the theoretical values (C, 74.99; H, 5.03%) and the IR spectrum contained a typical ester carbonyl stretch at 1725cm^{-1}, Scheme 2.10.9.

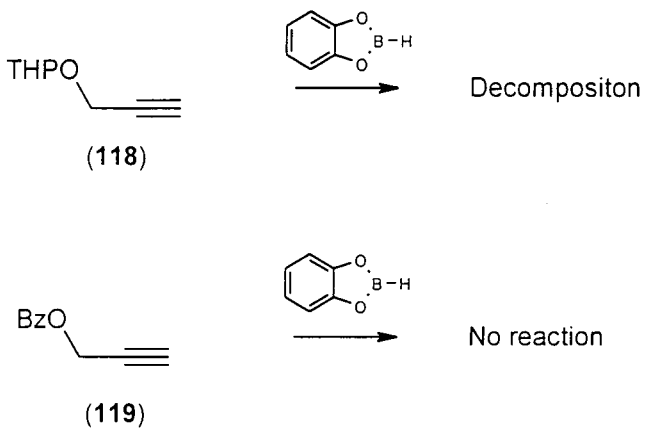


Scheme 2.10.9. Reagents: i, 2,3-dihydropyran, TsOH, 55%; ii, benzoyl chloride, DMAP, NEt_3, 74%.

2.10.6 Attempted Hydroboration of 118 and 119

The hydroboration of terminal alkynes with catecholborane has been shown to proceed readily (1h at 70°C) with the neat reagent to yield vinylboronates.[80a] In our hands, attempts to hydroborate the protected propargyl alcohols, **118** and **119**, under

these conditions failed. In the case of **118**, complete decomposition of the starting material was observed, whereas with **119**, no reaction took place, starting alkyne only being isolated, Scheme 2.10.10. The hydroboration of the THP-ether (**118**) was also attempted at room temperature and using THF as a solvent; again decomposition resulted.



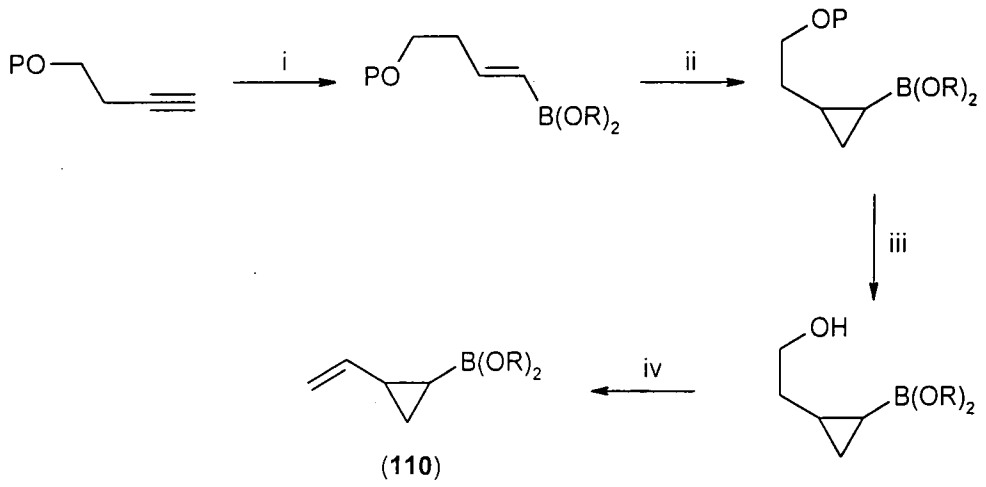
Scheme 2.10.10

The apparent instability/unreactivity of **118** and **119** towards catecholborane may be a result of the proximity of the allylic functionality to the reacting centre, presumably giving rise to steric interactions with the hydroborating reagent. It this regard, it has been suggested that, in certain cases, a separation of at least two carbon units must be present between pendant functionality and the alkyne linkage to allow adequate hydroboration to occur.[81b] In a recent publication, Pietruszka *et al*[83] have also commented on the possibility of "complex" formation between boranes and both benzyl and ether groups, again hindering the hydroboration process.

2.10.7 Preparation of Alkynes 120, 121 and 122

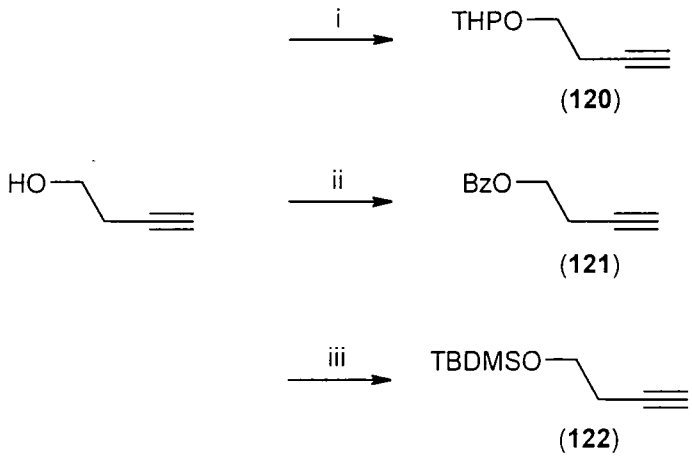
With the failure to successfully hydroborate the protected propargyl alcohols **118** and **119**, it was decided to increase the carbon linkage between the oxygenated functionality and the alkyne, thereby reducing possible steric interaction with the incoming borane reagent. The choice of protected 3-butyn-1-ol as the starting

material introduces a two carbon linkage whilst also necessitating the incorporation of a dehydration step in the synthetic sequence, Scheme 2.10.11.



Scheme 2.10.11. Transformations: i, hydroboration; ii, cyclopropanation; iii, deprotection; iv, dehydration.

THP and benzyl groups were once again selected to protect the alcohol functionality. Silyl ethers have also been shown to be un-reactive towards boranes,[83] and further, can be removed easily (with fluoride sources) in the presence of boron functionality.[83] The *tert*-butyldimethylsilyl ether of 3-butyn-1-ol was, therefore, additionally targeted. All three protections were a matter of routine, 3-butyn-1-ol being treated with dihydropyran/TsOH, benzoyl chloride/DMAP/NEt_3 and TBDMS-Cl/NEt_3 to provide THP (73%), benzoyl (80%) and TBDMS (80%) protection respectively, Scheme 2.10.12.



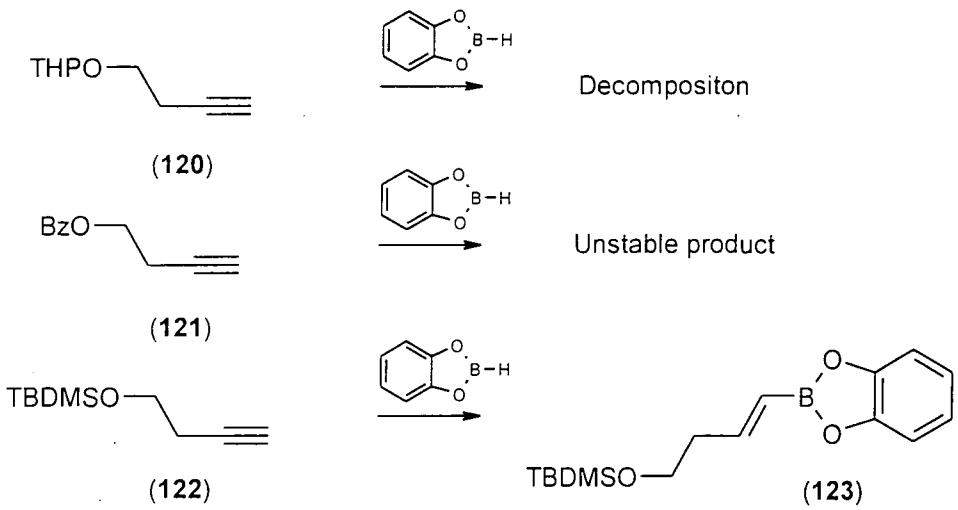
Scheme 2.10.12. Reagents: i, 2,3-dihydropyran, TsOH, 73%; ii, benzoyl chloride, DMAP, NEt_3, 80%; iii, TBDMS-Cl, DMAP, NEt_3, 80%.

The ^1H NMR spectrum recorded for the THP compound (**120**) contained a terminal alkyne peak at δ1.97 and the ^{13}C NMR spectrum contained the correct number of signals (9). Further, the IR spectrum was devoid of any alcohol stretch, confirming that successful cyclic ether protection had occurred. Benzoyl protection coincided with the appearance of typical ester stretches in the IR spectrum (1274, 1789cm^{-1}) and a molecular ion peak (*m/z* 174) was observed by EI-MS (1%), whereas, successful TBDMS protection corresponded with the appearance of characteristic Si-Me (δ0.07) and Si-^{t}Bu (δ0.89) signals in the ^1H NMR. An $M+NH_3^+$ (*m/z* 202) peak was also observed by CI-MS (100%).

2.10.8 Attempted Hydroboration of 120, 121 and 122

The hydroboration of **120**, **121** and **122** was again attempted with neat catecholborane at 70°C. The apparent incompatibility of THP-ether protection with catecholborane was not alleviated by the introduction of an extra methylene group between the alkyne and the oxygenated functionality, the reaction with **120** resulting in complete decomposition under these conditions. The reaction of the benzyl ester (**121**) was somewhat more successful. The progress of the reaction was monitored by ^1H NMR which indicated that a 50% conversion to the vinylboronate had occurred after 3 hours (extended reaction times did not appreciably increase the

yield). Unfortunately, the product proved to be thermally unstable as attempted purification by Kugelrohr distillation (125-200°C, 0.1mmHg) resulted in decomposition. In contrast, the reaction of the TBDMS protected alcohol (**122**) with catecholborane resulted in complete consumption of the starting material (crude ^{1}H NMR). The product (**123**) in this case showed sufficient thermal stability to allow purification by Kugelrohr distillation (200°C, 0.1mmHg) and was isolated as a moisture sensitive colourless oil in 57% yield, Scheme 2.10.13. The ^{1}H NMR spectrum recorded for **123** contained two vinyl protons at δ5.91 and δ6.85 together with four aromatic protons (δ6.95-δ7.34) corresponding to the catechol moiety. A strong (71%) M+NH_3^+ peak (*m/z* 322) was also observed by CI-MS.

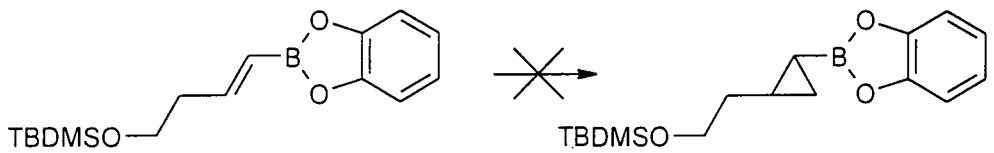


Scheme 2.10.13

2.10.9 Attempted Cyclopropanation of the Vinylboronate 123

Cyclopropanation of vinylboronate esters and acids has been demonstrated by Carboni *et al*[82] using either diazomethane in combination with palladium(II) acetate or the modified Simmons-Smith procedure, that is, diethyl zinc and methylene iodide. Although these techniques have been shown to be high yielding and tolerant of a wide range of functionality, attempted cyclopropanation of cyclopropylboronate **123** under these conditions failed. In the case of diazomethane/palladium(II) acetate, starting materials only were recovered, whereas the use of diethyl zinc methods

resulted in complete decomposition. Attempts to employ the traditional Simmons-Smith reagent generated from Zn/Cu couple and methylene iodide proved to be equally ineffectual and starting material was again the only compound isolated, Scheme 2.10.14.



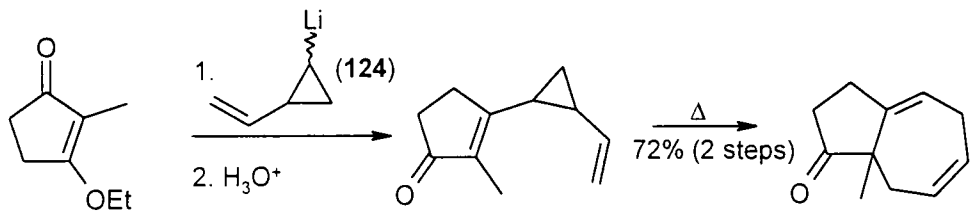
(**123**)

Scheme 2.10.14

The inability of **123** to undergo cyclopropanation may be attributable to the electron withdrawing nature of the pendant catechol group in which the oxygen lone electron pairs are drawn into resonance with the benzene ring.[81b] This renders the double bond electron deficient and, therefore, un-reactive towards carbenoids. This problem could be overcome by either conversion to the boronic acid or to a non-aromatic boronate, both of which are known to undergo efficient cyclopropanation.[82] However, handling and purification of boronic acids is known to be complicated by the formation of boroxines[83] and both options add further steps to the synthetic pathway. It was decided, therefore, to seek a less complicated/more efficient route to the desired cyclopropylboronate (**110**).

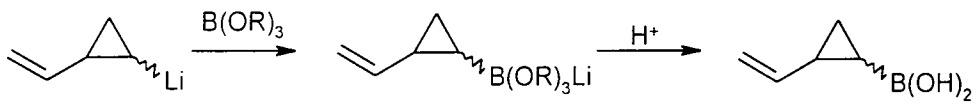
2.10.10 Synthesis of Cyclopropyl Bromides and Derivatives

Our continued interest in the synthesis of the cross-coupling cyclopropylboronate species (**110**, Scheme 2.10.2) led us to investigate the possible use of the 1-lithio-2-vinyl-cyclopropane, **124**. This species reacts readily with electrophiles and has been utilised effectively by several workers, for example, Wender *et al*[84] in their work towards functionalised cycloheptanes, Scheme 2.10.15.



Scheme 2.10.15

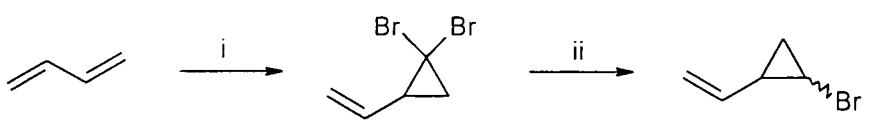
As the reaction of organolithiums with trialkoxyboranes provides a general route to boronic esters/acids via an "ate" complex,[85] we envisaged the preparation of **110** from 1-lithio-2-vinyl-cyclopropane (**124**) in this manner, Scheme 2.10.16.



(**124**) (**110**)

Scheme 2.10.16

1-Lithio-2-vinyl-cyclopropane (**124**) can be prepared by lithiation of the corresponding bromocyclopropane (**126**),[84] which in turn is accessed from 1,1-dibromo-2-vinylcyclopropane (**125**) by reaction with tri-*n*-butyltin hydride,[86] Scheme 2.10.17. Following a procedure by Skell and Woodworth,[87] therefore, neat 1,4-butadiene was treated with bromoform in the presence of potassium *t*-butoxide, and after the evaporation of excess diene, 1,1-dibromo-2-vinylcyclopropane (**125**) was obtained as an air sensitive oil (66%).

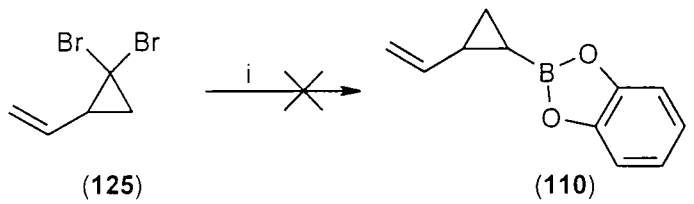


(**125**) (**126**)

Scheme 2.10.17. Reagents: i, $CHBr_3$, *t*-BuOK, 66%; ii, *n*-Bu_3SnH, 32%.

Successful preparation of **125** was indicated by the presence of three cyclopropane signals at δ1.58, δ1.97 and δ2.30 in the ^{1}H NMR and a correct molecular ion peak (*m/z* 226, 6%) in the mass spectrum (EI-MS).

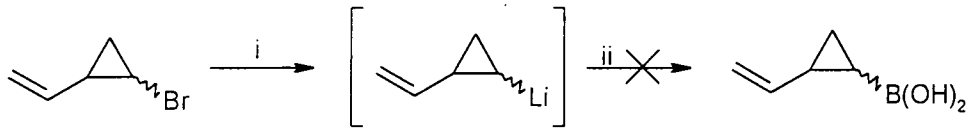
With **125** in hand, it was thought that direct access to **110** maybe possible *via* mono-lithiation, to generate the carbene with subsequent insertion into the boron-hydrogen bond of catecholborane as described for other dibromocyclopropanes by Danheiser and Savoca,[88] Scheme 2.10.18. The potential complication with such a strategy was the presence of the vinyl group which might facilitate the formation of a polymer under these conditions. Unfortunately this was the case and treatment of a solution of **125** in THF at –100°C (MeOH / l.N_2 slush bath) with one equivalent of *n*-BuLi followed by one equivalent of catecholborane resulted in a mixture of unidentifiable products.



Scheme 2.10.18. Reagents: i, *n*-BuLi, THF, -100°C, then catecholborane.

Undeterred by the previous result, and as originally planned, **125** was then converted to 1-bromo-2-vinyl-cyclopropane (**126**) with tri-*n*-butyltin hydride at 35°C according to a procedure by Seyferth and co workers.[86] **126** was isolated as an inseparable 1:1.5 mixture of isomers (GC) in a rather disappointing yield of 32% (cf. 62% literature yield). It was not possible to unambiguously assign the structure of the isomers (*cis/trans*) from coupling constants in the ^{1}H NMR spectrum in this case due to the complexity of the spectrum, however, Seyferth *et al* suggest a predominance of the least sterically compromised *trans* isomer in this reaction. The expected twin molecular ion peaks (*m/z* 148 and 146, 1% each) were present in the mass spectrum (EI-MS) recorded for **126**, furthermore, the presence of 10 distinct peaks (5 per isomer) in the ^{13}C NMR spectrum validated the structure as shown.

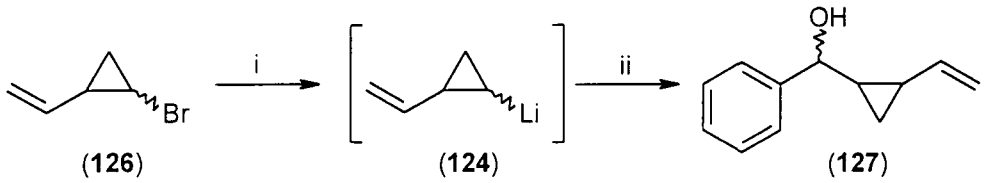
Lithium-bromide exchange of **126** was attempted by treatment with *t*-BuLi, in accordance with the method of Wender *et al*[84] (1.2eq, -78°C, ether solvent), followed by addition of trimethylborate and acid work-up (5% aq. HCl). Yet, these conditions failed to produce the required reaction and no discernible product could be isolated by standard techniques (FCC, acid-base extraction, trituration) from the crude reaction material, Scheme 2.10.19.



(126) (124) (110)

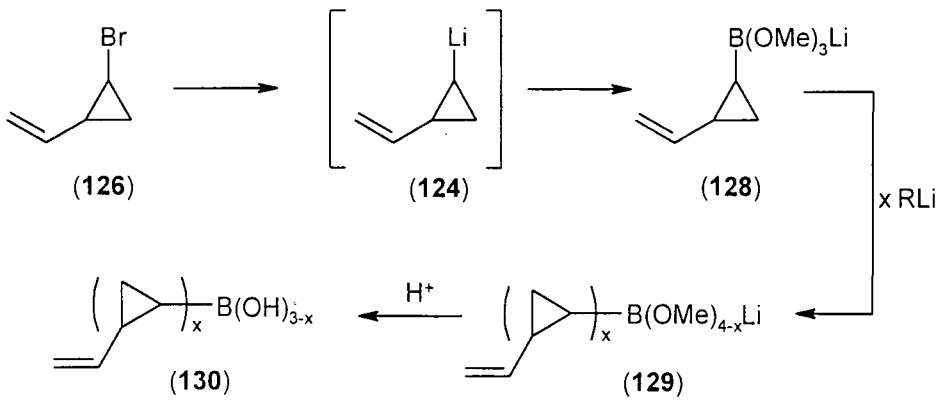
Scheme 2.10.19. Reagents: i, *t*-BuLi, ether; ii, $B(OMe)_3$.

Numerous other reaction conditions of varying solvent (e.g. ether, pentane, hexane), temperature (-78°C to room temperature), equivalents of RLi (*n*-BuLi/*t*-BuLi, 1eq. to 2.4eq.) with different alkoxyborates ($B(OMe)_3/B(O^iPr)_3$) were attempted,[89] unfortunately with the same results. Firstly, it was assumed that isolation of the product might have been hampered by the "waxy" nature of the crude material, therefore, in order to salvage any boronic acid present, the crude product was allowed to react (as a toluene solution) with diethanolamine. This technique has been reported to aid the isolation of boronic acids by forming more manageable, high melting point, solid complexes with the latter.[90] Again though, no product could be isolated. With the lack of positive results from these experiments, it was desirable to ascertain the degree of lithiation taking place. **126** was, therefore, treated with *t*-BuLi followed by reaction with an excess of benzaldehyde in order to form the sturdy benzyl alcohol derivative (**127**), Scheme 2.10.20.



Scheme 2.10.20. Reagents: i, *t*-BuLi, hexane/ether then canula into ii, benzaldehyde, ether, 25% (2 steps).

127 was isolated by FCC as a mixture of diastereoisomers in 25% yield. Further chromatography enabled separation of the major isomer, the IR spectrum of which contained an alcohol stretch at 3385cm^{-1}, whereas, the mass spectrum (EI-MS) contained a molecular ion peak (*m/z* 174, 1%). This result demonstrates that the desired cyclopropyllithium (**124**) was being formed under these conditions, although the lack of lithium-bromide exchange achieved was surprising. More bemusing, however, was the fact that having presumably formed the cyclopropyllithium (albeit in low concentration) in the reaction with borates, no quantity of isolable boronic acid was being generated in these reactions. A possible explanation of this result may be that the initial "ate" complex (**128**), formed between the cyclopropyllithium (**124**) and borate, undergoes further reaction with a second molecule of organolithium thereby forming a complicated mixture of borinic esters (**129**) rather than the desired boronic acid (**110**),[85] Scheme 2.10.21. Alternatively, and more simply, the reaction between cyclopropyllithium (**124**) and the borate reagent is low yielding, this coupled with the low concentration of cyclopropyllithium itself results in negligible product and thus the need for a degree of optimisation.

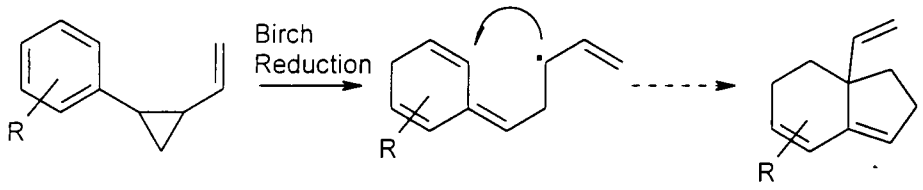


Scheme 2.10.21

2.11 The Synthesis of 3-(2′-vinylcyclopropyl)-N,N-diethyl benzamide (131)

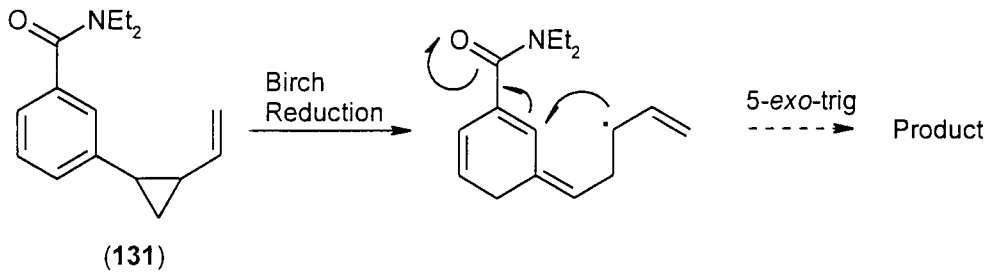
2.11.1 Introduction

The previous section (2.10) described several strategies targeting a vinylcyclopropyl cross-coupling partner (**110**, scheme 2.10.2). This species was designed to act as a common intermediate in the convergent synthesis of a wide range of substituted 1-phenyl-2-vinyl-cyclopropanes that were required to conduct a model study. In this, investigation into the Birch reduction chemistry of this class of compounds was planned with a view to generating indene structures *via* a vinyl-stabilised radical, Scheme 2.10.1 (see also section 2.10.1).



Scheme 2.10.1

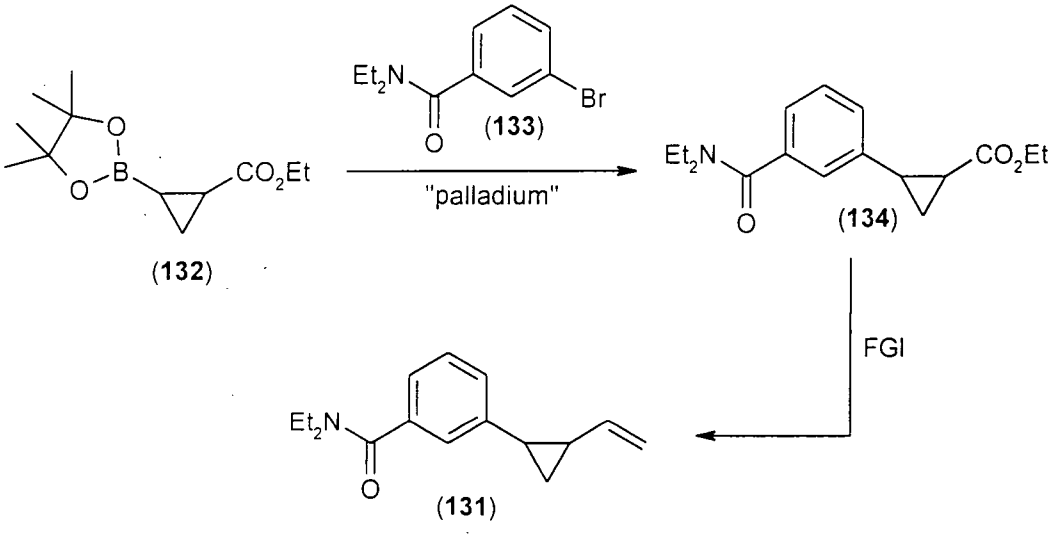
The failure of the aforementioned strategies led us to target, using a step-wise, more conventional approach, an individual vinyl-substituted phenylcyclopropane (**131**) which was regarded as the most likely structure to facilitate indene formation upon Birch reduction. **131** exhibits a Birch reduction resistant amide group in a *meta* position to the vinylcyclopropane moiety. This is necessary for two reasons. Firstly, the electron-withdrawing nature of the amide serves to direct reduction so as to leave the residual double bonds in favourable positions (see the "Birch rule", Scheme 2.2.2, page 27), that is, to provide the correct framework for the ring-closing step. Secondly, the presence of the amide group allows said cyclisation (5-*exo*-trig) to occur in a "Michael" fashion where the radical is stabilised by the amide carbonyl, Scheme 2.11.1.



(131)

Scheme 2.11.1

The planned preparation of **131**, as shown in scheme 2.11.2, involves the Suzuki coupling of the known cyclopropylboronate, **132**, and the aromatic bromide, **133**. Subsequent conversion of the ethyl ester group of **134** to a vinyl group then completes the synthesis. This approach was devised in the knowledge that both **132** and **133** are readily available and thus amenable to large-scale synthesis, **132** is stable to both air and moisture and hence easily handlable, and that successful Suzuki reactions have been demonstrated with pinacol boronic esters.[91]



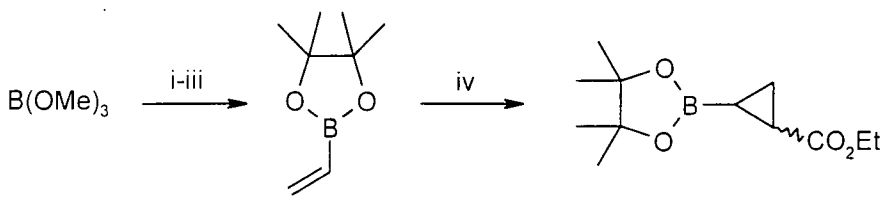
(132)

(131)

Scheme 2.11.2

2.11.2 Synthesis of Cyclopropylboronate 132

Cyclopropane **132** was accessed in a two step procedure from trimethylborate as depicted in scheme 2.11.3. In the first step, trimethylborate was treated, as an ether solution, with vinyl magnesium bromide as previously demonstrated by Hoffmann and Landmann.[92] Acid hydrolysis followed by reaction with pinacol then provided **135**, which, after distillation (ambient temperature, 5mmHg), was obtained as a colourless oil in 49% yield. The structure of **135** was validated by examination of the ^{1}H NMR and the mass spectra. The former contained a 12H-singlet at δ1.26, corresponding to the pinacol methyl groups and a 3H-multiplet between δ5.75 and δ6.20 arising from the vinyl group, whereas the latter contained a prominent (10%) molecular ion peak (*m/z* 154).



(**135**) (**132**)

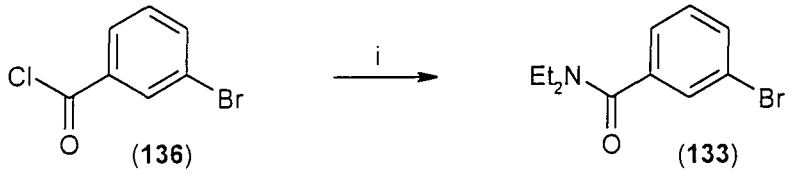
Scheme 2.11.3. Reagents: i, CH_2=CHMgBr; ii, HCl; iii, pinacol, 49% (3 steps); iv, N_2CHCO_2Et, $Pd(OAc)_2$, 81%.

The cyclopropanation of vinylboronate **135** was achieved by treatment with ethyl diazoacetate in the presence of palladium(II) acetate catalyst.[82] Kugelrohr distillation (110°C, 0.1mmHg) effected purification of **132** which was isolated as a 1:1 mixture of *cis* and *trans* isomers in high yield (81%). The formation of **132** was verified by elemental analysis, the results of which (C, 59.74; H, 8.80%) were in agreement with the calculated values (C, 59.54; H, 8.72%) for the structure as shown.

2.11.3 Synthesis of the Aromatic Amide (133)

The aromatic amide (**133**) was prepared by reaction of the corresponding (commercially available) acid chloride (**136**) with diethylamine in DCM, Scheme 2.11.4. No purification of this compound was necessary as the reaction proceeded in

98% yield providing an analytically pure oil after aqueous work-up. Elemental analysis confirmed the formation of **133** with the values obtained (C, 51.31; H, 5.22; N, 5.58%) in agreement with the calculated theoretical percentages for the amide as shown (C, 51.58; H, 5.51; N, 5.47%).

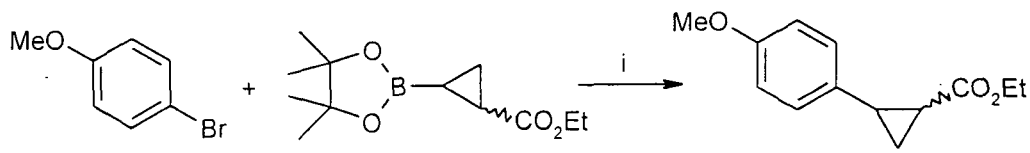


Scheme 2.11.4. Reagents: i, diethylamine, DCM, 98%.

2.11.4 Suzuki Coupling of 132 and 133

With both of the required fragments (**132** and **133**) in hand it was possible to attempt the Suzuki cross-coupling reaction.[93] However, with the array of bases, solvents and palladium catalysts available for this type of coupling, it was necessary, firstly, to identify conditions compatible with boronic ester **132**. Therefore, using the expendable, "bench" aromatic bromide, 4-bromoanisole (**137**), a number of preliminary experiments were conducted. Initially a combination of NaOH and $Pd(PPh_3)_4$ in toluene at 100°C was chosen; although this led to the destruction of the ethyl ester functionality (crude ^{1}H NMR). Substituting NaOH with $Na_4P_2O_7$ in the same system was similarly unsuccessful and failed to effect any reaction, starting materials only being isolated. More successful was the use of the conditions previously identified by Marsden *et al*[79] (*t*-BuOK, $Pd(PPh_3)_4$, DME) and Charette *et al*[78b] (*t*-BuOK, PPh_3, $Pd(OAc)_2$, DME) for the coupling of other cyclopropylboronic esters/acids. Both of these systems provided the desired product (**138**), although the best yield was obtained using a combination of $Pd(PPh_3)_4$ (**139**)[94] and K_3PO_4 in toluene/H_2O at 100°C, that is, the conditions adopted by Deng and co-workers,[78a,c] Scheme 2.11.5. Using this system, **138** was obtained, after FCC, in 38% yield as a mixture of diastereoisomers (1:1). Further chromatography allowed the separation of a single isomer from this mixture, which was isolated as a white solid (mpt. 82°C). As the cyclopropane signals in the ^{1}H NMR recorded for this compound all appeared as multiplets, it was not possible to unambiguously assign the isolated isomer as

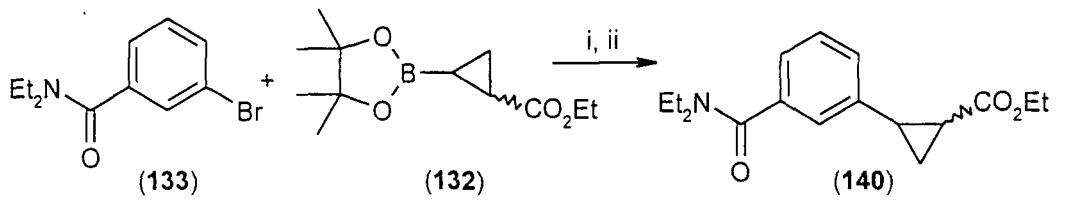
either the *cis* or *trans* from the associated coupling constants. Nonetheless, the structure was confirmed by elemental analysis, the results obtained from which (C, 70.54; H, 7.17%) being consistent with the molecular formula ($C_{13}H_{16}O_3$). Furthermore, the mass spectrum (EI-MS) exhibited the correct molecular ion peak (*m/z* 220, 33%).



(137) (132) (138)

Scheme 2.11.5. Reagents and conditions: i, $Pd(PPh_3)_4$, K_3PO_4, toluene/H_2O, 100°C, 12h, 38%.

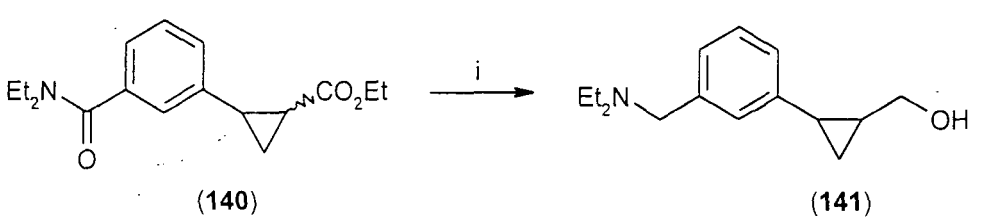
With an adequate coupling procedure now identified, the aromatic amide (**133**) and the cyclopropylboronate (**132**) were reacted under the same conditions. However, in this case, the reaction time was increased to the optimal time of 70h and an extra charge of catalyst was made. This resulted in the desired compound (**140**) being isolated in an improved yield of 48% after FCC, Scheme 2.11.6. GC-MS of the product revealed it to be a 1:1 mixture of diastereoisomers with both of the components having identical fragmentation patterns including strong (17%) molecular ion peaks (*m/z* 289). The retention times on silica of the two isomers were sufficiently different to allow separation by careful FCC and ^1H NMR spectra were subsequently recorded for the individual isomers. These both contained characteristic broad signals corresponding to the aromatic ethylamide functionality.



Scheme 2.11.6. Reagents and conditions: i, $Pd(PPh_3)_4$, K_3PO_4, toluene/H_2O, 100°C, 48h; then ii, $Pd(PPh_3)_4$, 100°C, 22h, 48% for 2 steps.

2.11.5 Synthesis of 142, 143 and 131

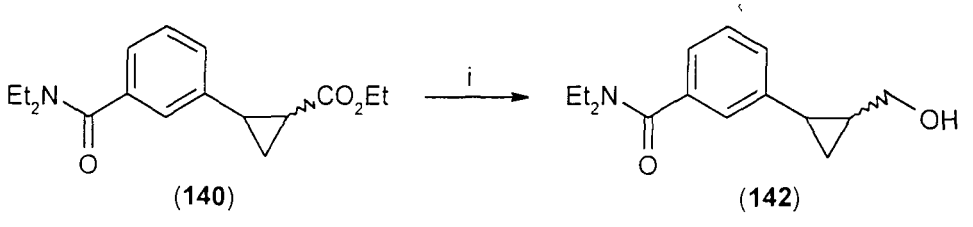
In order to complete the synthesis of the vinyl-substituted cyclopropane (**131**), it was necessary to convert the ethyl ester group to a vinyl group. As with the preparation of **84** (page 34) and **88** (page 39) a sequence of reduction-oxidation-olefination was attempted. Initially, the standard conditions for ester reduction were selected, the reaction being carried out with 1.1eq of $LiAlH_4$. Unsurprisingly, and as feared, this led to the reduction of all carbonyl functionality and in the formation of the amine **141** (35%), Scheme 2.11.7.



Scheme 2.11.7. Reagents and conditions: i, 1.1eq. $LiAlH_4$, THF, 0°C to rt, 35%.

Of the two diastereoisomers of **141** formed (GC-MS), it was only possible to isolate one in a pure state by FCC. The absence of any absorption in the carbonyl region of the IR spectrum (1600-1800cm^{-1}) recorded for **141** confirmed that both the ester and the amide had been reduced. Whereas the HRMS value of 233.1776 obtained provided unequivocal evidence for the structure of as shown. To achieve exclusive ester reduction, the use of DIBAL-H (2.2eq DIBAL-H, THF, -78°C to rt) and $NaBH_4$/LiCl (1eq $NaBH_4$, 1eq LiCl, diglyme, 80°C, 12h) was then investigated. In

the case of DIBAL-H, it was surprising to find that no reaction took place given that this is often the reagent of choice in these circumstances. The same was true of the $NaBH_4/LiCl$ combination, which has also been suggested as a selective method to effect ester reduction in the presence of amides.[95] In view of these failures, the use of $LiAlH_4$ was again sought. The conditions selected this time though were a more conservative 0.75eq of $LiAlH_4$ whilst maintaining the temperature at 0°C. Under these conditions the desired product (**142**) was obtained as a separable mixture of diastereoisomers (FCC) in an acceptable yield of 48% along with a quantity of re-cycleable starting material (21%), Scheme 2.11.8. Elemental analysis results (C, 72.56; H, 8.63; N, 5.41%) on a mixed isomer sample were consistent with the theoretical values calculated for the molecular formula ($C_{15}H_{21}NO_2$). The IR spectrum also confirmed the structure as shown, with both amide ($1614cm^{-1}$) and alcohol ($3410cm^{-1}$) stretches present.

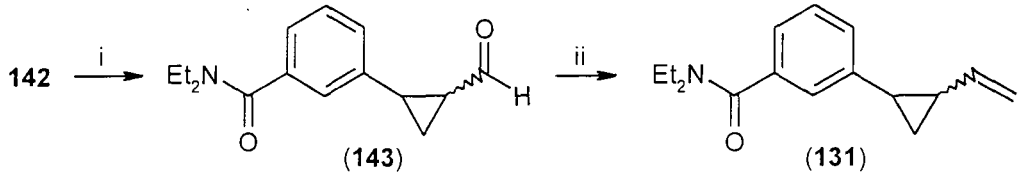


(**140**) (**142**)

Scheme 2.11.8. Reagents: i, $LiAlH_4$, THF, 48%.

Completion of the synthesis of **131** proved to be straightforward and high yielding, Scheme 2.11.9. In this, the primary alcohol (**142**) (two diastereoisomers) was converted to the corresponding aldehyde in 77% yield by treatment with PCC/alumina (see also page 34). The formation of **143** coincided with the appearance of two aldehyde peaks in the ^1H NMR (δ8.78 and δ9.35) (relating to two diastereoisomers) and a typical aldehyde carbonyl absorption in the IR spectrum ($1703cm^{-1}$). Subsequent reaction with the Wittig reagent generated from triphenylphosphonium iodide and *n*-BuLi then effectively installed the terminal alkene group evident in **131**. The two diastereoisomers of 3-(2'-vinylcyclopropyl)-N,N-diethyl benzamide (**131**) were isolated by FCC in 74% yield in a 1:1 ratio (^1H

NMR). The accurate mass recorded for this compound was 243.1622, which is consistent with the calculated mass for $C_{16}H_{21}NO$ (243.1623). Further, the ^{1}H NMR spectrum contained a complicated multiplet signal (δ4.83-δ5.15) integrating to five protons and assignable to the vinyl group, whereas two distinctive amide carbonyl signals (δ171.26 and δ171.29) were observed in the ^{13}C NMR spectrum.

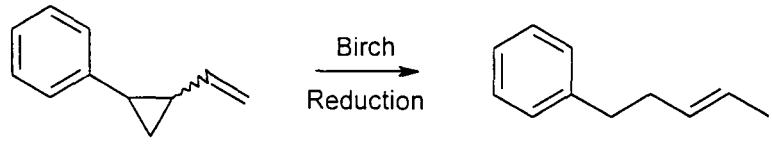


Scheme 2.11.9. Reagents: i, PCC/alumina, DCM, 77%; ii, Ph_3PCH_2I, *n*-BuLi, THF, 74%.

2.12 Lithium Birch Reduction of 3-(2′-vinylcyclopropyl)-N,N-diethyl benzamide (131) (Series 3)

2.12.1 Introduction

In the first two series of reductions 2-phenyl-vinylcyclopropane (**84**) was seen to reductively cleave in what is believed to be a radical process, Scheme 2.5.3. This is a desirable pathway if an indene structure is to be prepared by this methodology (as described earlier, scheme 2.10.1). With this in mind and for the sake of comparison 3-(2′-vinylcyclopropyl)-N,N-diethyl benzamide (**131**) was subjected to reduction under the same conditions as the first series of reductions (10eq Li, 200ml l.NH_3 per 1g Li, ether co-solvent, 2h, -78°C).

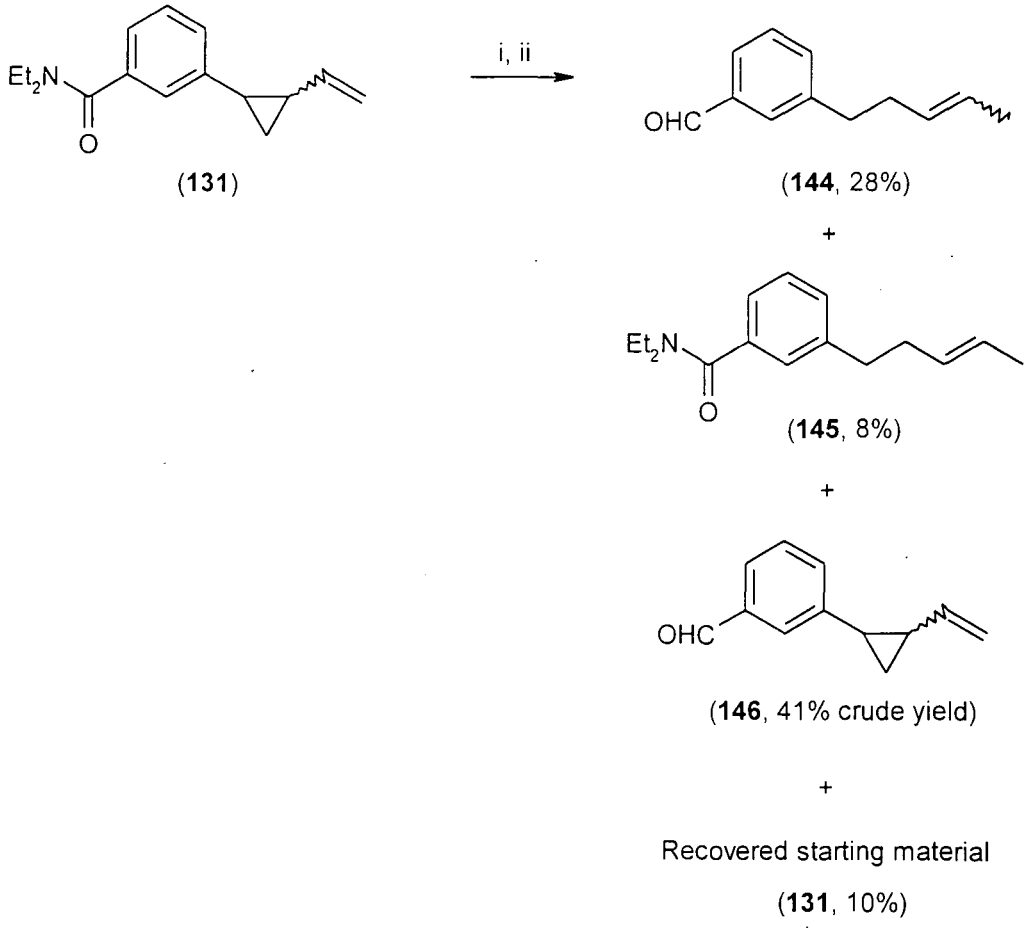


(**84**) (**105**, 57%)

Scheme 2.5.3

2.12.2 Series 3 Reductions -Results

Reaction of **131** (1:1 mixture of diastereoisomers) under the conditions described above resulted in a mixture of products. FCC allowed the separation and purification of the individual components (including 10% recovered starting material) as shown in Scheme 2.12.1.



(**131**)

(**144**, 28%)

+

(**145**, 8%)

+

(**146**, 41% crude yield)

+

Recovered starting material

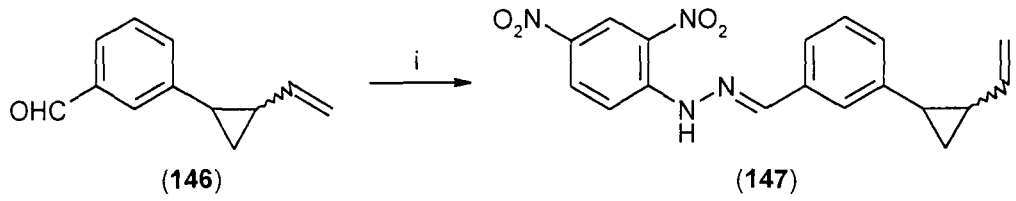
(**131**, 10%)

Scheme 2.12.1. Reagents and conditions: i, Li, l.NH_3, Et_2O, 2h; then ii, EtOH.

3-(Pent-2-ene)-benzaldehyde (**144**) was isolated (28%) as a mixture of E:Z isomers (2:1) as determined from the ^{1}H NMR spectrum. Evidence in support of the structure was obtained from the IR spectrum, which contained a prominent stretch at 1702cm^{-1} arising from the aldehyde carbonyl, and the mass spectrum (EI-MS), which exhibited both a molecular ion peak (*m/z* 174, 47%) and a tropylium ion peak (*m/z* 91, 41%). This was unambiguously validated by accurate mass determination, the value obtained from which (174.1045) was identical to the theoretical value for the structures molecular formula ($C_{12}H_{14}O$).

3-(Pent-3-ene)-N,N-diethyl-benzamide (**145**) was obtained in low yield (8%) as a single isomer. Although definite identification of the isomer structure was not obtained in this case it is reasonable to assume that the double bond has E geometry. This said, it is likely that both E and Z isomers were formed in the reaction, but, due to the low abundance of **145**, only the E isomer was formed in an isolable quantity. Spectroscopic evidence for the preparation of **145** included an amide stretch in the IR spectrum (1632cm^{-1}), a molecular ion peak in the mass spectrum (*m/z* 245, 29%) and four broad signals in the ^{1}H NMR at δ1.12 (3H), δ1.24 (3H), δ3.25 (2H) and δ3.54 (2H) corresponding to the rotationally restricted aromatic amide methyl and methylene groups respectively.

The final compound isolated from this reaction was 3-(2′-vinylcylopropyl)-benzaldehyde (**146**). Unfortunately, **146** was not isolated in a pure state from the initial chromatography and could not be purified further by chromatographic methods due to the small quantity of material involved. To afford an analytically pure sample then, **146** was allowed the react with 2,4-dinitrophenylhydrazine, Scheme 2.12.2, the hydrazone derivative (**147**) being obtained (34% from **131**) as a red solid (mpt. 124-125°C). Subsequent HPLC analysis indicated the solid to be a mixture of two diastereoisomers (1:1.2) which is reflective of the starting material.



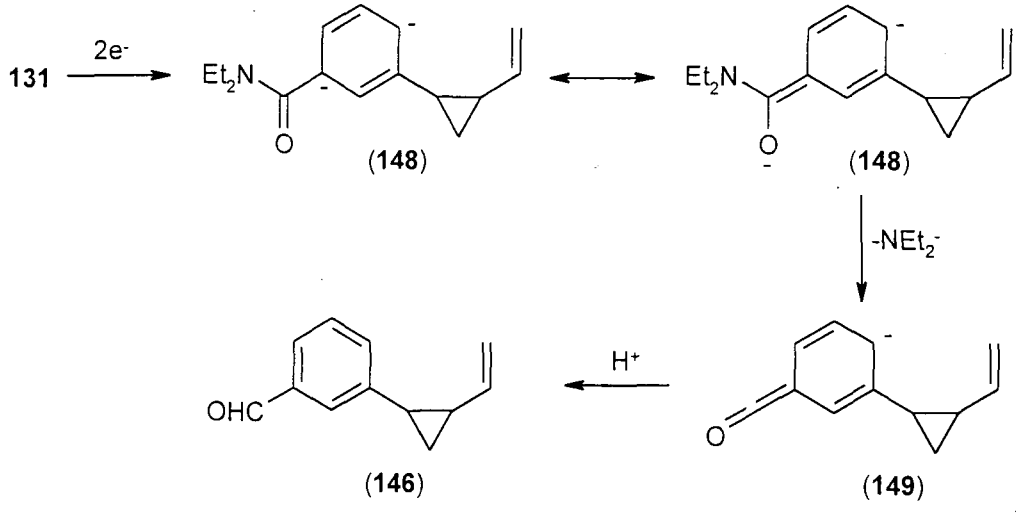
(146) (147)

Scheme 2.12.2. Reagents and conditions: i, 2,4-dinitrophenylhydrazine (solution in HCl (aq)/EtOH), 50°C, 34% from **131**.

The structure of **147** was confirmed by the appearance of nitro (1330cm^{-1}), imine (1615cm^{-1}) and amine (3286cm^{-1}) stretching bands in the IR spectrum and from accurate mass determination, the value from which (352.1166) was in agreement with the theoretical value (352.1172) for the structure as shown.

As with the previous Birch reductions (i.e. series one and two), no indene-type compounds were isolated from this reaction. The major products were the result of cyclopropane ring cleavage (**145**, 8%), amide reduction (**146**, 41%) and a combination of the two (**144**, 28%). This said however, the isolation of recovered starting material suggests that neither process is particularly facile.

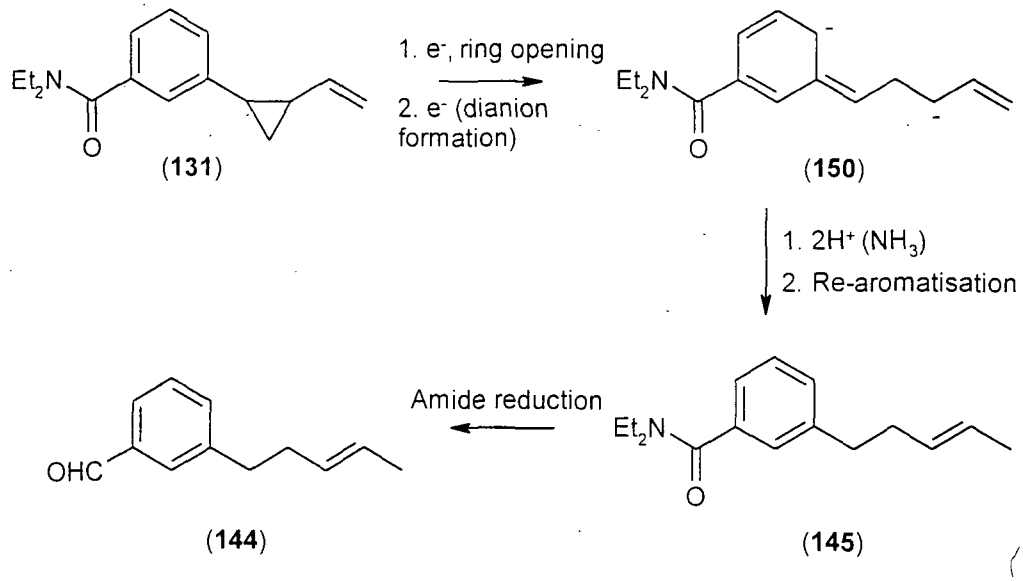
The formation of benzaldehydes from the Birch reduction of aromatic amides has been previously noted by Macielag and Schultz.[96] The suggested mechanism, as depicted for the formation of **146**, is shown below, Scheme 2.12.3.



Scheme 2.12.3

In this mechanism (scheme 2.12.3) the high electron affinity of the aromatic amide results in not single but double electron capture and the formation of a dianion (**148**). Subsequent loss of a diethylamide ion then yields an acyl anion (**149**), which upon protonation forms the aldehyde (**146**).

As a small quantity of the aromatic amide, **145**, was isolated (8%) in this reaction (scheme 2.12.1) it seems feasible that this could be an intermediate in the formation of the other major product, the aromatic aldehyde **144**. A possible mechanism firstly involves radical ring cleavage of the cyclopropane (as a radical-anion) in the normal way (described previously, Scheme 2.9.3), Scheme 2.12.4. In the next step, conversion to **145** is required. This seems straight-forward although the omittance of a proton source in this reaction requires that the intermediate species involved undergo protonation by ammonia. Radical-anions are generally not considered basic enough to abstract a proton from ammonia,[97] thereby implying the involvement of a dianion (**150**). Overall then, the sequence becomes double electron capture (dianion formation) followed by double protonation (by ammonia) and finally re-aromatisation. **145** is then subject to amide reduction as described earlier (scheme 2.12.3) to yield the final compound (**144**).



Scheme 2.12.4

2.12.3 Conclusion -Series 3

The results from this series of reductions suggest that, under these conditions, the dominant process associated with the Birch reduction of **131** is that of amide reduction which results from the rapid formation of a dianion. Having said this, radical cyclopropane ring opening also occurs, albeit to a lesser extent. Although, once ring opening has occurred, it appears that 5-*exo*-trig cyclisation, and thus indene generation, is once again hampered by the formation of a dianion which results in re-aromatisation being the preferred process.

It has been suggested[96] that normal aromatic reduction of amides can be achieved (i.e. dianion and benzaldehyde formation is avoided) under Birch conditions if potassium is used in place of lithium and a weakly acidic alcohol is present during the reaction. These reaction conditions have been investigated and are discussed in the next section.

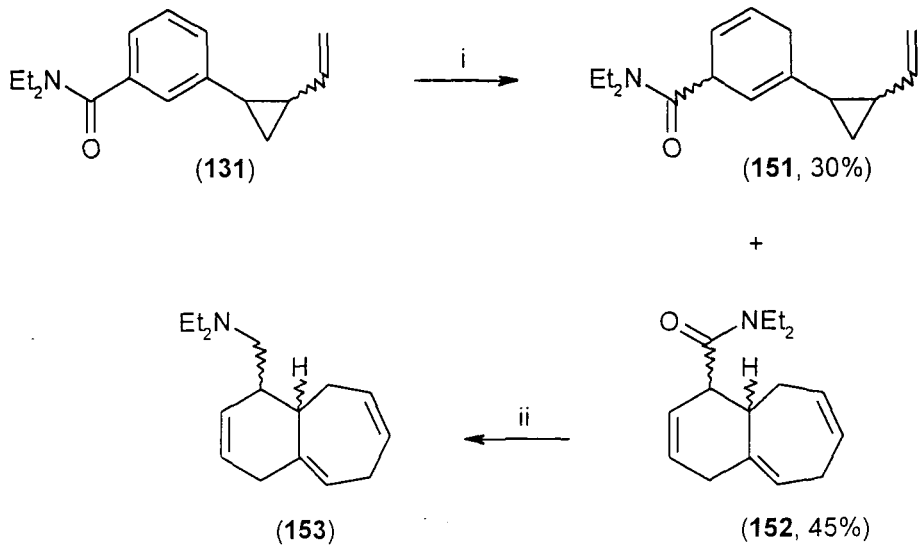
2.13 Potassium Birch Reduction of 3-(2′-vinylcyclopropyl)-N,N-diethyl benzamide (131) (Series 4)

2.13.1 Introduction

The Birch reduction of 3-(2′-vinylcyclopropyl)-N,N-diethyl benzamide (**131**) using lithium in the previous section was plagued by the formation of benzaldehyde products; a result of dianion formation and associated amide reduction. In order to avoid this and with a view to increasing the extent of the necessary radical cyclopropane ring opening, a reduction using 2.5eq. of potassium in the presence of *tert*-butyl alcohol was conducted. Using this technique Macielag and Schultz[96] have suggested that amide reduction can be completely avoided and dihydro products can be obtained in up to 92% yield.

2.13.2 Series 4 Reductions -Results

The reduction of **131** was conducted on a 1:1 mixture of diastereoisomers under the conditions highlighted (*vide supra*). After extractive work-up, tlc analysis of the crude material (petrol:ethyl acetate, 7:3) indicated that two major products had been produced. FCC allowed the separation of one component (**151**) (as a 1:1 mixture of diastereoisomers) in a pure state (30%), although, even after repeated chromatography, the second component could not be purified to analytical levels, Scheme 2.13.1. As a result the ^{1}H NMR spectrum was unclear and a confident structural assignment could not be made. However, the IR spectrum recorded for this material indicated that the amide was still intact (1643cm^{-1}) as did the mass spectrum which contained a peak at *m/z* 100 (100%) corresponding to the loss of the fragment, $Et_2NC{=}O^+$. A decision, therefore, was made to convert the amide to the corresponding carboxylic acid and thereby effect purification by acid–base extraction. To this end, hydrolysis was attempted by refluxing with large excesses (10eq.) of sodium hydroxide in THF/H_2O (4:1). However, even after 24h at reflux, this technique failed, starting material only being isolated. The use of potassium *tert*-butoxide (6eq.) in wet Et_2O, as suggested by Gassman *et al*,[98] was then investigated. This also proved unsuccessful. Finally, it was decided to adopt an alternative strategy and reduce the amide to the amine. This was successfully accomplished with $LiAlH_4$ and led to the isolation (without additional purification) of a pure material (**153**, 89%) as a 1:1 mixture of diastereoisomers (as ascertained by GC-MS), Scheme 2.13.1.



Scheme 2.13.1. Reagents and conditions: i, $l.NH_3$, potassium, *t*-BuOH, -78°C, 2h; ii, $LiAlH_4$, Et_2O, rt, 18h, 89%.

Although in a pure form, the ^1H NMR spectra (including COSY) recorded for **153** were uninformative (even at 500MHz) other than to provide integrals. This was in part due to all the allylic and vinylic signals coming into resonance together in a small areas of the spectrum (δ1.97-δ2.96 and δ5.41-δ5.88 respectively) but was also compounded by the presence of two diastereoisomers. The structure was finally solved using a combination of ^{13}C (figures 2.13.1 and 2.13.2), DEPT (figure 2.13.3) and HSQC NMR. These techniques indicated that 28 carbon atoms were present (n.b. 14 per diastereoisomer) of which two were quaternary, fourteen were methine, ten were methylene and two were methyl. This is correct for the structure of **153** as shown. Supporting evidence was obtained from the IR spectrum, which was devoid of an amide carbonyl absorption but contained a prominent C-N stretch at $1067cm^{-1}$ and the value of the accurate mass (232.2070), which is consistent with the theoretical value (232.2065).

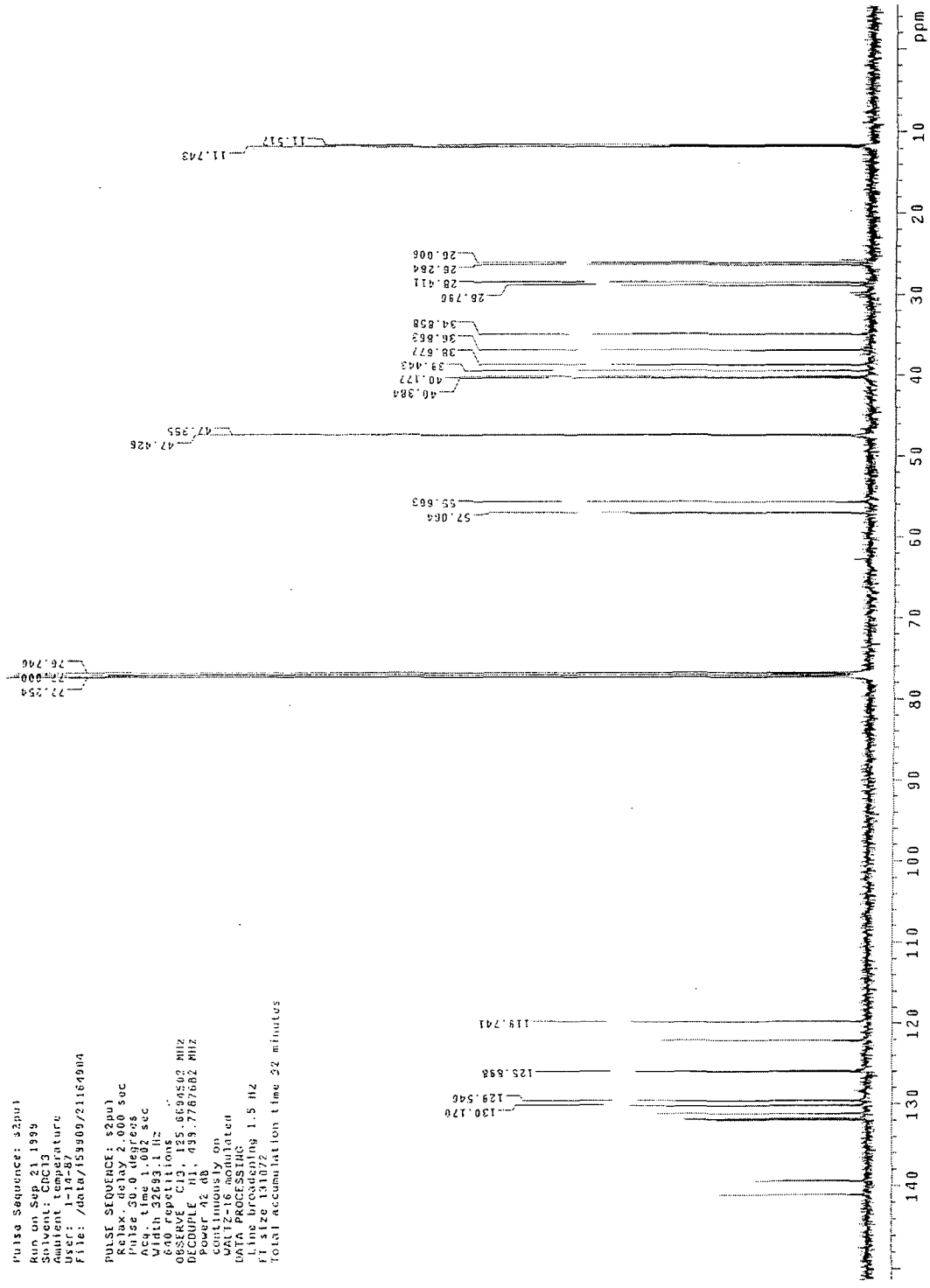

Pulse Sequence: s2pul
Run on Sep 21 1999
Solvent: CDCl3
Ambient temperature
User: 1-10-87
File: /data/159909/2116404
PULSE SEQUENCE: s2pul
Relax. delay 2.000 sec
Pulse 90.0 degrees
Acq. time 1.002 sec
Width 12563.1 Hz
640 repetitions
OBSERVE C13, 125.6694502 MHz
DECOUPLE H1, 499.7787602 MHz
Power 42 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.5 Hz
FT size 131072
Total accumulation time 32 minutes
ppm
11.517
11.743
26.006
26.264
28.411
28.796
34.858
36.862
38.677
39.443
40.177
40.384
47.355
47.426
55.663
57.064
76.746
77.000
77.254
119.741
125.858
129.546
130.170

Figure 2.13.1

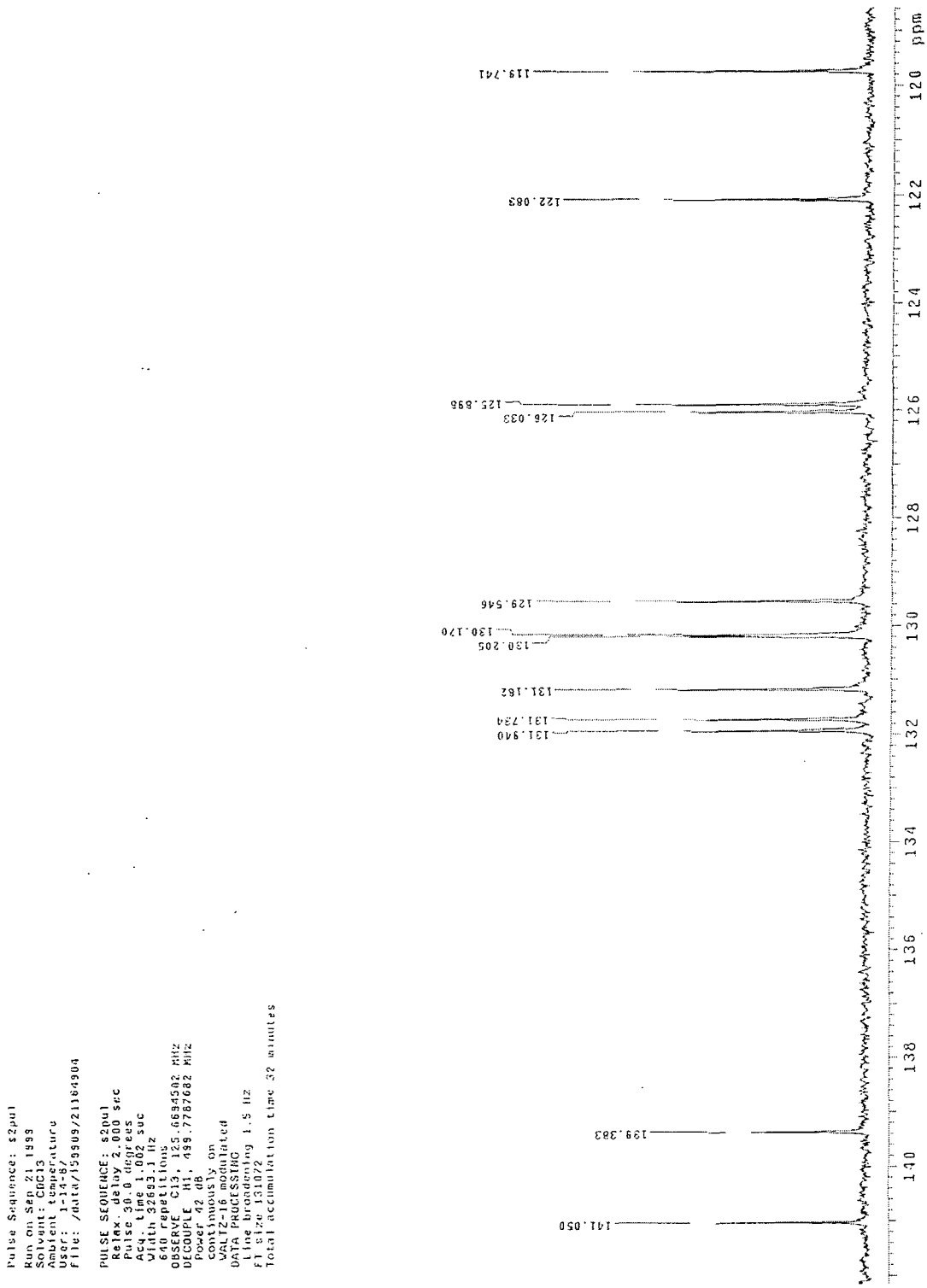

Pulse Sequence: s2pul
Run on Sep 21 1999
Solvent: CDCl3
Ambient temperature
User: 1-14-8/
File: /data/1999sep21/1d4904
PULSE SEQUENCE: s2pul
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 1.002 sec
640 repetitions
Width 32693.1 Hz
OBSERVE C13, 125.6894502 MHz
DECOUPLE H1, 499.7787682 MHz
Power 42 dB
Continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.5 Hz
FT size 131072
Total accumulation time 32 minutes
141.050
139.383
131.940
131.734
131.162
130.205
130.170
129.546
126.033
125.896
122.083
119.741
140
138
136
134
132
130
128
126
124
122
120
ppm

Figure 2.13.2

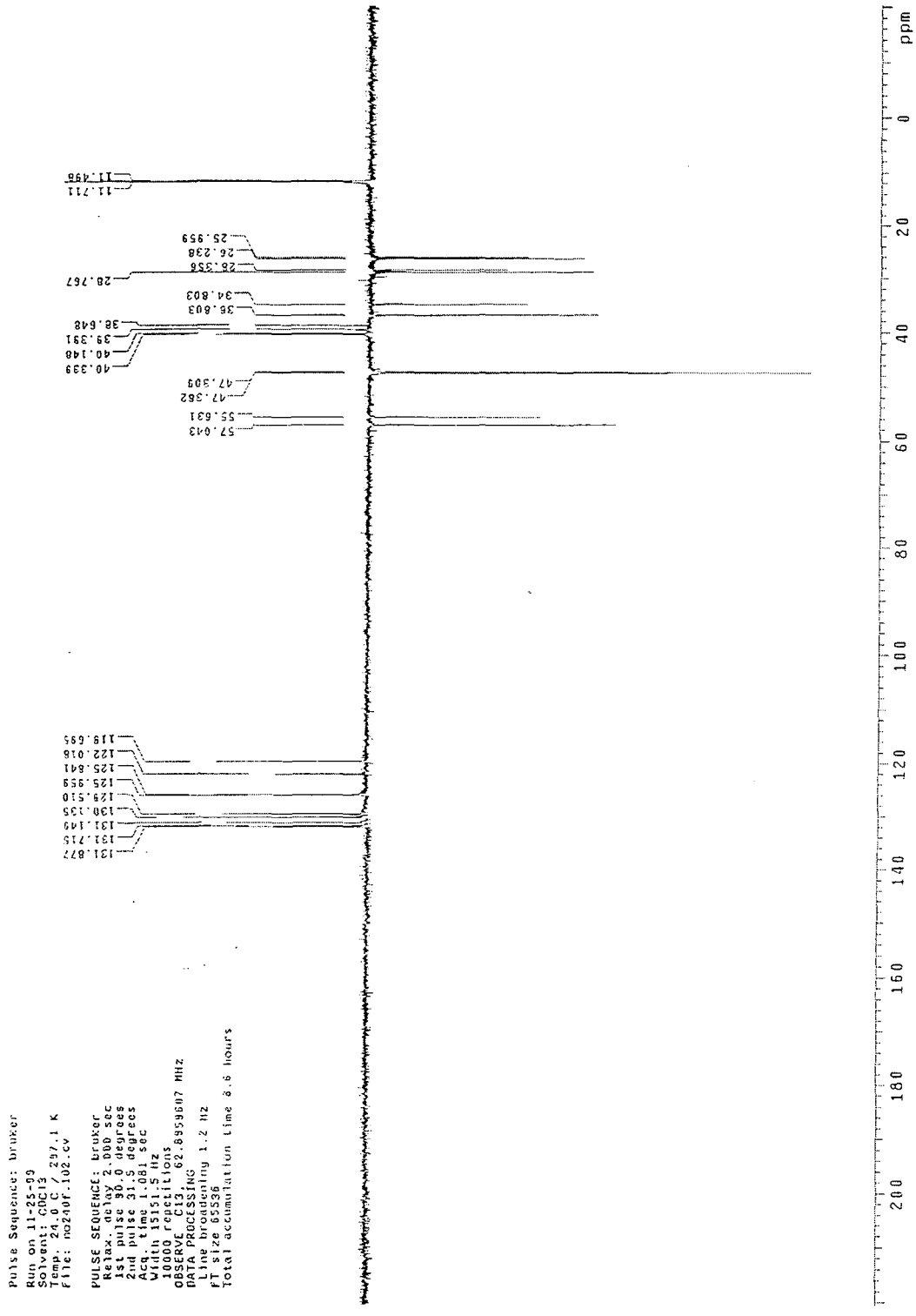
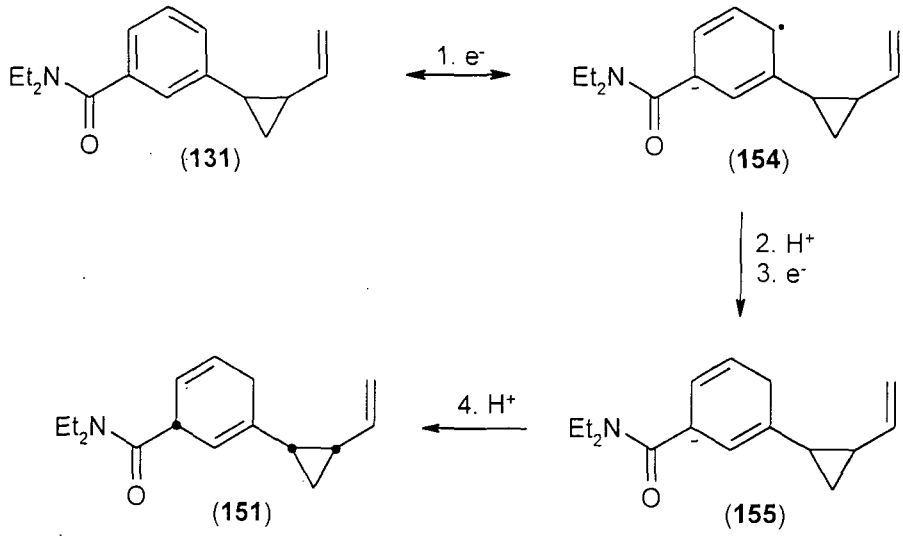

Pulse Sequence: bruker
Run on 11-25-99
Solvent: CDCl3
Temp. 24.0 C / 297.1 K
File: no240f.102.cv
PULSE SEQUENCE: bruker
Relax. delay 2.000 sec
1st pulse 90.0 degrees
2nd pulse 31.0 degrees
Acq. time 1.081 sec
Width 15151.5 Hz
10000 repetitions
OBSERVE C13 62.8959607 MHz
DATA PROCESSING
Line broadening 1.2 Hz
FT size 65536
Total accumulation time 8.6 hours
11.498
11.711
25.959
26.238
26.358
28.767
34.803
36.603
38.648
39.391
40.148
40.339
47.303
47.562
55.631
57.043
119.695
122.018
125.641
125.959
129.510
130.135
131.149
131.715
131.877
ppm
200
180
160
140
120
100
80
60
40
20
0

Figure 2.13.3

The structural determination of **151** was somewhat more straightforward as it was possible to assign the ^{1}H NMR spectrum including the cyclohexadiene CH_2 signals between δ2.48 and δ2.70 and the distinctive cyclohexadiene CH signals (doubly allylic and adjacent to a carbonyl) downfield at δ3.95. The retention of the amide group was easily determined from the IR spectrum (1636cm^{-1}) and was confirmed by the presence of a prominent peak at *m/z* 72 in the mass spectrum (EI-MS) relating to NEt_2^+. Unequivocal evidence for **151** was supplied by HRMS, the value obtained (245.1777) being in agreement with the theoretical accurate mass (245.1780) calculated ($C_{16}H_{23}NO$).

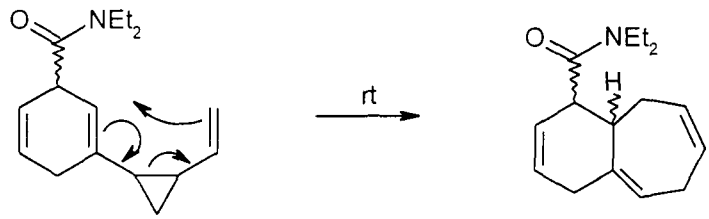
The formation of these products can be easily explained. Firstly, as predicted by Macielag and Schultz,[96] **131** was seen to undergo aromatic rather than amide reduction as depicted in Scheme 2.13.2.



Scheme 2.13.2

In the above mechanism, the radical anion, **154**, does not react with another electron to form a dianion (n.b. dianion formation results in amide reduction) but is protonated to form a radical. This is due both to the use of potassium, which has a lower reducing potential in ammonia than lithium,[51] and also the presence of *t*-BuOH as a proton source. Acceptance of a further electron followed by protonation then provides the dihydro product, **151**.

During this mechanism (scheme 2.13.2), a third chiral centre is introduced upon protonation of the anion **155** in the final step. Thus a total of three chiral centres are present in the product which equates to the possibliity of eight stereoisomers or four pairs of diastereoisomers. The fact that only two diastereoisomers (1:1) of **151** were isolated provides compelling evidence for the formation of the other product, **152**. In this, **152** can be viewed as a product of the Cope rearrangement[44] of the *cis* diastereoisomers (two sets) of **151** (n.b. *trans* isomers require high temperatures, *circa* 200°C, to undergo this rearrangement)[44], Scheme 2.13.3.



(151) (152)

Scheme 2.13.3

Absolute proof of this hypothesis could be obtained if **151** was shown to be a mixture of *trans* diastereoisomers. Unfortunately the cyclopropane signals in the ^{1}H NMR recorded for **151** appeared as multiplets and thus the distinctive small "*trans*" coupling constants[65] were not discernible.

2.13.3 Conclusion -Series 4

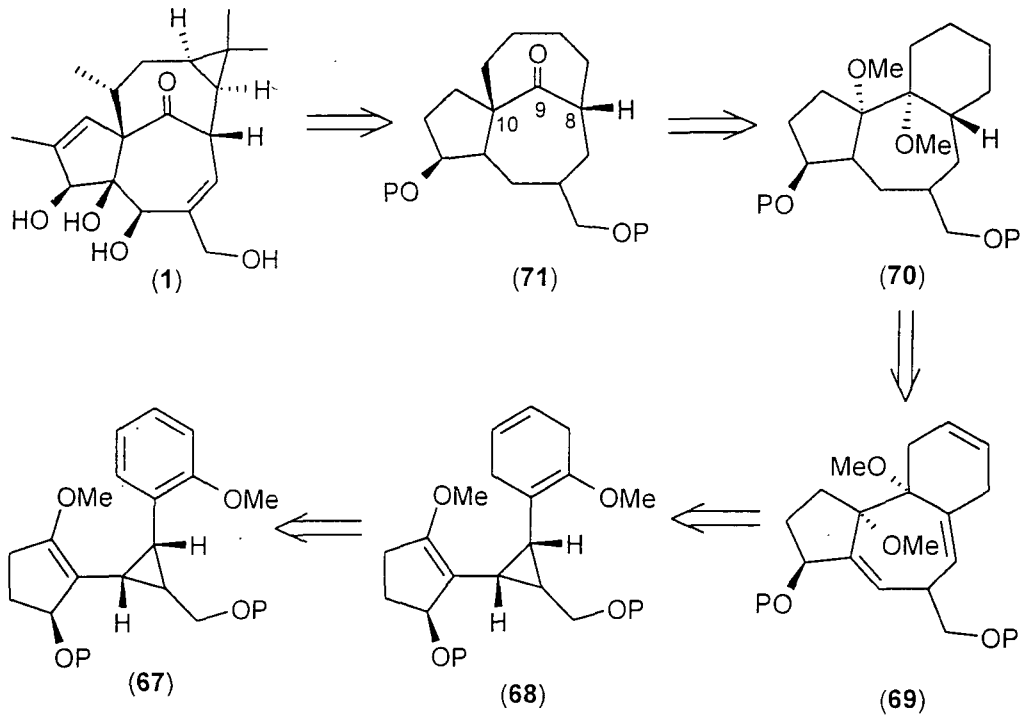
Although the presence of electron-withdrawing group seems to be essential (on paper) to facilitate ring closure to an indene structure using this methodology, this unfortunately also leads to the aromatic unit having a high electron affinity. In the third series of reductions this led to the formation of dianion species and thus amide reduction and in this series, even though over-reduction to the aldehyde was avoided, resulted in the formation of an anion (**155**) once a radical had been formed (as proposed in scheme 2.13.2). The major products were, therefore, the result of aromatic reduction and related Cope rearrangements rather than radical ring cleavage and 5-*exo*-trig cyclisation (indene formation).

3.0 Results and Discussion –Part 2

-Synthetic Work Towards Ingenol

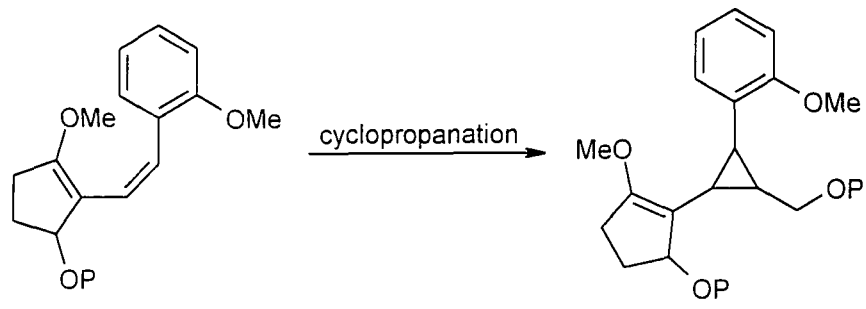
3.1 Introduction

Our synthetic approach to Ingenol, as outlined below (scheme 1.6.1), required the preparation of the 1-phenyl-2-vinyl-cyclopropane **67**. Birch reduction of this compound, as directed by the methoxy group, would provide the *cis*-di-vinylcyclopropane **68** which is expected to undergo a spontaneous (thermal) Cope rearrangement to yield **69**.



Scheme 1.6.1

It was envisaged that the preparation of **67** could be achieved by cyclopropanation of a *cis*-diene such as **156**, Scheme 3.1.1. Three strategies for the preparation of *cis*-dienes of this type have been explored and are detailed in the next sections. In short, these are cross-coupling of a Z-*bis*-stannane (section 3.2), application of a *cis*-vinyl iodide (section 3.3) and Wittig reaction of a cyclopentyl substituted phosphonium salt (section 3.4).



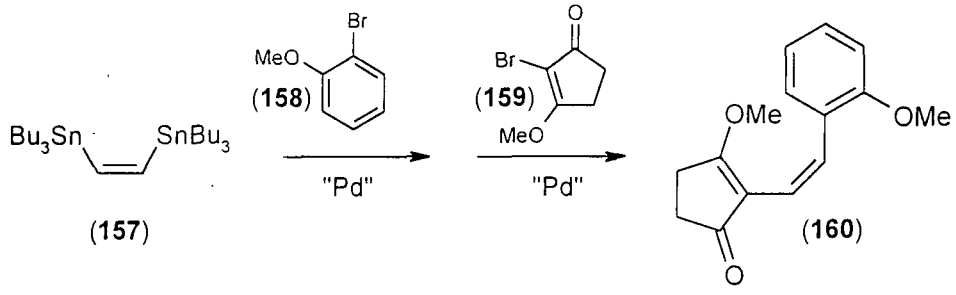
(156) (67)

Scheme 3.1.1

3.2 Application of Z-*bis*-stannane (157)

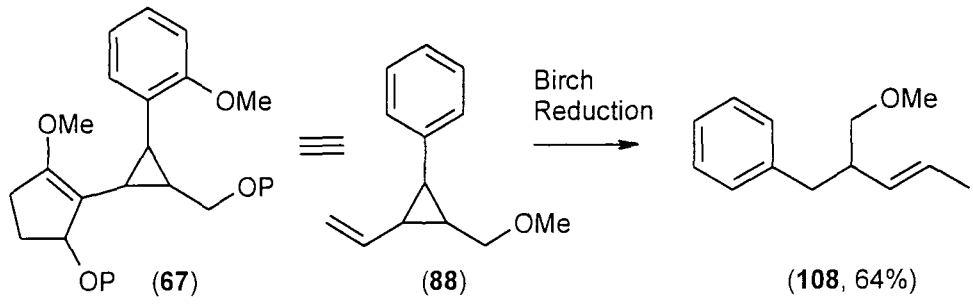
3.2.1 Introduction

In this approach, two successive palladium catalysed cross-coupling reactions of the *bis*-stannane (**157**) with aromatic bromide (**158**) and bromoenone (**159**) provides the *cis*-diene **160**, Scheme 3.2.1.



Scheme 3.2.1

The results from the model study discussed in the previous chapter (2.0) suggest that the Birch reduction of 1-phenyl-2-vinyl-cyclopropanes results in the unavoidable reductive cleavage of the cyclopropane ring. This was the case for **88**, which also serves as a good model compound for the more substituted ingenol precursor **67**, Scheme 3.2.2.



Scheme 3.2.2

For the cleavage mechanism to occur the cyclopropane Walsh orbitals must have good overlap with the adjacent aromatic π-system. It has been suggested that maximal overlap is achieved when the cyclopropane adopts a bisected conformation relative to the aromatic ring,[99] Figure 3.2.1.

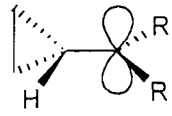
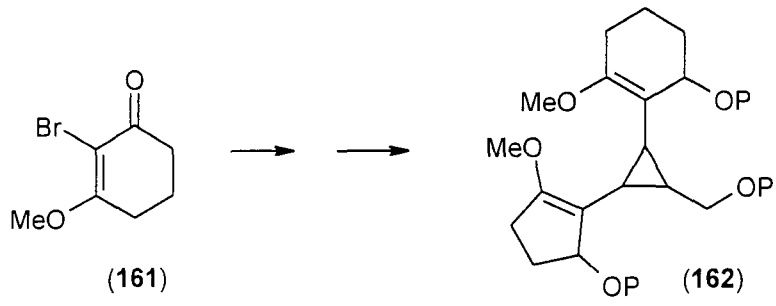


Figure 3.2.1

In the case of **67**, this premature fragmentation of the cyclopropane maybe avoided due steric crowding which forces the aromatic ring to twist out of optimal alignment with the cyclopropane. Nevertheless, in order to prepare for this eventuality, it was decided to additionally target the six-membered enone (**161**), which serves as a replacement for the aromatic bromide (**158**). Introduction of **161** into the cross-coupling sequence with the Z-*bis*-stannane (**157**) provides the required di-vinylcyclopropane Cope substrate without the need for a Birch reduction step, Scheme 3.2.3.

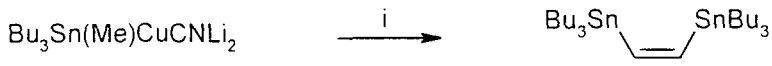


(161) (162)

Scheme 3.2.3

3.2.2 Preparation of (Z)-1,2-*bis*(tri-*n*-butylstannanyl)ethene (157)

The *bis*-stannane, **157**, was obtained following a procedure by Pulido *et al.*[100] In this, the mixed higher-order cyano-cuprate (**163**) was prepared from hexabutylditin and treated with acetylene and tri-*n*-butyltin chloride. After quenching the reaction with NH_4Cl, the crude product was obtained as oil, Scheme 3.2.4.



(163) (157)

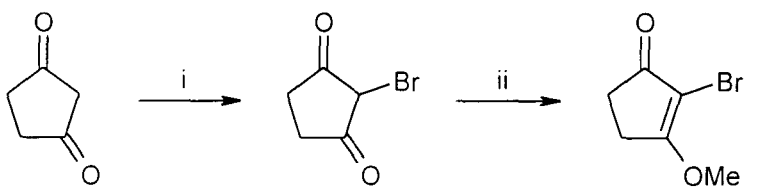
Scheme 3.2.4. Reagents and conditions: i, acetylene, -78°C then Bu_3SnCl, –78°C to 0°C.

The ^1H NMR spectrum recorded for this material contained a 2H-singlet at δ7.34 corresponding to the vinyl protons in the product, however, the *n*-butyl signals (δ0.75-δ1.71) over-integrated, presumably due to the presence of tetra-butyltin which is generated during the reaction. Removal of this contaminant proved not to be straightforward. The authors suggest that purification could be achieved by chromatography and recorded a 98% yield for the reaction, yet, in our hands, both components appeared to have the same R_f value (0.7) in petrol, thus precluding separation by this technique. Distillation attempts also failed, resulting in product decomposition (inferred from ^1H NMR). To avoid the formation of tetra-butyltin as a by-product, the cuprate species (**163**) can also be prepared from tri-*n*-butyltin chloride instead of hexabutylditin.[101] This method was not investigated as the

product (**157**) was clean except for the presence of tetra-butyltin, which, being inert, was not expected to interfere with the planned Stille cross-coupling reactions. Further inspection of the ^{1}H NMR spectrum indicated the product to be 68% w/w *bis*-stannane, which equates to a 92% yield.

3.2.3 Preparation of Bromoenones

Preparation of the required bromoenones, **159** and **161**, was attempted in accordance with a method utilised by Curran and Jasperse.[102] In the case of the five membered enone (**159**), this involved treatment of a chloroform solution of 1,3-cyclopentadione (**164**) with NBS, thus forming the bromo-diketone (**165**). Without isolation, this compound was subjected to acid catalysed methanolysis, providing the crude product, Scheme 3.2.5.



(164) (165) (159)

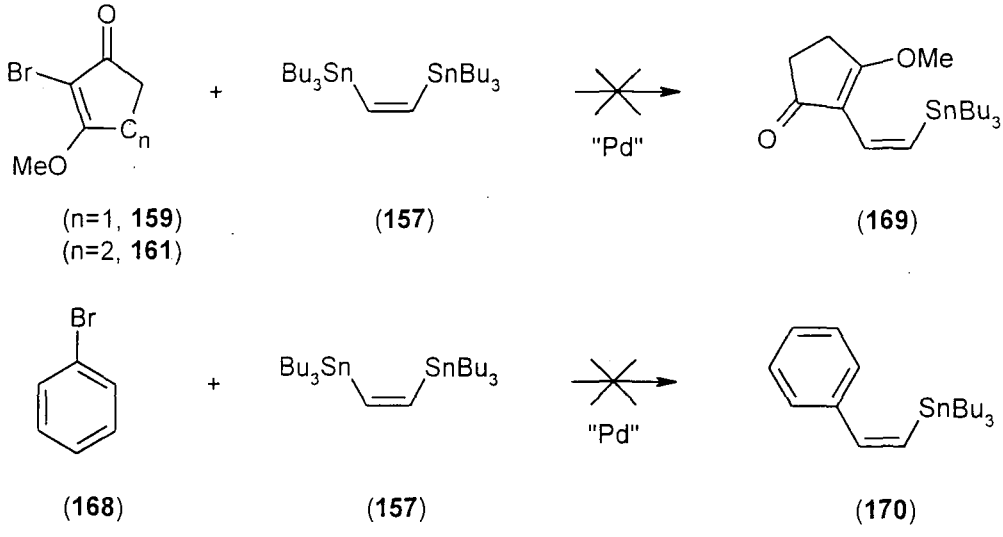
Scheme 3.2.5. Reagents and conditions: i, NBS, $CHCl_3$, reflux; then ii, MeOH, TsOH, reflux, 40% (2 steps).

Re-crystallisation of this material (ether:ethyl acetate, 4:1) provided **159** as a white crystalline solid in 40% yield. HRMS analysis of the crystals (189.9629) verified the structure as did the mass spectrum (EI-MS) and the IR spectrum. The former contained twin molecular ion peaks at *m/z* 190 and *m/z* 192 (both 100%) indicating the presence of one bromine atom and the latter contained a strong α,β-unsaturated ketone stretching band at 1688cm^{-1}.

Repeating this reaction with 1,3-cyclohexadione (**166**) in order to form **161** was curiously unsuccessful and resulted in a mixture of unidentifiable products (crude ^{1}H NMR). Although mysterious, these observations have also been reported elsewhere and maybe the result of the product being hydrolytically[103] and thermally[104] unstable.

3.2.4 Stille Cross-Coupling Reactions of (Z)-1,2-*bis*(tri-*n*-butylstannanyl)ethene (157) with Bromoenones

As mentioned elsewhere in this thesis (section 2.10.2), vinylstannanes have been shown to undergo efficient palladium catalysed cross-coupling reactions with a range of halogenated compounds including aryl and vinyl bromides.[73] Many different catalysts and solvents for this reaction have been examined, however, the most universal have been shown to be combinations of $Pd(PPh_3)_4$ and $Pd(MeCN)_2Cl_2$ in THF, DMF or toluene. The cross-coupling reaction of the *bis*-stannane (**157**) with bromobenzene (**168**) and both of the previously prepared bromoenones (**159** and **161**) was, therefore, attempted under these conditions. These included experiments conducted at a number of different temperatures (rt to 100°C) and varying duration (2h to 3 days). Unfortunately, no coupled products were observed in this series of reactions; high temperatures tended to result in decomposition (crude ^{1}H NMR) otherwise starting materials only were evident in the crude reaction mixtures (tlc), Scheme 3.2.7.



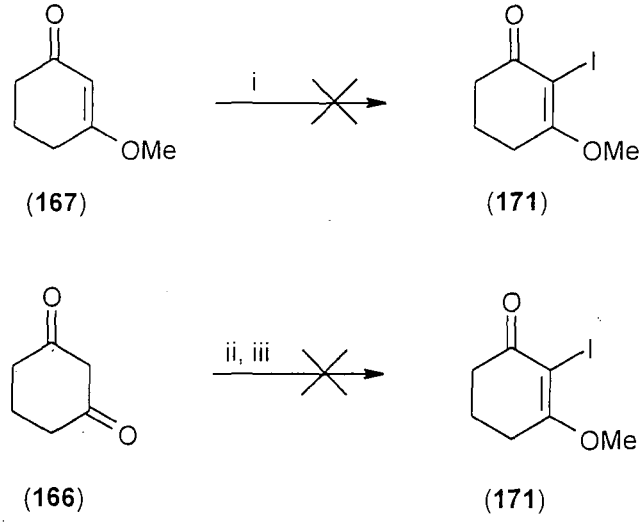
Scheme 3.2.7

The failure of these reactions was not expected, but perusal of the literature revealed that other workers have also commented on the low reactivity of bromoenones in cross-coupling reactions with organotins.[106] No such problems have been reported with aryl bromides, although it is possible that a high temperature is required for this

reaction to occur and at such a temperature *bis*-stannane degradation occurs. A more reactive substrate was therefore sought and attention turned to the synthesis of iodo substrates, which are known to exhibit greater reactivity than their bromo equivalents.[73]

3.2.5 Synthesis of Iodoenones

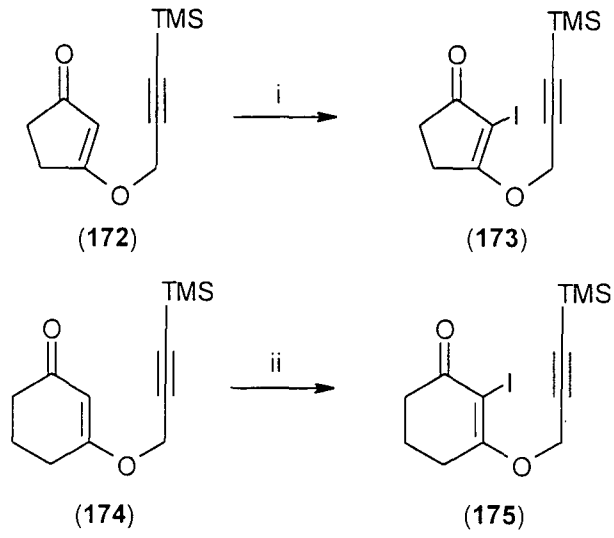
In order to replace the unreactive bromoenones (**159** and **161**), preparation of five and six membered iodoenone equivalents were required. Initially, the methods that had been successful for the preparation of the bromoenones were investigated but with the obvious replacement of NBS with NIS. This entailed treatment of 1,3-cyclohexadione (**166**) with NIS followed by acid catalysed methanolysis and treatment of the previously prepared methyl enol ether (**167**) with NIS, Scheme 3.2.8.



Scheme 3.2.8. Reagents and conditions: i, NIS, 1,2 DCE, 0°C-rt; ii, NIS, $CHCl_3$, reflux; then iii, MeOH, TsOH, reflux.

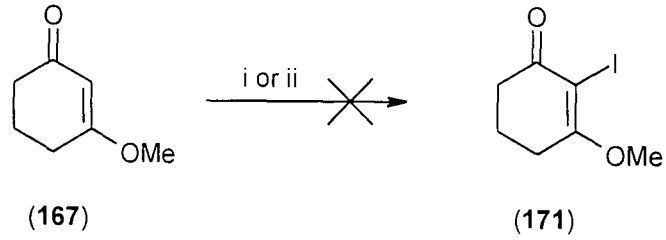
As can be seen from Scheme 3.2.8, both of these methods proved to be unsuccessful, resulting in complete decomposition in both cases (crude ^{1}H NMR). Evidently the increased reactivity of the iodo compounds compared to the bromo compounds results in a proportional decrease in stability of these products necessitating alternative methods of preparation.

The α-iodination of five and six-membered unsubstituted enones has been effected in high yield with elemental iodine in carbon tetrachloride/pyridine.[107] In a modification of this procedure, where DMF or acetonitrile is used as the solvent, the vinyligous esters **173** and **175**, which are akin to the required system (**171**), have been prepared, Scheme 3.2.9.[108]



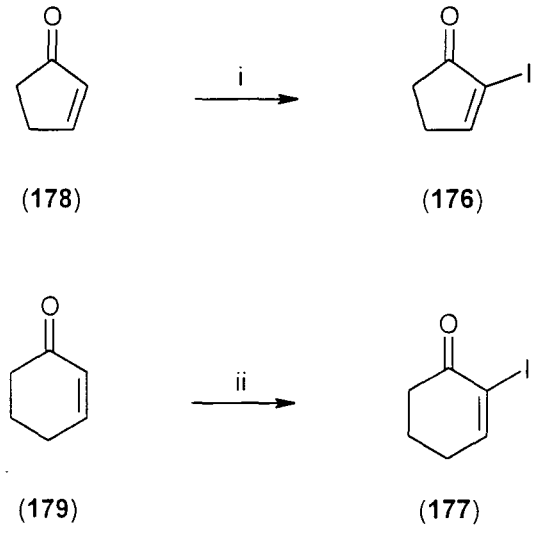
Scheme 3.2.9. Reagents and conditions: i, I_2, DMF, pyridine, 2h, 88%; ii, I_2, DMF, pyridine, 2.5h, 85%.

Attempts to α-iodinate the methyl enol ether (**167**) under these conditions failed, forming only unidentifiable decomposition products, Scheme 3.2.10. Repeating the reaction with acetonitrile, on the other hand, did not destroy the starting material but equally effected no reaction.



Scheme 3.2.10. Reagent and conditions: i, I_2, DMF, pyridine; ii, I_2, CH_3CN, pyridine.

With the associated complications of introducing iodine to the α-position of **167**, attention turned to the preparation of the known and less complicated α-iodoenones, **176** and **177**. Thus, following the previously mentioned procedure[107] (except substituting carbon tetrachloride with DCM), 2-cyclopent-1-one (**178**) and 2-cyclohexen-1-one (**179**) were allowed to react with iodine in the presence of pyridine. In this case, the absence of a methoxy group had a marked effect and both the six and five membered compounds were successfully prepared, both being isolated as white crystalline solids in good yield, Scheme 3.2.11.

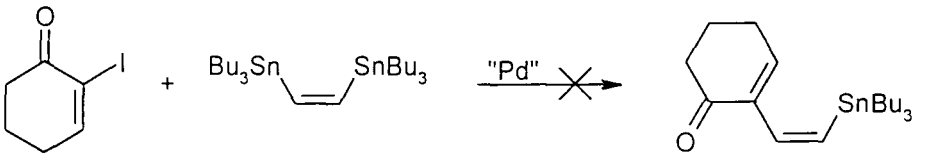


Scheme 3.2.11. Reagents and conditions: i, I_2, DCM, pyridine, 0°C-rt, 43%; ii, I_2, DCM, pyridine, 0°C-rt, 57%.

The formation of **176** and **177** was confirmed with the usual analysis. In the ^1H NMR spectra downfield 1H-triplet signals corresponding to the vinyl protons were evident (at δ8.00 for **176** and δ7.77 for **177**). Strong molecular ion peaks were also present in the mass spectra; in the case of **176**, at *m/z* 208 (71%), and for **177** at *m/z* 222 (100%). Further, the melting points recorded for both compounds (71°C for **176** and 47-49°C for **177**) were consistent with the literature values (71°C and 48-48.5°C respectively).[107]

3.2.6 Stille Cross-Coupling Reactions of (Z)-1,2-*bis*(tri-*n*-butylstannanyl)ethene (157) with Iodo compounds

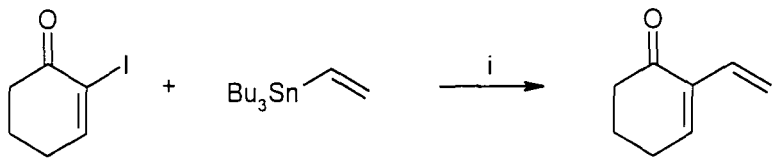
Johnson and co-workers[106] have developed a set of conditions for the successful Stille type coupling of α-iodoenones. These are $Pd(MeCN)_2Cl_2$ catalyst and DMF solvent together with copper(I) iodide and triphenylarsine as additional additives. The six membered enone (**177**) and *bis*-stannane (**157**) were allowed to react under these conditions. Monitoring the reaction by tlc, no products were observed at room temperature and disappointingly at elevated temperatures (up to 100°C) starting material degradation was observed. With some reservations about the solubility of the *bis*-stannane in DMF, the reaction was also re-run in THF. This again produced the same results. Further experimentation involved reactions in which no additives were used and reactions in which the catalyst was changed to $Pd(PPh_3)_4$. Again, no reaction appeared to take place at low temperatures and at higher temperatures, decomposition of the starting material was evident, Scheme 3.2.12.



(177) (157)

Scheme 3.2.12

As can be seen from these reactions, no coupling was observed at elevated temperatures due to decomposition, either of the coupled product or the starting materials. The failure of the reaction at ambient temperature may be due to steric crowding. Indeed, several examples of cross-coupling of the E-compound exist in the literature[109] whereas none are evident for the Z-compound. To access whether coupling could be achieved at ambient temperature if steric crowding was reduced, the iodoenone, **177**, was allowed to react with tri-butylvinylstannane (**180**) according to Scheme 3.2.13. In this reaction, $Pd(PhCN)_2Cl_2$ was chosen as a direct replacement for $Pd(MeCN)_2Cl_2$ and NMP was used as the solvent since it has been suggested as an excellent solvent in this type of reaction.[110]



(177) (180) (181)

Scheme 3.2.13. Reagents and conditions: i, $Pd(PhCN)_2Cl_2$, CuI, Ph_3As, NMP, rt, 12h, 19%.

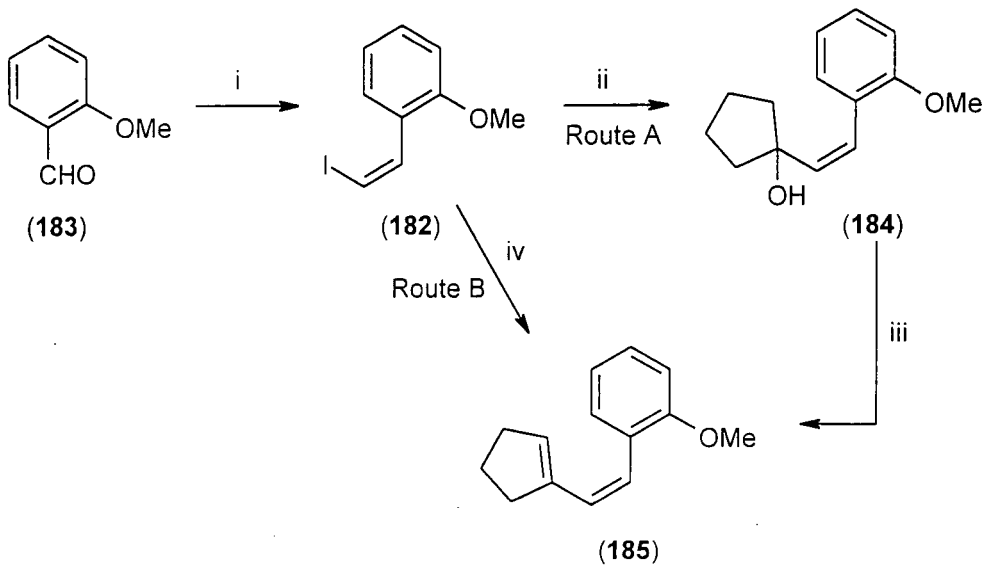
From this reaction, the diene **181** was isolated after careful work-up (ambient temperature) and FCC as a thermally unstable oil in 19% yield. The ^1H NMR spectrum recorded for **181** was consistent with the literature data,[106] containing 1H-doublet peaks at δ5.18 (J=12Hz) and δ5.67 (J=18Hz), relating to the terminal vinylic protons, and a 1H-doublet of doublets signal at δ6.55 (J=12 and 18Hz), corresponding to the remaining acyclic vinylic proton.

The successful reaction of tri-butylvinylstannane (**180**) with iodoenone (**177**) but the failure of the Z-*bis*-stannane (**157**) to undergo reaction under similar conditions strongly suggests that steric hindrance associated with the Z-*bis*-stannane (**157**) precludes effective coupling. Furthermore, purification of **157** was troublesome and the synthesis (involving the use of acetylene) is not amenable to scale-up which would be required at a later date. Other methods of preparing *cis*-dienes were, therefore, investigated.

3.3 Application of 1-(2′-iodovinyl)-2-methoxy benzene (182)

3.3.1 Introduction

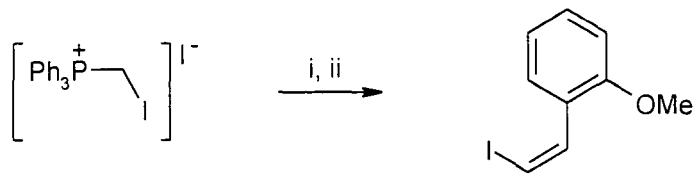
This strategy was investigated in parallel with the Z-*bis*-stannane (**157**) work (section 3.2) and was designed to gain rapid access to the required *cis*-diene. Here, the Z-vinyl iodide (**182**) is constructed, by way of a Wittig reaction, from a benzaldehyde. **182** is a flexible intermediate as it provides the option of attaching the cyclopentyl ring *via* a number of different routes. For example, nucleophilic addition-dehydration (Route A) or Stille reaction (Route B), Scheme 3.3.1.



Scheme 3.3.1. Reactions: i, olefination ii, nucleophilic addition; iii, dehydration; iv, cross-coupling.

3.3.2 Preparation of Vinyl Iodide (182)

Stork *et al*[111] demonstrated the stereoselective preparation of Z-vinyl iodides by reaction of aldehydes with the Wittig reagent generated from iodomethyltriphenylphosphonium iodide (**186**). A quantity of this salt was therefore prepared by reaction of triphenylphosphine with diiodomethane in benzene. **186** was isolated, as a white solid (54%), by crystallisation from the reaction mixture. The successful preparation of **186** was confirmed by elemental analysis, the values from which (C, 43.09; H, 3.19%) being consistent with the calculated values (C, 43.05; H, 3.23%). The melting point (229-230°C) was also in agreement with the literature value (228-230°C).[112] In the next step, **186** was treated with potassium hexamethyldisilazide and subsequently reacted with *o*-anisaldehyde in the presence of HMPA to form the desired vinyl iodide (**182**), Scheme 3.3.2.



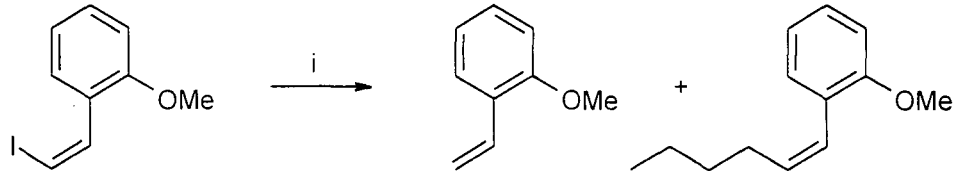
(186) (182)

Scheme 3.3.2. Reagents and conditions: i, KHMDS, THF, rt; then ii, HMPA, *o*-anisaldehyde, -78°C to rt, 73%.

182 was isolated, after distillation (150°C, 0.1mmHg), in 73% yield as a single isomer. The presence of two 1H-doublets in the ^{1}H NMR spectrum at δ6.56 and δ7.73, both with coupling constants of 8.5Hz, confirmed the Z geometry of the double bond (typical values Z geometry are J=0-12Hz, typical values for E geometry are J=12-18Hz),[65] whereas prominent peaks in the mass spectrum (EI-MS) at *m/z* 260 (45%, M^+) and *m/z* 133 (96%, M^+-I) provided compelling evidence for the overall structure.

3.3.3 Attempted Reaction of Vinyl Iodide (182) with Cyclopentanone

This reaction (i.e. Route A, scheme 3.3.1) was attempted by treating the vinyl iodide (**182**) with *n*-BuLi (1.2eq.) in THF followed by addition of cyclopentanone. These conditions produced a complicated mixture of products (tlc) which proved difficult to separate by chromatography. Nevertheless, two isolable products were formed in the reaction. These were identified as the styrenes **187** (14%) and **188** (26%), Scheme 3.3.3.



(182) (187, 14%) (188, 26%)

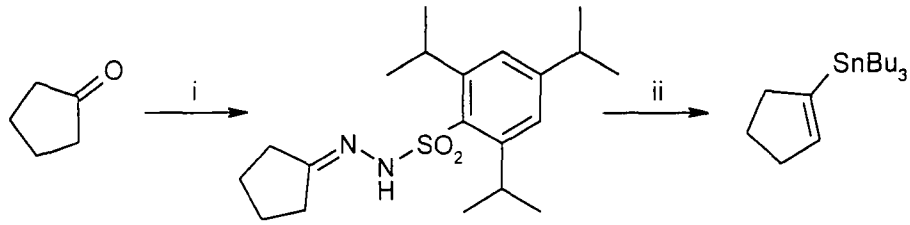
Scheme 3.3.3. Reagents and conditions: i, *n*-BuLi, THF, -78°C, then cyclopentanone, -78°C-rt.

Evidence for the structure of **187** was provided by the mass spectrum which contained a prominent molecular ion peak (*m/z* 134, 68%) and a tropylium ion peak (*m/z* 91, 100%). Signals at δ5.27, δ5.74 and δ7.06 attributable to the three terminal alkene protons of **187** were also conspicuous in the ^{1}H NMR spectrum. For **188**, the appearance of four distinct signals in the alkyl region of the ^{1}H NMR (δ0.93-δ2.30), integrating to a total of 9 protons, validated that an *n*-butyl group was present. In the same spectrum, the coupling constants for the vinyl protons at δ5.77 and δ6.54 were both 12.2Hz. This value (as discussed in section 3.3.2) lies between the ranges expected for E or Z alkenes and, therefore, does not provide conclusive evidence for the geometry of the double bond. This said though, retention of double bond configuration during lithiation can be assumed and so **188** has been assigned Z geometry. A prominent molecular ion (52%) in the mass spectrum (EI-MS) of **188** at *m/z* 190 provided conclusive evidence for the structure.

The formation of these compounds confirms that halogen-lithium exchange of **182** occurs under these conditions, although it appears that the resultant vinyllithium does not show adequate nucleophilic character to attack the carbonyl group of cyclopentanone. **187** can be viewed then, simply as the product of vinyllithium protonation, whereas **188** is the result of butyl group transfer from *n*-BuLi. The other unisolable products observed in this reaction may be the result of competitive cyclopentanone deprotonation. The use of *t*-BuLi (2.2eq.), which has often been shown to give better results in this type of reaction, in place of *n*-BuLi, was also investigated. Yet the crude product from this reaction proved to be an even more complicated mixture (GC, tlc) and contained no discernible products.

3.3.4 Preparation of Vinyl Stannane 189

In order to investigate the possible Stille cross-coupling of the vinyl iodide (i.e., Route B, scheme 3.3.1), preparation of the vinyl stannane **189** was required. **189** can be synthesised from cyclopentanone *via* the hydrazone, **190**.[113] To this effect, cyclopentanone was stirred with 2,4,6-triisopropylbenzenesulfonylhydrazide in methanol. Subsequent addition of concentrated HCl provided, after crystallisation, the desired compound as a white solid (60%),[114] Scheme 3.3.4.



(190) (189)

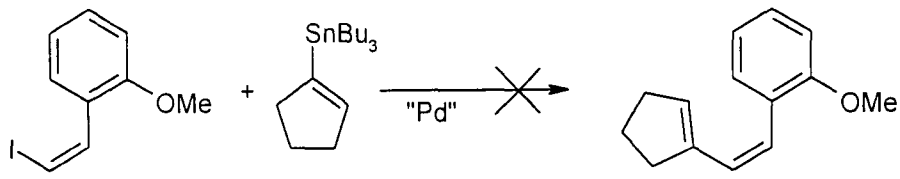
Scheme 3.3.4. Reagents and conditions: i, 2,4,6-triisopropylbenzenesulfonylhydrazide, c.HCl, MeOH, rt, 60%; ii, *s*-BuLi, pentane/TMEDA, -78°C, then *n*-Bu_3SnCl, 22%.

The absence of a ketone carbonyl peak in the IR spectrum indicated that successful preparation of the hydrazone (**190**) had taken place. The results from the elemental analysis of **190** (C, 65.89; H, 8.67; N, 7.90; S, 8.92%) were consistent with the theoretical values (C, 65.89; H, 8.85; N, 7.68; S, 8.80%) calculated for the structure as shown ($C_{20}H_{32}N_2O_2S$).

With **190** in hand, treatment with *s*-BuLi and reaction then with tri-*n*-butyltin chloride achieved conversion to the vinyl stannane (**189**), which was obtained after Kugelrohr distillation (0.2mmHg, 150°C) in 22% yield. The ^1H NMR spectrum of **189** contained a typical *n*-butyl methyl triplet at δ0.89 (9H) together with *n*-butyl methylene signals between and δ1.21 and δ1.62 (18H total). The vinyl proton was also evident and came into resonance at δ5.87.

3.3.5 Attempted Stille Coupling 182 and 189

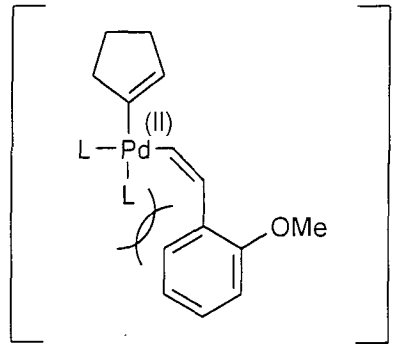
The Stille cross-coupling of vinyl iodide **182** and vinyl stannane **189** was attempted using standard conditions for this reaction.[73] Thus both $Pd(PPh_3)_4$ and $Pd(MeCN)_2Cl_2$ were investigated as catalysts (5% catalyst charge) and both THF and DMF were selected as solvents. The reactions were conducted at room temperature and 60°C. Unfortunately no reaction was observed under any of these conditions (tlc), Scheme 3.3.5.



(182) (189) (185)

Scheme 3.3.5

The Stille reaction is generally a very reliable and high yielding method of carbon-carbon bond formation. This is especially true if a vinyl iodide is used as one of the coupling partners. The failure of this reaction then was somewhat surprising but may be a result of the *cis* geometry of the vinyl iodide double bond. This introduces unfavourable steric interactions in the square planar metal complex (**191**), which must be formed during the reaction, Figure 3.3.1. It has been speculated that this may also be the reason for the lack of coupling observed with the Z-*bis*-stannane (**157**) in the previous section (section 3.2.6).



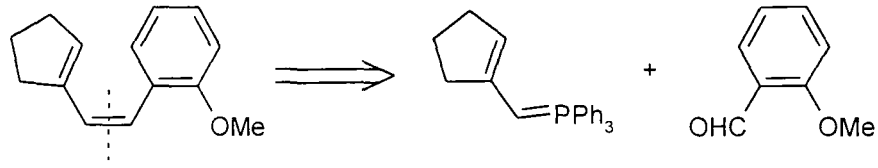
(191)

Figure 3.3.1

3.4 Wittig Approach to *cis*-Diene

3.4.1 Introduction

After finding that Stille cross-coupling reaction was not successful in the preparation of the desired *cis*-diene (**185**), a new strategy utilising a Wittig reaction was devised, Scheme 3.4.1. The reaction is expected to produce the *cis* rather than the *trans* alkene as the phosphorus ylide, **192**, is unstabilised.[115]

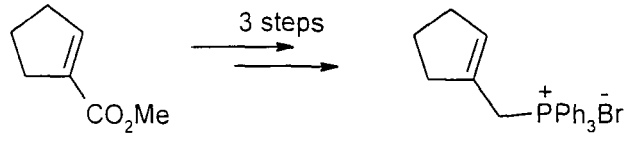


(**185**) (**192**) (**183**)

Scheme 3.4.1

3.4.2 Synthesis of Phosphonium Salt (193)

The phosphonium salt **193** was accessed from the commercially available methyl (cyclopent-1-ene)carboxylate (**194**) in a modification of a previously described procedure,[116] Scheme 3.4.2.



(**194**) (**193**)

Scheme 3.4.2

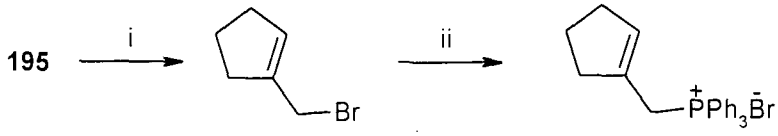
In the first step, the ester (**194**) was treated with DIBAL-H. After work-up with Hyflo filter aid, the resultant allylic alcohol (**195**) was isolated in a pure form in 82% yield. Confirmatory evidence for the successful reduction was obtained from the ^{1}H

NMR spectrum, which was devoid of a methyl ester signal but contained an alcoholic singlet at δ1.47. Retention of the double bond was also confirmed by the presence of a vinyl proton signal at δ5.62 in the same spectrum, Scheme 3.4.3.

(194) (195)

Scheme 3.4.3. Reagents and conditions: i, DIBAL-H, hexane, -78°C to rt, 82%.

The allylic alcohol (**195**) was then allowed to react with PBr_3 to effect conversion to the vinyl bromide (**196**). Filtration of the crude reaction mixture through a short column of alumina provided **196** as an unstable oil (darkened on standing) in 81% yield, Scheme 3.4.4. The instability of **196** necessitated swift conversion to the phosphonium salt, however, the ^1H and ^{13}C NMR spectra were firstly recorded. The former contained a 2H-singlet at δ4.07 assignable to the CH_2 group adjacent to the bromine atom and a signal at δ5.78 corresponding to the vinyl proton, whereas the latter contained a total of six signals including two in the vinyl region of the spectrum at δ130.9 and δ140.4.



(196) (193)

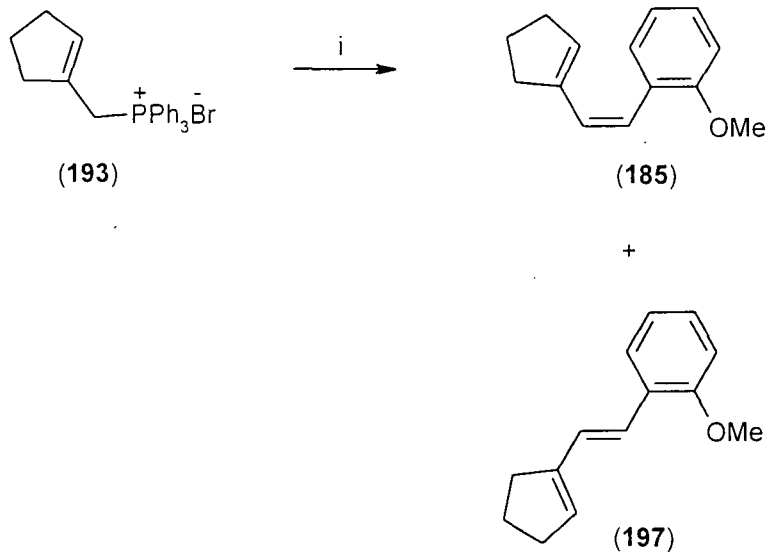
Scheme 3.4.4. Reagent and conditions: i, PBr_3, pyridine, pentane, -40°C, 81%; ii, PPh_3, toluene, reflux, 89%.

The final step in the sequence was achieved simply by reacting with triphenylphosphine in toluene,[117] the desired salt (**193**) being isolated by filtration in 89% yield, Scheme 3.4.4. The preparation of **193** was validated by elemental analysis, the values from which (C, 68.01; H, 5.57%) being in agreement with the

theoretical values (C, 68.09; H, 5.71%). A peak at *m/z* 343 was also observed in the mass spectrum (ESI-MS) which equates to the mass of **193** minus the bromine atom.

3.4.3 Wittig Reaction of Phosphonium Salt (193)

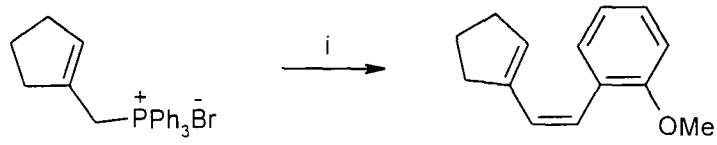
Initially, the Wittig reaction between the phosphonium salt **193** and *o*-anisaldehyde was conducted in THF using *n*-BuLi as the base, Scheme 3.4.5. This method was successful in that it led to the formation of the correct product (38%), although, inspection of the crude ^{1}H NMR spectrum revealed that the product was a mixture of *cis* and *trans* dienes (2:1). Separation of the desired *cis*-diene (**185**) by chromatography was unsuccessful, however, it was possible to isolate a small quantity of the *trans* compound (**197**). This was identified by characteristic vinyl protons in the ^{1}H NMR at δ6.75 and δ7.02. Both these signals were doublets with an associated, large, "*trans*" coupling constant (16.2Hz).[65] A strong (100%) molecular ion (*m/z* 200) was also obtained by EI-MS.



(193) (185) + (197)

Scheme 3.4.5. Reagents and conditions: i, *n*-BuLi, THF, then *o*-anisaldehyde, 0°C, 38% total.

The production of *trans* isomer was remedied by switching to the so-called "salt-free" conditions in which lithium bases are avoided. Thus, the reaction was repeated using sodium hexamethyldisilazide in place of *n*-BuLi and at the lower temperature of –78°C. Under these conditions, the *cis*-diene (**185**) was isolated, after FCC, as the sole product (77%), Scheme 3.4.6.



(**193**) (**185**)

Scheme 3.4.6. Reagents and conditions: NaHMDS, THF, 0°C to rt, then *o*-anisaldehyde, -78°C to rt, 77%.

In the ^{1}H NMR spectrum of **185** ($CDCl_3$) the two vinyl protons were coincidental, appearing as a 2H-singlet at δ6.42. Re-recording of the spectrum in C_6D_6 separated the two signals which came into resonance as doublets at δ6.64 and δ6.87 (J=12.4Hz for both). The accurate mass recorded for **185** (200.1202) was consistent with the calculated mass (200.1201).

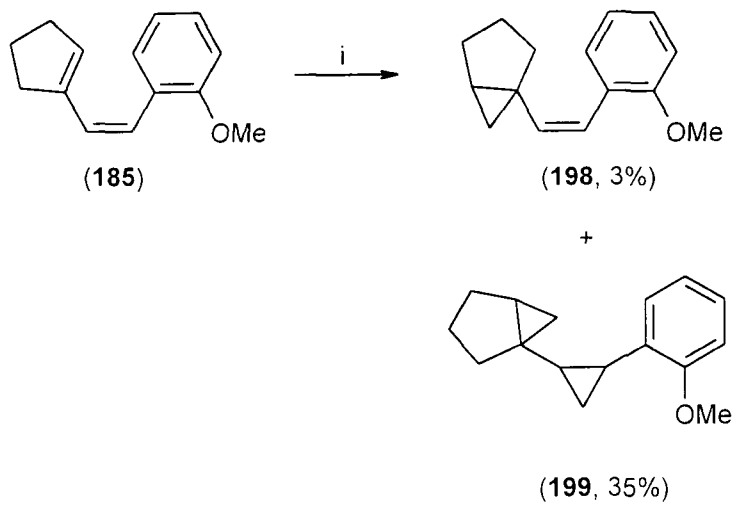
3.5 Installation of the Cyclopropane Ring

3.5.1 Introduction

The next step in the synthesis required the cyclopropanation of the *cis*-diene (**185**). This was approached assuming that the steric repulsion between the terminal ring systems in the molecule would render the internal, acyclic, double bond strained and thus more reactive towards a carbene/carbenoid than the cyclopentyl double bond.

3.5.2 Cyclopropanation of *cis*-Diene (185)

Initially, this reaction was attempted by treatment of **185** with a combination of diiodomethane and diethylzinc. This produced a mixture of products. From this mixture, careful FCC effected the isolation of mono-cyclopropane **198** (3%) and di-cyclopropane **199** (35%) as a 1:1 mixture of diastereoisomers (GC), Scheme 3.5.1.



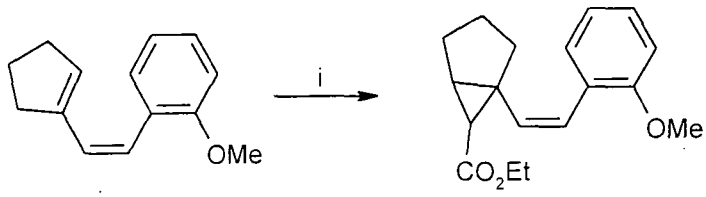
(**185**) (**198**, 3%) + (**199**, 35%)

Scheme 3.5.1. Reagents and conditions: i, CH_2I_2, $ZnEt_2$, benzene, reflux.

The preparation of **198** corresponded with the disappearance of the cyclopentyl vinyl proton in the ^{1}H NMR spectrum. The two remaining signals in the vinyl region of the spectrum at δ5.83 and δ6.48 were assignable to the residual *cis* double bond. In the mass spectrum (EI-MS), a strong (79%) molecular ion was observed at *m/z* 214 and the base peak was attributable to a tropylium ion (*m/z* 91).

The ^{1}H NMR spectrum recorded for **199** was complicated due to the presence of two diastereoisomers, however, two distinct methoxy peaks (3H-singlets) were clearly visible at δ3.88 and δ3.89. In the ^{13}C NMR spectrum, a total of 32 signals were observed which is correct for the structure as shown (16 per diastereoisomer) and in the mass spectrum a molecular ion (*m/z* 228) was evident (8%).

The cyclopropanation of **185** was also attempted using EDA. The use of $Rh_2(OAc)_4$ and $CuOTf.C_6H_6$ were investigated as catalysts, yet, in both cases mixtures of products were generated which proved difficult to separate by FCC. Nevertheless, repeated FCC of the crude material from the $CuOTf.C_6H_6$ catalysed reaction effected separation of a single diastereoisomer of **200**, Scheme 3.5.2.



(185) **(200)**

Scheme 3.5.2. Reagents and conditions: i, EDA, $CuOTf.C_6H_6$, DCM, 2%.

The preparation of **200** corresponded with the appearance of an ester carbonyl stretch in the IR spectrum (1726cm^{-1}) and a molecular ion peak (*m/z* 286, 14%) in the mass spectrum (EI-MS), whilst in the ^{1}H NMR spectrum, two vinyl signals were still evident at δ5.93 and δ6.65 (both 1H-doublets, J=12.2Hz).

The preferential cyclopropanation of the cyclopentyl bond over the acyclic double bond observed in these reactions suggests that this bond is more electron-rich. In order to rationalise this, the *cis*-diene (**185**) was subjected to molecular modelling (supplied by Merck Sharp and Dohme). The results from this analysis suggest that, in the preferred conformation (figure 3.5.1), the acyclic double bond is almost planar and thus conjugated with the aromatic ring. Its electron density is thereby lowered by delocalization. In contrast, the cyclopentyl ring is twisted out of this plane and thus non-conjugated. Furthermore, the cyclopentyl ring is more substituted, again increasing its relative electron density.

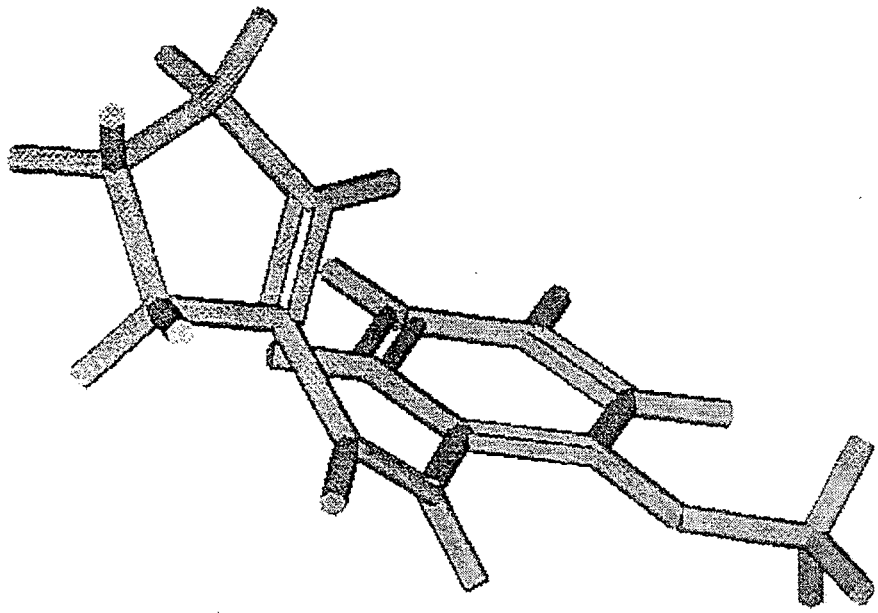


Figure 3.5.1

3.5.3 Dihydroxylation of *cis*-Diene (185)

Initial attempts to cyclopropanate the acyclic double bond of the *cis*-diene (**185**) resulted in cyclopropanation of the cyclopentyl ring. Protection of the cyclopentyl double bond was therefore sought. To this end, diol protection was selected. This has several advantages. Firstly, dihydroxylations are high yielding, and secondly, the reaction yields an allylic alcohol as the product. These compounds are known to undergo efficient cyclopropanation by way of hydroxyl-directed carbenoid addition.[68]

Initially, the dihydroxylation of **185** was attempted using OsO_4 and *N*-methylmorpholine *N*-oxide in H_2O/*t*-BuOH.[118] Unfortunately this was unsuccessful and only starting material was isolated (tlc). Better results were achieved using trimethylamine *N*-oxide and OsO_4 in H_2O/*t*-BuOH/pyridine as described for hindered alkenes by Matteson *at al.*[119] Under these conditions the diol **201** was prepared, after FCC, in 68% yield, Scheme 3.5.3.

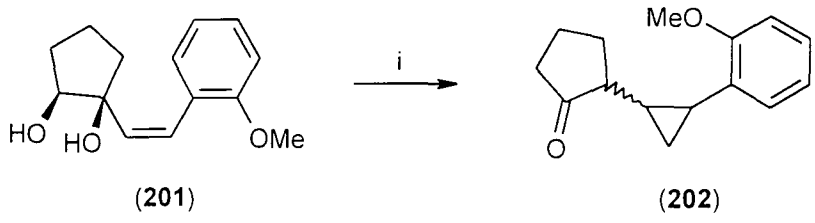
(**185**) (**201**)

Scheme 3.5.3. Reagents and conditions: i, OsO_4, Me_3N-O.H_2O, *t*-BuOH, H_2O, pyridine, reflux, 68%.

The preparation of **201** coincided with the appearance of an alcohol stretch in the IR spectrum between 3080 and 3630cm^{-1} and the disappearance of the cyclopentyl vinyl proton in the ^{1}H NMR spectrum. An accurate mass was also obtained (234.1260), which compares well with the theoretical value (234.1256).

3.5.4 Cyclopropanation of Diol (201)

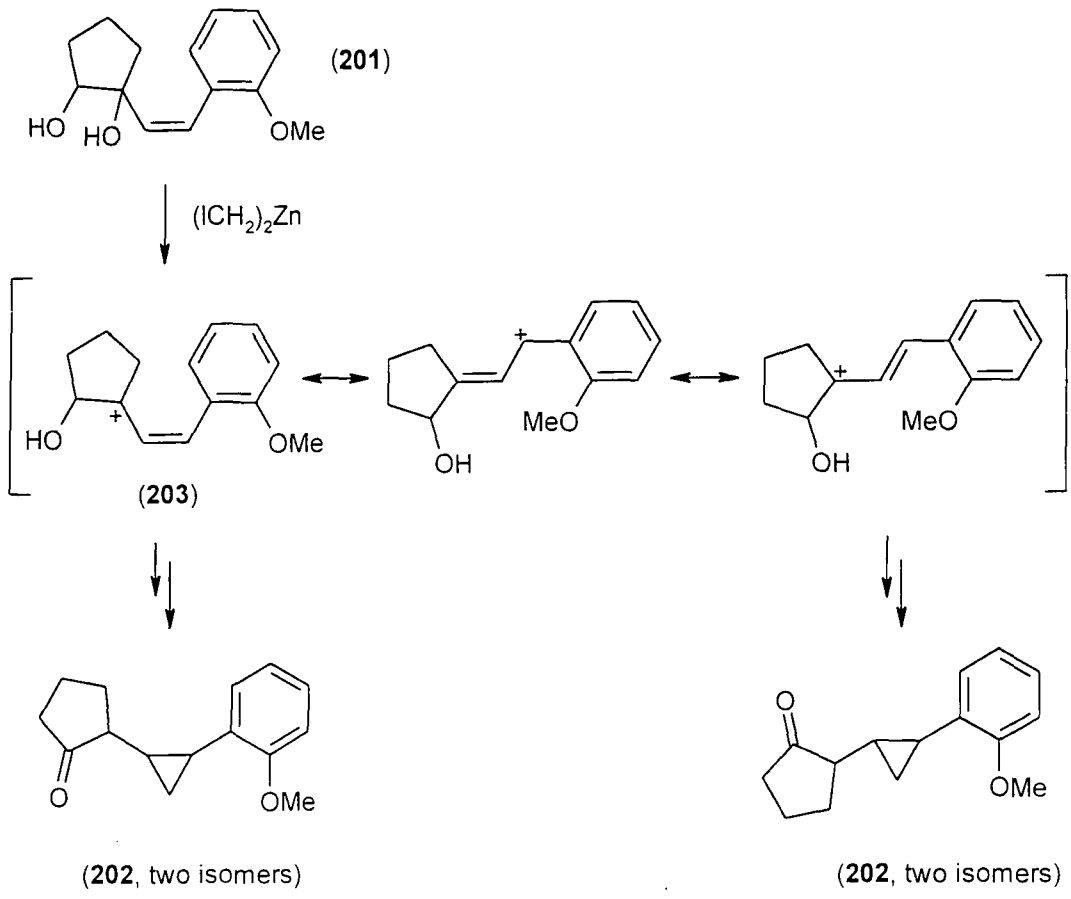
With the successful protection of the cyclopentyl double bond undertaken, the cyclopropanation of the remaining acyclic double bond of **201** was attempted using a combination of diiodomethane and diethylzinc. This reaction was carried out in toluene at 80°C and resulted in a mixture of products. FCC allowed the isolation of one component (**202**), which, on closer inspection by GC-MS, was found to compose of four isomers (1:1:1:1) all with identical fragmentation patterns including a molecular ion (*m/z* 230, 16%) and tropylium ion (*m/z* 91, 52%). The ^{1}H NMR spectrum was very complicated but an absence of signals in the vinyl region suggested that cyclopropanation had taken place. The IR spectrum also indicated the presence of a ketone (1737cm^{-1}) as did the ^{13}C NMR spectrum, which contained four peaks at δ158.0, δ158.2, δ159.0 and δ159.4. This data provides compelling evidence for the formation of the cyclic ketone, **202**, Scheme 3.5.4.



(**201**) (**202**)

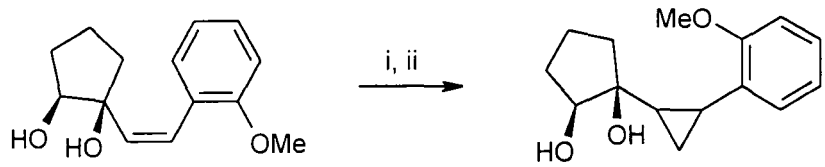
Scheme 3.5.4. Reagents and conditions: i, $ZnEt_2$, CH_2I_2, toluene, 80°C, 51%.

The formation of **202** can by viewed as the product of a zinc-alkoxide promoted pinacol rearrangement followed by cyclopropanation.[120] The generation of four isomers from this reaction can be explained by scrambling of the double bond geometry after formation of the initial cation (**203**), Scheme 3.5.5.



Scheme 3.5.5

The problem of ketone formation was overcome by reverting to the classical Simmons-Smith protocol (Zn-Cu/CH_2I_2) with ethyldiisopropylamine as an additive. The use of a base lowers the Lewis acidity of the reaction by complexing with the zinc reagent ($(I_2CH_2)_2Zn$) and associated zinc iodide,[68] thereby avoiding the possibility of an unwanted pinacol rearrangement. The optimal conditions for this reaction were found to be 20eq. of reagents at room temperature. Increasing to 40eq. did not appear to improve the yield of product and raising the temperature to 80°C resulted in the onset of the pinacol rearrangement. However, even at these optimal levels, the reaction was not efficient and complete consumption of the starting material (^{1}H NMR spectroscopy) required two reaction cycles whereby the product (**204**) was obtained, after FCC, in 40% yield (over two steps), Scheme 3.5.6.



(**201**) (**204**)

Scheme 3.5.6. Reagents and conditions: i, Zn-Cu, CH_2I_2, *i*-Pr_2NEt, monoglyme, rt; ii, as i, 40% over 2 steps.

Scrutiny by GC-MS (CI+) showed that the product (**204**) had been isolated as a 1:2 mixture of diastereoisomers as evidenced by the identical fragmentation patterns produced by the two components. The spectra contained peaks corresponding to MH^+ (*m/z* 249, 11%), MH^+-H_2O (*m/z* 231, 99%) and MH^+-$2H_2O$ (*m/z* 213, 100%). Further chromatography enabled the separation of the major isomer, the ^1H NMR of which contained 1H peaks at δ2.00 (singlet) and δ2.14 (doublet, J=6.0Hz) attributable to the hydroxyl groups and a 3H peak at δ3.90 (singlet) typical of a methoxy group. Furthermore, all fifteen carbon atoms in this compound were visible in the ^{13}C NMR spectrum and the results from elemental analysis (C, 72.28, H, 7.84%) were consistent with the calculated percentages (C, 72.17; H, 7.94%).

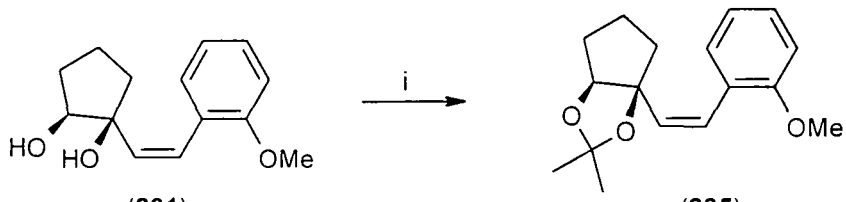
3.6 Alternative Strategies for Diol (201) Cyclopropanation

3.6.1 Introduction

Although successful preparation of the cyclopropyl diol (**204**) had been achieved, the cyclopropanation step relied on the use of the original but low yielding Simmons-Smith technique, namely a zinc-copper couple and methylene iodide combination. Attempts at cyclopropanation of **201** using diethylzinc, which has often been shown to give greater yields,[68] resulted in unwanted pinacol rearrangement products. Protection of the diol functionality of **201** was therefore sought to avoid this eventuality and thereby optimise the cyclopropanation step.

3.6.2 Preparation and Cyclopropanation of Acetonide 205

To effect protection of both hydroxyl groups, conversion to the acetonide (**205**) was chosen. Acetonides are also easily prepared and removed under mild conditions.[121] This transformation was achieved using 2,2-dimethoxypropane with TsOH as an acid catalyst, Scheme 3.6.1.

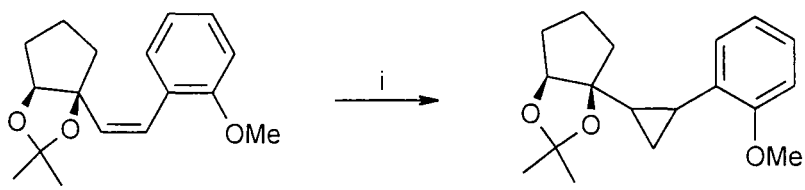


(**201**) (**205**)

Scheme 3.6.1. Reagents and conditions: i, $CH_3OC(CH_3)_2OCH_3$, TsOH, DMF, rt, 59%.

Installation of the acetonide was evidenced by the disappearance of hydroxyl stretches in the IR spectrum and the appearance of a molecular ion peak in the mass spectrum (CI-MS) at *m/z* 275 (MH^+). Elemental analysis (C, 74.19; H, 8.13%) provided unequivocal evidence for the structure as shown.

Because in previous reactions elevated temperatures tended to encourage the pinacol rearrangement, the cyclopropanation of **205** was conducted adopting a low temperature method.[122] This entailed forming the zinc reagent from chloroiodomethane and diethylzinc prior to the drop-wise addition of the acetonide at 0°C. Under these conditions, the cyclopropane (**206**) was produced as a single diastereoisomer in 40% yield, Scheme 3.6.2.



(**205**) (**206**)

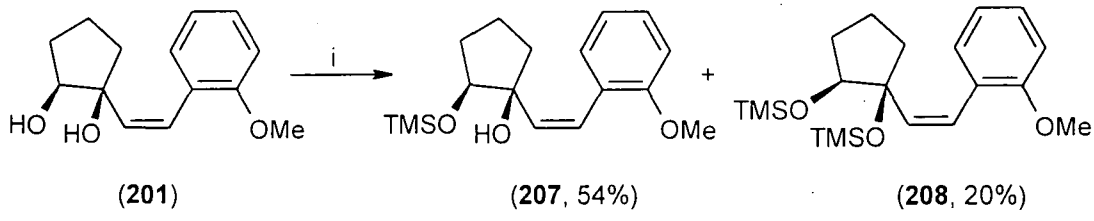
Scheme 3.6.2. Reagents and conditions: i, $ClCH_2I$, Et_2Zn, 1,2-DCE, 0°C-rt, 40%.

The ^{1}H NMR spectrum of **206** contained peaks attributable to the cyclopropane at δ0.84-1.00, δ1.06 and δ2.18, furthermore, the results from elemental analysis (C, 74.90; H, 8.46%) were concordant with the theoretical values (C, 74.97; H, 8.39%).

Although this methodology was successful in avoiding pinacol rearrangement side-products during cyclopropanation, two steps had been added to the synthetic pathway and the overall yield of the sequence (24% over two steps) was too low to give any advantage over the existing method (i.e. Scheme 3.5.6) of cyclopropane installation.

3.6.3 Preparation and Attempted Cyclopropanation of TMS and TBDMS Protected Diol

The protection of diol **201** with silyl groups was also investigated. In this case, it was desirable to mono-protect the diol at the secondary alcohol. This provides an allylic alcohol, which are recognised as excellent substrates for cyclopropanation.[68] Yet, in bids to effect TMS protection using TMS-Cl and triethylamine the production of a quantity of *bis*-TMS product (**208**) proved unavoidable. The use of TMS-OTf was also unavailing, Scheme 3.6.3.

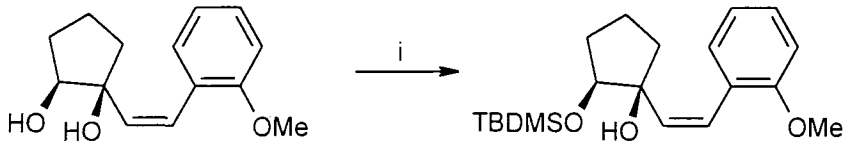


(**201**) (**207**, 54%) (**208**, 20%)

Scheme 3.6.3. Reagents and conditions: i, TMS-Cl, Et_3N, DMF, rt.

The IR spectrum of **207** contained an alcohol stretch at 3545cm^{-1} whereas the ^{1}H NMR spectrum hosted a TMS group signal at δ0.00 (9H, singlet). In contrast, no alcohol stretch was evident in the IR spectrum of **208** and two TMS peaks were visible in the ^{1}H NMR spectrum (δ0.05 and δ0.15). Both of the structures were validated by elemental analysis.

The use of the bulkier TBDMS-Cl in the presence of DMAP and triethylamine proved more successful and after some experimentation the desired allylic alcohol (**209**) was obtained in 86% yield, Scheme 3.6.4.

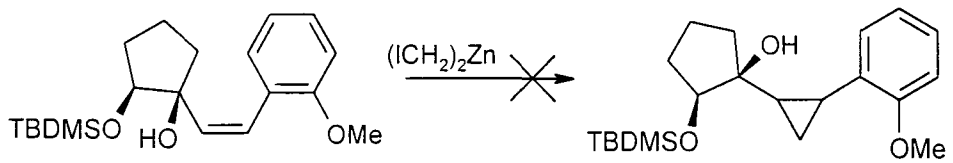


(**201**) (**209**)

Scheme 3.6.4. Reagents and conditions: i, TBDMS-Cl, DMAP, Et_3N, DMF, rt, 86%.

Two diastereomeric TMS signals indicative of a TBDMS group were evident in the ^1H NMR spectrum of **209** (δ0.08 and δ0.10) as was the *t*-butyl group (δ0.92). Furthermore, The IR spectrum contained an alcohol stretch (3545cm^{-1}) and CI-MS provided a molecular ion (*m/z* 328). Unequivocal evidence for the structure was again obtained by elemental analysis (C, 68.78; H, 9.33%. $C_{20}H_{32}O_3Si$ requires C, 68.92; H, 9.25%).

Cyclopropanation of **209** was now required. This was attempted using the previously discussed diethylzinc/chloroiodomethane method (section 3.6.2) and the zinc-copper couple/diiodomethane/diisopropylethylamine combination. In the former, multiple products were produced (tlc), none of which could be isolated, and in the latter, no noticeable reaction occurred (tlc), Scheme 3.6.5. The lack of cyclopropanation in these experiments was regrettable but may in part be attributable to the steric bulk of the TBDMS group, which interferes with the incoming carbenoid.

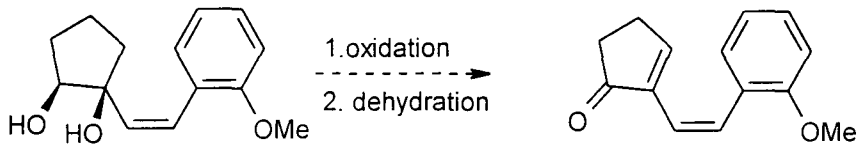


(**209**)

Scheme 3.6.5

3.6.4 Oxidation of Diol (201)

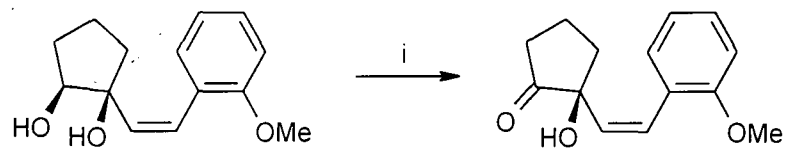
In addition to protection, removal of the diol functionality was also considered. In this, oxidation to an α-hydroxy ketone followed by dehydration would provide an enone (**210**). This has the advantage of re-introducing the required cyclopentyl ring but rendering it electron deficient and thus resistant to carbenoid attack during the impending cyclopropanation step, Scheme 3.6.6.



(**201**) (**210**)

Scheme 3.6.6

Several procedures to effect secondary alcohol oxidation were investigated including PCC/alumina, TPAP/NMO and Swern reaction. Of these methods only the Swern oxidation provided the desired product (**211**), albeit in low yield (20%). The others resulted in mixtures of unidentifiable products, Scheme 3.6.7.



(**201**) (**211**)

Scheme 3.6.7. Reagents and conditions: i, $(COCl)_2$, DMSO, **201** then NEt_3, 20%.

The above transformation was accompanied by the appearance of a carbonyl stretching band in the IR spectrum (1745cm^{-1}) and the loss of an hydroxyl signal in the ^{1}H NMR spectrum. The remaining tertiary hydroxyl group was evident as a singlet at δ2.95 (disappeared on D_2O shake). An accurate mass was also obtained (232.1100) which is identical to the theoretical value.

It was hoped that spontaneous dehydration of the tertiary alcohol of **211** would occur on work-up. This was not the case. As the yield of **211** was also very low (20%), no further work was conducted in this area.

3.7 Birch Reduction of Cyclopropyl Diol (204)

3.7.1 Introduction

Although the optimisation of the cyclopropanation step in the previous section was not successful, the necessary substrate (**204**) was at hand to explore the Birch reduction step, vital to the preparation of the required *cis*-divinylcyclopropane (Cope) substrate (see Scheme 1.6.1). The presence of diol functionality was not expected to interfere with the reduction process and can actually be viewed as an advantage as the absence of a vinyl group should ensure that aromatic reduction occurs rather than reductive cyclopropane cleavage.

3.7.2 Birch Reduction Results

The reduction of **204** (as a 2:1 mixture of diastereoisomers) was carried out under the conditions identified for similar unactivated substrates in the previously conducted model study (chapter 2.0). That is, 10eq. Li, 200ml NH_3 per 1g Li, 3eq. ethanol, 2h, -78°C. The reduction of **204** under these conditions provided, after FCC, a white waxy solid, which proved to be a 2:1 mixture (GC-MS) of diastereoisomers (reflective of the starting material). Further chromatography allowed the separation of the major isomer. Using 2D techniques (COSY, HSQC), the ^{1}H and ^{13}C NMR spectra recorded for this compound (recorded in C_6D_6 since $CDCl_3$ resulted in product degradation –see section 3.7.3) could be completely assigned and showed that the 2,5-dihydro product had been produced as opposed to the desired 1,4-dihydro product, Scheme 3.7.1.

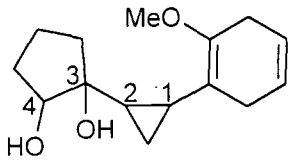
(204) (212)

Scheme 3.7.1. Reagents: i, Li, l.NH_3, EtOH, Et_2O, 50%.

In the COSY spectrum recorded for **212**, the key resonance was that of the cyclohexadiene proton (δ3.13) adjacent to the cyclopropane. This showed a coupling to the cyclopropane proton (δ0.65) and a long-range (^5J) coupling to the methylene protons of the cyclohexadiene (δ2.50-2.70), Figure 3.7.1. The HSQC spectrum showed the cyclohexadiene ring comprised 1 quaternary (δ172.6), 4 tertiary (δ53.3, δ108.3, δ139.9, δ145.9) and 1 secondary carbon atoms (δ43.4), which is correct for the structure as shown. Elemental analysis was also obtained (C, 71.73; H, 9.09%) and was consistent with the theoretical values (C, 71.97; H, 8.86%).

The regioselectivity observed in this reaction was not foreseen as both the methoxy and cyclopropyl substituents are electron-donating and were, therefore, expected to direct the residual double bonds to the 1,4 positions (see Birch rule, p27). In order to rationalise this result, molecular modelling (supplied by Merck, Sharp and Dohme) was conducted on both the 1,4 (**213**) and 2,5 (**212**) regioisomers. The results from this analysis are shown for single enantiomers in Figure 3.7.2.

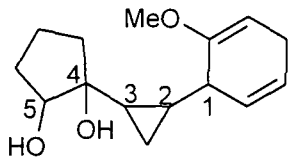
Figure 3.7.1



(**213**)

1 2 3 4 (kcal/mol)

R S S S -104.03 (0.0 relative)
S R S S -100.05 (+3.98)



(**212**)

1 2 3 4 5 (kcal/mol)

S S R R R -103.13 (+0.90)
* S R S R R -102.43 (+1.60)
* R S R R R -103.15 (+0.88)
R R S R R -101.26 (+2.77)

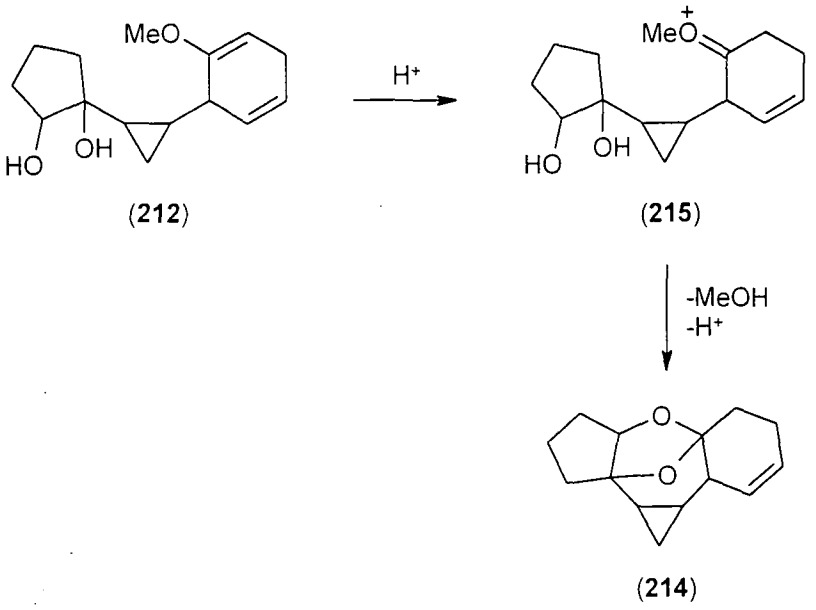
Figure 3.7.2

As can be seen from Figure 3.7.2, the lowest energy conformation for either the 1,4 (**213**) or 2,5 (**212**) regioisomers is the RSSS form of **213**. As none of this material was produced it can be assumed that the reaction is under kinetic rather than thermodynamic control. In the reaction, only two of a possible four diastereoisomers of the 2,5-regioisomer (**212**) were produced. Given that the starting material (**204**) was a 2:1 mixture of diastereoisomers with one isomer having the cyclopropane on the same face as the diol moiety and visa versa for the second isomer, this must also be the case for the two diastereoisomers of the product (**212**). The lowest energy configuration for the former, that is RSRR (or SRSS) for the cyclopropyl/cyclopentyl rings, is represented by the SRSRR enantiomer in figure 3.7.2, whilst the lowest energy configuration of the latter is represented by the RSRRR enantiomer. Consequently, these are the most likely configurations for **212**.

3.7.3 Anomalous Acetal Formation

During characterisation, it was noticed that a $CDCl_3$ solution of cyclopropane **212** underwent rapid (20min) and clean (tlc) conversion to a new compound. This transformation was accompanied by the appearance of a 3H-singlet peak at δ3.48 in the ^1H NMR spectrum attributable to methanol. After concentration, IR analysis indicated the absence of hydroxyl groups, whereas the mass spectrum contained a molecular ion peak at *m/z* 218, a loss of 32 mass units, which again suggested that methanol had been liberated. The structure was solved utilising 2D NMR techniques

(COSY, HSQC) and was found to be the acetal, **214**, Scheme 3.7.2. Conclusive evidence for **214** was obtained from elemental analysis, the results from which (C, 77.21; H, 8.19%) were consistent with the theoretical values (C, 77.03; H, 8.31%). As traces of HCl are often found in $CDCl_3$, the formation of **214** can be viewed as the product of the acid-catalysed mechanism depicted below, Scheme 3.7.2.



(**212**) (**215**) (**214**)

Scheme 3.7.2

The reaction could also be initiated by heating a C_6D_6 solution of **212** (200°C, 48h) in a Youngs-tap NMR tube or refluxing (24h) an ether solution of **212** in the presence of a Lewis acid ($ZnCl_2$, 0.1eq.).

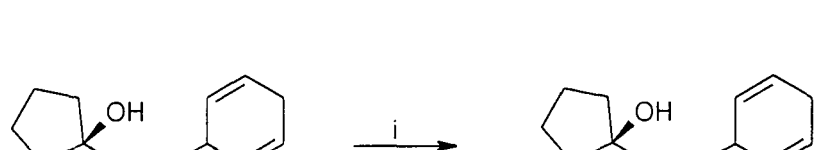
3.8 Regeneration of the Cyclopentene Ring

3.8.1 Introduction

Although the Birch reduction of **204** produced the wrong regioisomer, that is, the 2,5-dihydro derivative (**212**), for future purposes it was still desirable to re-generate the cyclopentyl ring. This was envisaged *via* dehydration of the tertiary alcohol of **212**. This firstly necessitated protection of the secondary alcohol.

3.8.2 Silyl Protection of 212

The secondary alcohol of **212** was selectively protected as the silyl ether by treatment with TBDMS-Cl, DMAP and triethylamine in DMF (see also the preparation of **209**). Under these conditions, **216** was isolated, after FCC, in 77% yield as a 2:1 mixture of diastereoisomers (reflective of the starting material). Further chromatography effected separation of the two isomers, which were characterised individually, Scheme 3.8.1.



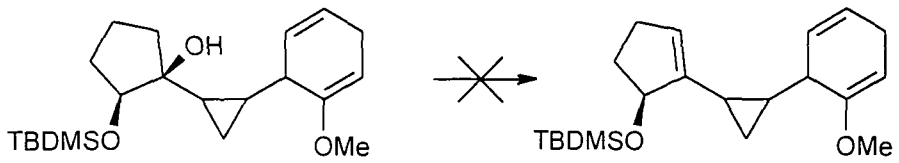
(**212**) (**216**)

Scheme 3.8.1. Reagents: i, TBDMS-Cl, DMAP, Et_3N, DMF, 77%.

The ^1H NMR and ^{13}C NMR spectra recorded for both isomers were solved using 2D NMR techniques (COSY, HSQC) and were consistent with the structure shown (*vide supra*). Concurring elemental analysis was also obtained for both isomers (major isomer: C, 69.47; H, 10.23%, minor isomer: C, 69.21; H, 10.03%). The calculated values for $C_{21}H_{36}O_3Si$ are C, 69.18; H, 9.95%.

3.8.3 Attempted Dehydration Strategies

Dehydration of **216** was attempted using a variety of methods including treatment with TsOH (in benzene), H_2SO_4 (in benzene), $POCl_3$/pyridine, $SOCl_2$/pyridine, MsCl/Et_3N. Of these, the TsOH, $SOCl_2$ and MsCl methods resulted in decomposition products, whereas treatment with H_2SO_4 and $POCl_3$ effected no reaction, Scheme 3.8.2.

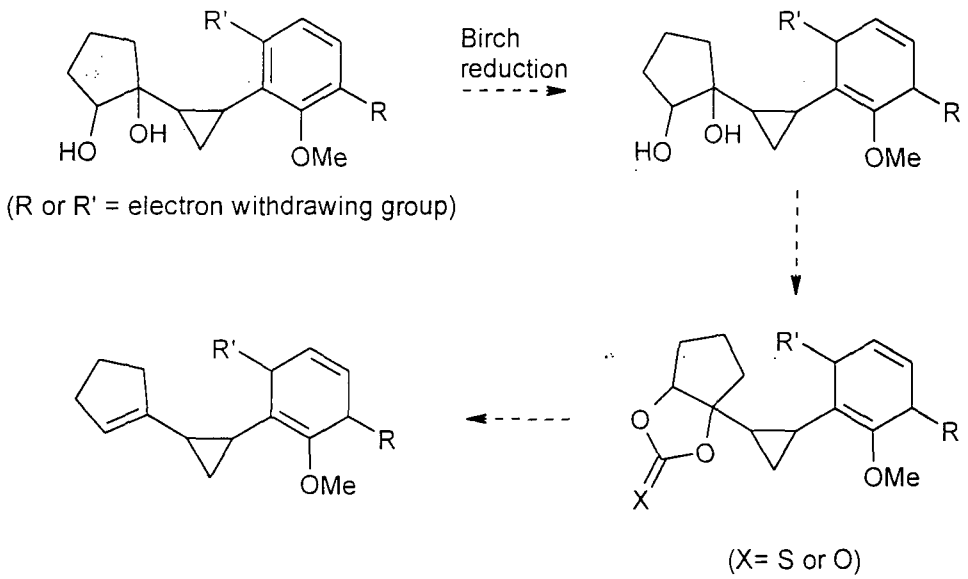


(216) (217)

Scheme 3.8.2

3.9 Conclusion

After some experimentation, a route to the required Birch reduction substrate (**204**) has been devised by way of the *cis*-diene, **185**, which was accessed by Wittig reaction between (1-cyclopentylmethyl)triphenylphosphonium bromide (**193**) and *o*-anisaldehyde. Subsequent diol protection of the cyclopentyl double bond followed by cyclopropanation, provided **204**. Unfortunately the Birch reduction step yielded the 2,5 (**212**) rather than the desired 1,4-regioisomer. Installation of an electron-withdrawing group, such as an amide, in the 3 or 6 position of the aromatic unit prior to reduction may alleviate this problem. Regeneration of the cyclopentyl ring may then be possible *via* the carbonate or thiocarbonate, Scheme 3.9.1.



Scheme 3.9.1

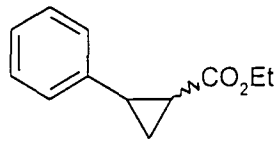
4.0 Experimental Details

4.1 Introduction

All reaction were undertaken in an inert gas atmosphere of dry nitrogen or argon in pre-dried glassware. Nuclear magnetic resonance (NMR) spectra were recorded on Varian Gemini 200 (^{1}H, at 199.975MHz, ^{13}C at 50.289MHz), Varian XL-200 (^{1}H at 200.057MHz), Varian VXR-400 (^{1}H at 399.952MHz, ^{13}C at 100.577MHz), Bruker AC250 (^{1}H at 250.133MHz, ^{13}C at 62.9MHz), Bruker AM360 (^{1}H at 360.134MHz, ^{13}C at 90.556MHz), Varian Unity 300 (^{1}H at 299.909, ^{13}C at 75.420), Varian Mercury 200 (^{1}H at 199.992, ^{13}C at 50.293) spectrometers with $CDCl_3$ (δ=7.26) as solvent (unless otherwise stated) and are recorded in ppm (δ units) downfield of tetramethylsilane (δ=0). Infrared (IR) spectra were recorded on a Perkin Elmer FT-IR 1720X spectrometer. Low resolution mass spectra were recorded on a VG Analytical 7070E machine and gas chromatography – mass spectra (GC-MS) were recorded using a Hewlett Packard 5890 series II gas chromatograph connected to a Fisons VG Trio 1000 machine. High-resolution mass spectra were recorded on a Micromass Autospec. Molecular modelling was conducted using the MOPAC AM1 programme. Flash column chromatography was performed on silica gel (60-240 mesh). Tlc was performed on Whatman silica gel 60 glass backed plates and visualised using either UV light and/or PMA, $KMNO_4$, anisaldehyde and iodine dyes. Melting points were determined using Gallenkamp melting point apparatus and are uncorrected. All solvents were distilled prior to use following standard protocols. Petroleum ethers refer to the fraction boiling between 40 and 60°C unless otherwise stated.

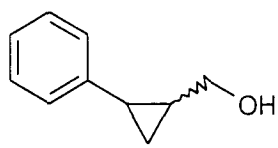
4.2 Experimental Detail

Cis/trans ethyl 2-phenylcyclopropanecarboxylate (**83**)[64]



At room temperature, with the aid of a syringe pump, ethyl diazoacetate (0.34g, 3.00mmol) was added to a stirred solution of rhodium(II) acetate dimer (7mg, 0.016mmol) in styrene (3.12g, 30mmol) over 6h. Effervescence was observed. After a further 4h, the mixture was diluted with ether and washed with sat.$NaHCO_3$ (aq.). The organic portion was separated, dried over $MgSO_4$ and evaporated to yield a yellow oil. Excess styrene was removed under high vacuum (0.1mmHg) and subsequent FCC yielded the title ester as a colourless oil (0.54g, 95%). ^1H NMR analysis indicated a 6:4 *trans:cis* ratio. Further chromatography enabled separation of the two diastereoisomers. **Analysis** (**83**, two diastereoisomers): $^{\upsilon}$max (neat): 1185, 1725cm^{-1}; δ_C (63MHz): 11.7, 14.6, 14.9, 17.7, 22.2, 24.8, 26.1, 26.8, 60.8, 61.3, 126.8, 127.1, 127.3, 128.5, 129.1, 129.9, 137.2, 141.0, 171.2, 174.2; MS (EI+): *m/z* 190 (33%, M^+), 117 (100%, M^+-CO_2Et); δ_H (200MHz) ***trans* isomer**: 1.22 (4H, m, CH_3 + cpr CH_2), 1.53 (1H, m, cpr CH_2), 1.85 (1H, m, cpr CHC=O), 2.45 (1H, m, cpr ArCH), 4.11 (2H; q, J=6.0, OCH_2), 7.15 (5H, m, Ar); δ_H (200MHz) ***cis* isomer**: 0.97 (3H, t, J=7.5, CH_3), 1.33 (1H, m, cpr CH_2), 1.72 (1H, m, cpr CH_2), 2.10 (1H, m, cpr CHC=O), 2.60 (1H, q, J=9.0, cpr ArCH), 3.89 (2H, q, J=7.5, OCH_2), 7.28 (5H, m, Ar).

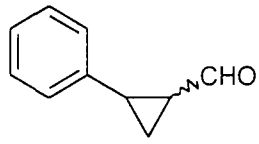
Cis/trans 2-phenyl cyclopropylcarbinol (**92**)[123]



Ester (**83**)(10g in 10ml ether, 52.63mmol) was added *via* canulla to a stirred ethereal suspension of $LiAlH_4$ (2g in 48ml ether, 52.63mmol) at 0°C. After stirring at room

temperature for 1.5h, the reaction was cooled to 0°C and quenched by dropwise addition of water (2ml) followed by NaOH (aq.)(1ml, 15%). The white ppt formed was filtered with the aid of celite and washed with ethyl acetate. Concentration of the combined washings yielded the crude product (7.81g). FCC (petrol:ethyl acetate, 7:3) provided the title alcohol as a colourless oil (6.92g, 89%). **Analysis** (**92**, two diastereoisomers, a and b): $^{\upsilon}$max (neat): 3125-3550cm^{-1}; δ_H (250MHz): 0.98-1.17 (4H (2a/2b), m, cpr CH_2), 1.52-1.66 (2H (1a/1b), m, cpr C<u>H</u>CH_2OH), 1.70 (2H (1a/1b), s, OH), 1.93 (1Ha, m, PhCH), 2.30 (1Hb, m, PhCH), 3.38 (1Hb, dd, J=8+13, C<u>H</u>$_2$OH), 3.55 (1Hb, dd, J=8+13, C<u>H</u>$_2$OH), 3.71 (2Ha, m, C<u>H</u>$_2$OH), 7.16-7.40 (10H (5a/5b), m, Ar); δ_C (63MHz): 8.5, 14.5, 21.3, 21.5, 21.9, 25.9, 63.5, 67.1, 126.3, 126.4, 126.6, 129.0, 129.5, 143.1; MS (EI+): *m/z* 148 (19%, M^+), 117 (100%, M^+-CH_2OH).

<u>*Cis/trans* 2-phenyl cyclopropylcarboxaldehyde (**93**)</u>[124]

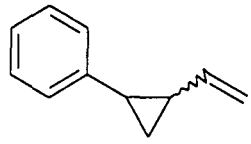


Preparation of PCC on alumina (20%w/w):
Alumina (52g) was added to an aqueous solution of PCC (13g in 120ml H_2O). After stirring at 50°C for 0.5h, water was removed *in vacuo* yielding a homogeneous, free flowing orange powder.

Alcohol (**92**)(4.46g in 20ml DCM, 30.16mmol) was added rapidly to a stirred suspension of PCC/alumina (20%w/w)(65g, 60.31mmol) in DCM (100ml). An exotherm accompanied the addition and the reaction turned brown. After stirring at room temperature for 16h, the solids were removed by filtration and washed with ether. The combined washings were concentrated to yield the crude product (4.51g). FCC (petrol:ether, 4:1) provided the title aldehyde as a colourless oil (3.36g, 76%). **Analysis** (**93**, two diastereoisomers, a and b): $^{\upsilon}$max (neat): 1703, 2732, 2835cm^{-1}; δ_H (250MHz): 1.60-1.74 (2H (1a/1b), m, cpr CH_2), 1.84 (1Ha, m, cpr CH_2), 1.98 (1Hb, m, cpr CH_2), 2.18-2.30 (2H (1a/1b), m, cpr C<u>H</u>CHO), 2.70 (1Ha, m, PhCH), 2.92

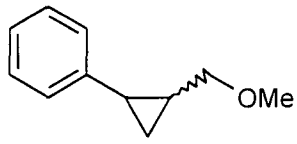
(1Hb, m, PhCH), 7.20-7.42 (10H (5a/5b), m, Ar), 8.76 (1Hb, d, J=6.5, CHO), 9.42 (1Ha, d, J=4.7, CHO); δ_C (63MHz): 12.3 (cpr), 17.2 (cpr), 24.4 (cpr), 27.1 (cpr), 30.4 (cpr), 34.5 (cpr), 127.0 (Ar), 127.5 (Ar), 127.8 (Ar), 128.6 (Ar), 129.2 (Ar), 129.9 (Ar), 136.4 (Ar), 200.3 (CHO), 202.11 (CHO); MS (EI+): *m/z* 146 (19%, M^+), 117 (100%, M^+-CHO).

Cis/trans 2-phenyl vinylcyclopropane (**84**)[125]



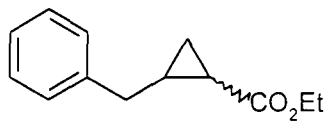
To a stirred suspension of methyl triphenylphosphonium iodide (10.96g, azeo-dried with toluene, 27.12mmol) in THF (500ml) at 0°C was added *n*-BuLi (18.65ml, 1.6M in hexanes, 29.84mmol). 2-phenyl cyclopropylcarboxaldehyde (**93**)(3.30g in 15ml THF, 22.60mmol) was subsequently added *via* canulla to the resultant solution at room temperature. After stirring for 1h, the reaction was treated with sat. NH_4Cl (aq.) and extracted with ether. The combined extracts were washed with water, dried over $MgSO_4$ and concentrated to yield the crude product (4.04g). FCC (petrol) provided 2.41g (74%) of the title compound (colourless oil) as a mixture of inseparable diastereoisomers (a:b, 1:1). **Analysis** (**84**, two diastereoisomers, a and b): υmax (neat): 697, 897, 1497, 1604, 1636cm^{-1}; δ_H (200MHz): 1.00-1.35 (4H (2a/2b), m, cpr CH_2), 1.75 (1Ha, m, cpr PhCHC<u>H</u>), 1.85-2.00 (1Ha, m, cpr PhCH) / 1Hb, m, cpr PhCHC<u>H</u>), 2.38 (1Hb, m, cpr PhCH), 4.82-5.00 (2H, m, olefinic), 5.08-5.20 (3H, m, olefinic), 5.45-5.65 (1H, m, olefinic), 7.00-7.40 (10H (5a/5b), m, Ar); δ_C (63MHz): 12.4, 17.4, 23.6, 24.0, 25.9, 28.1, 113.2, 114.7, 126.3, 126.6, 128.7, 129.0, 129.8, 138.8, 139.4, 141.3, 143.0; MS (CI+, NH_3): *m/z* 162 (22%, M+NH_4^+), 145 (100%, M+1$^+$).

Cis/trans 2-phenyl cyclopropylcarbinol methyl ether (**85**)[126]



At room temperature, rapid additions of 2-phenyl cyclopropylcarbinol (**92**)(2.3g in 10ml DMSO, 15.54mmol) followed by MeI (4.41g, 31.08mmol) were made to a stirred suspension of powdered KOH (3.48g in 20ml DMSO, 62.16mmol). After stirring for 6h, water was added and the aqueous mixture was extracted with DCM. The combined extracts were washed with water, dried over $MgSO_4$ and concentrated to yield the crude product (2.43g). FCC (petrol:ether, 9:1) provided 2.27g (90%) of the title compound (colourless oil) as an inseparable mixture of diastereoisomers (a:b, 1:2). **Analysis** (**85**, two diastereoisomers, a and b): $^{\upsilon}$max (neat): 1107cm^{-1}; δ_H (250MHz): 0.90-1.25 (4H (2a/2b), m, cpr CH_2), 1.55 (2H (1a/1b), m, cpr $C\underline{H}CH_2OCH_3$), 1.95 (1Hb, m, PhCH), 2.38 (1Ha, m, PhCH), 3.10-3.20 (2Ha, m, $C\underline{H_2}OCH_3$), 3.28 (3Hb, s, OCH_3), 3.43-3.60 (3Ha, s, OCH_3 / 2Hb, m, $C\underline{H_2}OCH_3$), 7.20-7.40 (10H (5a/5b), m, Ar); δ_C (63MHz): 8.8, 14.6, 18.5, 21.2, 22.0, 23.0, 59.0, 73.2, 76.7, 126.2, 126.5, 126.6, 128.6, 128.9, 129.9, 139.0, 143.2; MS (CI+, NH_3): *m/z* 180 (61%, M+NH_4^+), 148 (63%, M+1$^+$-CH_3), 131 (100%, M$^+$-OMe).

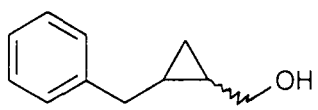
Cis/trans ethyl 2-benzyl cyclopropylcarboxylate (**86**)[127]



At room temperature, ethyl diazoactetate (0.87g in 1.2ml CH_3Cl, 7.63mmol) was added to a stirred solution of allyl benzene (0.99g, 8.39mmol) and rhodium(II) acetate dimer (18.5mg, 0.042mmol) in chloroform (2ml) over 8h. The reaction was then diluted with chloroform and catalyst was removed by washing with sat. $NaHCO_3$ (aq.). The organic portion was separated, dried over $MgSO_4$ and concentrated to yield the crude product (2.1g). FCC (petrol:ether, 9:1) provided the title ester as a clear colourless oil (0.91g, 59%). Crude ^{1}H NMR analysis revealed

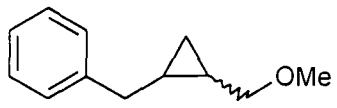
the product to be a mixture of diastereoisomers (a:b, 1:2). **Analysis** (**86**, two diastereoisomers, a and b): υmax (neat): 1724cm^{-1}; δ_H (400MHz): 0.84 (1Ha, m, cpr CH_2), 1.13 (1Hb, m, cpr CH_2), 1.20-1.36 (8H (4a/4b), m, $OCH_2C\underline{H}_3$ + cpr CH_2), 1.51 (1Ha, m, cpr $CHCO_2Et$), 1.60-1.85 (1Ha, m, cpr $C\underline{H}CH_2Ph$ / 2Hb, m, cpr $CHCO_2Et$ + cpr $C\underline{H}CH_2Ph$), 2.58 (1Ha, dd, J=7.2+14.8, $PhCH_2$), 2.76 (1Ha, dd, J=7.2+14.8, $PhCH_2$), 2.85 (1Hb, dd, J=8.0+14.0, $PhCH_2$), 2.94 (1Hb, dd, J=8.0+14.0, $PhCH_2$), 4.10-4.35 (4H (2a/2b), m, $OC\underline{H}_2CH_3$), 7.18-7.35 (10H (5a/5b), m, Ar); δ_C (100MHz): 13.6, 14.2, 14.3, 15.2, 18.5, 20.2, 22.5, 23.0, 38.4, 60.4, 60.4, 125.9, 126.20, 128.28, 128.30, 128.35, 128.37, 140.1, 151.0, 174.1; MS (EI+): *m/z* 204 (21%, M^+), 131 (60%, M^+-CO_2Et), 104 (100%, M^+-CH_2CHCO_2Et).

Cis/trans 2-benzyl cyclopropylcarbinol (**95**)[128]



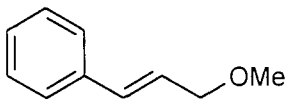
Ethyl 2-benzyl cyclopropylcarboxylate (**86**)(2g in 20ml ether, 9.80mmol) was added *via* canulla to a stirrred ethereal suspension of $LiAlH_4$ (0.37g in 80ml ether, 9.80mmol) at 0°C. After stirring at room temperature for 2h, the reaction was cooled to 0°C and quenched by dropwise additions of water (0.37ml), NaOH (aq.)(0.37ml, 15%) and water (1.11ml). The white ppt formed was filtered with the aid of celite and washed with ethyl acetate. Concentration of the combined washings yielded the crude product (1.75g). FCC (petrol:ethyl acetate, 7:3) provided the title alcohol as a colourless oil (1.32g, 83%). **Analysis** (**95**, two diastereoisomers, a and b): υmax (neat): 3100-3500cm^{-1}; δ_H (200MHz): 0.20 (1Hb, q, J=5.0, cpr $C\underline{H}CH_2OH$), 0.50 (1Ha, m, cpr $C\underline{H}CH_2OH$ / 2Hb, m, cpr CH_2), 0.80-1.25 (2Ha, m, cpr CH_2 / 1Hb, m, cpr $PhCH_2C\underline{H}$), 1.25 (1Ha, m, cpr $PhCH_2C\underline{H}$), 1.85 (2H (1a/1b), s, OH), 2.60 (2Ha, d, J=6.0, $PhCH_2$), 2.75 (2Hb, d, J=6.0, $PhCH_2$), 3.45 (2Ha, d, J=6.0, $C\underline{H}_2OH$), 3.58 (1Hb, m, $C\underline{H}_2OH$), 3.88 (1Hb, m, $C\underline{H}_2OH$), 7.15-7.40 (10H (5a/5b), m, Ar); δ_C (63MHz): 10.7, 17.4, 18.8, 19.0, 21.9, 37.9, 39.9, 63.7, 67.4, 126.6, 128.7, 128.9, 129.0, 129.1, 142.3, 142.6; MS (EI+): *m/z* 162 (1%, M^+), 91 (100%, tropylium).

2-Benzyl cyclopropylcarbinol methyl ether (**87**)



At room temperature, rapid additions of 2-benzyl cyclopropylcarbinol (**95**)(1g in 1ml DMSO, 6.17mmol) followed by MeI (1.75g, 12.34mmol) were made to a stirred suspension of powdered KOH (1.38g in 6ml DMSO, 24.68mmol). After stirring for 16h, water was added and the aqueous mixture was extracted with DCM. The combined extracts were washed with water, dried over $MgSO_4$ and concentrated to yield the crude product (0.87g). Filtration through a plug of silica (petrol:ether, 9:1) provided the title compound (0.78g, 72%) as a mixture of diastereoisomers (a:b, 1:2). **Analysis** (**87**, two diastereoisomers, a and b): HRMS (EI+): Found M^+ 176.1201, $C_{12}H_{16}O$ requires M^+ 176.1201; $^{\upsilon}$max (neat): 1106cm^{-1}; δ_H (250MHz): 0.18 (1Ha, q, J=5.3, cpr CH_2) 0.49 (2Ha, m, cpr CH_2 + cpr C<u>H</u>CH_2OCH_3 / 1Hb, m, cpr CH_2), 0.80-1.00 (1Ha, m, cpr $PhCH_2C$<u>H</u> / 2Hb, m, cpr CH_2 + cpr C<u>H</u>CH_2OCH_3), 1.17 (1Hb, m, cpr $PhCH_2C$<u>H</u>), 2.44-2.54 (2H (1a/1b), m, $PhCH_2$), 2.69 (1Hb, dd, J=6.4+14.9, $PhCH_2$), 2.82 (1Ha, dd, J=5.5+15.1, $PhCH_2$), 3.16-3.50 (10H (5a/5b), m, OCH_3 + C<u>H</u>$_2OCH_3$), 7.20-7.40 (10H (5a/5b), m, Ar); δ_C (63MHz): 10.9, 16.2, 17.4, 18.6, 18.8, 35.1, 39.9, 58.9, 59.1, 73.6, 126.6, 128.9, 142.3, 143.0; MS (CI+, NH_3): *m/z* 194 (100%, $M+NH_4^+$), 162 (52%, MH^+-CH_3).

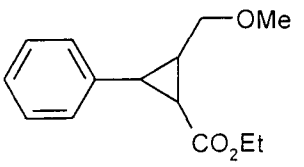
Cinnamyl methyl ether (**97**)[67]



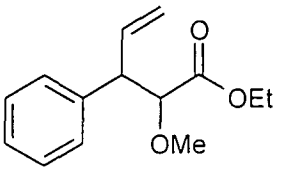
At room temperature, rapid additions of cinnamyl alcohol (10g in 20ml DMSO, 74.63mmol) followed by MeI (21.19g, 149.23mmol) were made to a stirred suspension of powdered KOH (16.72g in 50ml DMSO, 298.57mmol). After stirring for 2h, water was added and the aqueous mixture was extracted with DCM. The combined extracts were washed with water, dried over $MgSO_4$ and concentrated

yielding the crude product (10.76g). Distillation (70°C, 0.1mmHg) provided the title compound as a colourless oil (9.80g, 89%). Analysis (**97**): Bpt: 70°C (0.1mmHg); $^{\upsilon}$max (neat): 1121cm^{-1}; δ_H (250MHz): 3.51 (3H, s, OCH_3), 4.20 (2H, dd, J=1.3+6.0, $C\underline{H}_2OCH_3$), 6.38 (1H, dt, J=6.0+15.9, PhCH=C<u>H</u>), 6.73 (1H, d, J=15.9, PhC<u>H</u>=CH), 7.20-7.45 (5H, m, Ar); δ_C (63MHz): 58.6 (OCH_3), 73.7 ($\underline{C}H_2OCH_3$), 126.6 (PhCH=<u>C</u>H), 127.1 (Ar), 128.3 (Ar), 129.2 (Ar), 133.1 (Ph<u>C</u>H=CH), 137.3 (Ar); MS (EI+): *m/z* 148 (89%, M^+), 177 (100%, M^+-OCH_3).

<u>Ethyl 2-methoxymethyl-3-phenyl cyclopropanecarboxylate (**98**)[67] and ethyl 3-methoxy-3-vinyl-3-phenyl propionate (**99**)[67]</u>



(**98**)

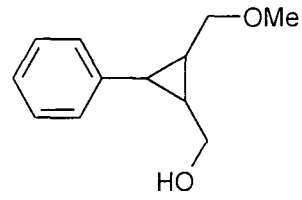


(**99**)

At room temperature, ethyl diazoactetate (6.8g, 59.65mmol) was added to cinnamyl methyl ether (**97**)(9.7g, 65.54mmol) containing rhodium(II) acetate dimer (0.13g, 0.29mmol) over 12h. The reaction was then diluted with ether and catalyst was removed by washing with sat. $NaHCO_3$ (aq). The organic portion was separated, dried over $MgSO_4$ and concentrated to yield the crude product (15.37g). Repeat FCC (of 6g) (petrol:ether, 4:1) effected purification of the two products, **99** (0.41g, 8%) and **98** (0.23g, 4%); both being obtained as colourless oils. **98** was isolated as a single diastereoisomer. **99** was isolated as a mixture of two diastereoisomers (a:b, 1:1). **Analysis** (**98**): $^{\upsilon}$max (neat): 1182, 1723cm^{-1}; δ_H (250MHz): 1.38 (3H, t, J=7.1, $OCH_2C\underline{H}_3$), 2.10 (1H, m, cpr C<u>H</u>CH_2OCH_3), 2.22 (1H, m, cpr C<u>H</u>CO_2Et), 2.69 (1H, t, J=5.8, cpr CHPh), 3.44 (3H, s, OCH_3), 3.73 (1H, dd, J=8.2+10.3, $C\underline{H}_2OCH_3$), 3.92 (1H, dd, J=5.8+10.3, $C\underline{H}_2OCH_3$), 4.28 (2H, q, J=7.1, $OC\underline{H}_2CH_3$), 7.19-7.42 (5H, m, Ar); δ_C (63MHz): 14.9 (cpr), 28.4 (cpr), 30.4 (cpr), 30.5 ($OCH_2\underline{C}H_3$), 59.1 (OCH_3), 61.4 ($\underline{C}H_2OCH_3$), 70.2 ($O\underline{C}H_2CH_3$), 127.0 (Ar), 127.3 (Ar), 129.2 (Ar), 140.0 (Ar), 172.0 ($\underline{C}O_2CH_2CH_3$); MS (EI+): *m/z* 235 (1%, $M+1^+$), 189 (17%, M^+-OEt), 115 (100%, M^+-CO_2Et/CH_2OMe). **Analysis** (**99**, two diastereoisomers, a and b): δ_H (250MHz): 1.22 (3Ha, t, J=7.1, $OCH_2C\underline{H}_3$), 1.31 (3Hb, t, J=7.1, $OCH_2C\underline{H}_3$), 3.42

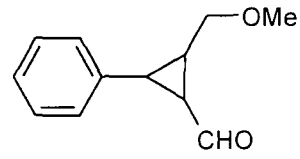
(3Hb, s, OCH_3), 3.48 (3Ha, s, OCH_3), 3.82 (2H (1a/1b), m, PhCH), 4.07-4.30 (6H (3a/3b), m, $OC\underline{H}_2CH_3$ + $C\underline{H}OCH_3$), 5.15-5.29 (4H (2a/2b), m, $CH=C\underline{H}_2$), 6.10-6.38 (2H (1a/1b), m, $C\underline{H}=CH_2$), 7.20-7.40 (10H (5a/5b), m, Ar); δ_C (63MHz): 14.8, 53.6, 53.9, 59.4, 61.5, 85.1, 117.7, 118.1, 127.7, 129.1, 137.1, 137.7, 140.4, 140.7, 172.0; MS (CI+, NH_3): *m/z* 252 (5%, $M+NH_4^+$), 235 (100%, MH^+).

2-Methoxymethyl-3-phenyl cyclopropylcarbinol (**100**)



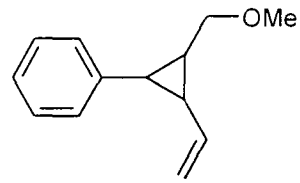
Ester (**98**)(225mg in 2ml ether, 0.96mmol) was added *via* canulla to a stirrred ethereal suspension of $LiAlH_4$ (37mg in 9ml ether, 0.96mmol) at 0°C. After stirring at room temperature for 2.5h, the reaction was cooled to 0°C and quenched by dropwise addition of water (0.04ml), NaOH (aq)(0.04ml, 15%) and water (0.12ml). The white ppt formed was filtered with the aid of celite and washed with ethyl acetate. Concentration of the combined washings yielded the crude product (150mg). FCC (petrol:ethyl acetate, 7:3) provided the title alcohol as a colourless oil (130mg, 70%). **Analysis (100)**: HRMS (EI+): Found M^+ 192.1149, $C_{12}H_{16}O_2$ requires M^+ 192.1150; $^{\upsilon}$max (neat): 3100-3600cm^{-1}; δ_H (200MHz): 1.60-1.85 (2H, m, cpr $C\underline{H}CH_2OCH_3$ + cpr $C\underline{H}CH_2OH$), 2.47 (1H, m, cpr CHPh), 3.30-3.47 (5H, m, $C\underline{H}_2OH$ + OCH_3), 3.95 (2H, m, $C\underline{H}_2OCH_3$), 7.12-7.41 (5H, m, Ar); δ_C (50MHz): 25.8 (cpr), 27.4 (cpr), 29.3 (cpr), 58.5 (OCH_3), 62.2 (CH_2OH), 72.2 ($\underline{C}H_2OCH_3$), 125.8 (Ar), 125.9 (Ar), 128.4 (Ar), 141.0 (Ar); MS (CI+, NH_3): *m/z* 210 (20%, $M+NH_4^+$), 192 (70%, M^+), 175 (100%, M^+-OH).

2-Methoxymethyl-3-phenyl-cyclopropylcarboxaldehyde (**101**)



To a stirred solution of oxalyl chloride (98mg, 0.77mmol) in DCM (1ml) at -78°C was added DMSO (120mg in 1.5ml DCM, 1.54mmol) followed, after 10min, by alcohol (**100**)(123mg in 4ml DCM, 0.64mmol). After a further 10min, the resultant white ppt was treated with triethylamine (0.31g, 3.08mmol) and the reaction was allowed to warm to room temperature. After stirring for 1h, water was added and the aqueous mixture was extracted with DCM. The organic extracts were washed with water, dried over $MgSO_4$ and concentrated to yield the crude product (114mg). FCC (petrol:ethyl acetate, 4:1) afforded 100mg (82%) of the desired aldehyde as a colourless oil. **Analysis (101)**: HRMS (EI+): Found M^+ 190.0994, $C_{12}H_{14}O_2$ requires M^+ 190.0994; $^{\upsilon}$max (neat): 1701, 2749, 2828cm^{-1}; δ_H (250MHz): 2.28 (1H, m, cpr C<u>H</u>CH_2OCH_3), 2.40 (1H, m, cpr C<u>H</u>CHO), 2.89 (1H, t, J=5.0, cpr PhCH), 3.38 (3H, s, OCH_3), 3.55-3.63 (1H, m, C<u>H</u>$_2$$OCH_3$), 3.84-3.90 (1H, m, C<u>H</u>$_2$$OCH_3$), 7.13-7.37 (5H, m, Ar), 9.71 (1H, d, J=3.9, CHO); δ_C (63MHz): 31.2 (cpr), 33.1 (cpr), 37.8 (cpr), 57.5 (OCH_3), 69.9 (<u>C</u>H_2OCH_3), 127.6 (Ar), 128.1 (Ar), 129.3 (Ar), 139.5 (Ar), 149.5 (CHO); MS (EI+): *m/z* 190 (1%, M^+), 145 (24%, M^+-CH_2OCH_3), 45 (100%, $CH_2OCH_3^+$).

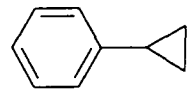
2-Methoxymethyl-3-phenyl vinylcyclopropane (**88**)



To a stirred suspension of methyl triphenylphosphonium iodide (255mg, 0.63mmol) in THF (10ml) at 0°C was added *n*-BuLi (0.44ml, 1.6M in hexanes, 0.70mmol) followed after 0.5h by aldehyde (**101**)(100mg in 4ml THF, 0.53mmol). The reaction

was then allowed to warm to room temperature and stirred for 1.75h before it was treated with sat. NH_4Cl (aq). The aqueous layer was separated and extracted with ether. The combined organic extracts were washed with water, dried over $MgSO_4$ and concentrated to yield the crude product (223mg). FCC (petrol:ether, 13:1) afforded the desired product as a colourless oil (42mg, 43%). **Analysis (88)**: HRMS (EI+): Found M^+ 188.1202, $C_{13}H_{16}O$ requires M^+ 188.1201; υmax (neat): 1603, 1633cm^{-1}; δ_H (200MHz): 1.04 (1H, m, cpr C<u>H</u>CH_2OCH_3), 1.93 (1H, m, cpr C<u>H</u>$CH{=}CH_2$), 2.11 (1H, m, cpr PhCH), 3.53 (3H, s, OCH_3), 3.62 (1H, dd, J=6.9+10.2, C<u>H_2</u>OCH_3), 3.78 (1H, dd, J=6.9+10.2, C<u>H_2</u>OCH_3), 5.21-5.42 (2H, m, $CH{=}C$<u>H_2</u>), 5.78-5.98 (1H, m, C<u>H</u>$=CH_2$), 7.22-7.45 (5H, m, Ar); δ_C (63MHz): 28.9 (cpr), 29.7 (cpr), 32.0 (cpr), 59.2 (OCH_3), 72.3 (<u>C</u>H_2OCH_3), 116.4 (olefinic), 126.5 (Ar), 126.6 (olefinic), 129.1 (Ar), 136.3 (Ar), 142.1 (Ar); MS (EI+): *m/z* 188 (7%, M^+), 143 (100%, M^+-CH_2OCH_3).

<u>Phenylcyclopropane (**81**)</u>[68]



To a stirred solution of styrene (8.32g, 80mmol) in benzene (60ml) was added diethyl zinc (150ml, 1.6M in hexanes, 240mmol). After heating to reflux, staggered additions of methylene iodide (25.8ml total, 320mmol) were made at 1ml/h (the sequence was as follows: 1st addition (10ml) – then reflux for 7hrs – 2nd addition (10ml) – reflux 14hrs - 3rd addition (5.8ml) – reflux 17hrs). The reaction was then cooled to room temperature, quenched with HCl (1.0M, 60ml) and extracted with ether. After washing with sat. $NaHCO_3$ (aq) and water, the organic portion was dried over $MgSO_4$ and concentrated to yield the crude product (28.84g). Excess styrene was removed by Spaltrohr distillation (60-70°C, 40mmHg). Distillation (22°C, 0.1mmHg) of the residue provided a pale green liquid (12.56g). ^1H NMR analysis indicated the product to be a 1.6:1 mixture of methylene iodide and phenylcyclopropane (21.7%wt penylcyclopropane, 29% yield). **Analysis (81):** υmax (neat): 1108cm^{-1}; δ_H (250MHz): 0.75 (2H, m, cpr CH_2), 1.00 (2H, m, cpr CH_2), 1.92

(1H, m, cpr CH), 7.23 (5H, m, Ar); δ_C (63MHz): -37.4 (cpr CH), 10.0 (cpr CH_2), 125.8 (Ar), 126.0 (Ar), 128.7 (Ar), 144.5 (Ar); MS (EI+): *m/z* 118 (56%, M^+).

Z-3-hydroxy-propenyl(tributyl)tin (**114**)[74]

Propargyl alcohol (0.5g, 8.93mmol) was added dropwise to a stirred solution of $LiAlH_4$ (0.17g, 4.47mmol) in THF (15ml) at 0°C. After stirring for 24h at room temperature, the reaction was cooled to -78°C and an ethereal solution of tri-*n*-butyl tin triflate (1.12g in 7ml ether, 2.55mmol) was added over 5h. The reaction was then treated with l.NH_3 (40ml) and methanol (10ml). Subsequent evaporation of ammonia/solvent followed by addition of fresh ether and filtration of the resulting ppt provided the crude product (1.45g). Partial purification was achieved by FCC (petrol:ethyl acetate, 13:1) which delivered the semi-pure title compound as a colourless oil (0.65g, ≈73%). **Analysis (114):** υmax (neat): 3100-3600cm^{-1}; δ_H (200MHz): 0.71-1.71 (27H, m, Bu_3Sn), 4.12 (2H, dt, J=1.1+5.7, CH_2OH), 6.08 (1H, dt, J=1.1+12.8, CH=C<u>H</u>SnBu$_3$), 6.70 (1H, dt, J=5.7+12.8, C<u>H</u>=CHSnBu$_3$); MS (EI+): 291 (1%, M^+-Bu), 41 (100%, C_3H_5), tin isotope patterns observed in spectrum.

2-Tributylstannanyl cyclopropylcarbinol (**115**)[74]

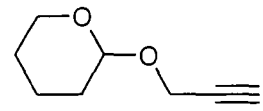
A suspension of diiodomethane (8ml, 99.31mmol) and zinc-copper couple (3.61g, 55.21mmol) in monoglyme (80ml) was heated to reflux (≈0.5h) until initiation was observed (purple colour evident). Heat was then removed and additions of N-ethyldiisopropylamine (9.62ml, 55.21mmol) followed by vinyl stannane (**114**)(1.93g, 5.52mmol) were made. After stirring for 3h at room temperature, the reaction was treated with sat. NH_4Cl (aq), filtered through a pad of celite and extracted with ether. The organic extracts were washed with water, dried over $MgSO_4$ and concentrated to yield the crude product (9.1g). Excess diiodomethane was removed by Kugelrohr

distillation (75°C, 0.1mmHg) and FCC (petrol:ethyl acetate, 19:1) of the residue provided the title cyclopropane as a colourless oil (0.9g, 45%). **Analysis (115):** $^{\upsilon}$max (neat): 3100-3500cm^{-1}; δ_H (250MHz): 0.00 (1H, m, cpr CH_2), 0.20 (1H, m, cpr CH_2), 0.75-1.61 (29H, m, $\underline{Bu_3}Sn$ + cpr $C\underline{H}CH_2C\underline{H}$), 3.24 (1H, m, $C\underline{H_2}OH$), 3.55 (1H, m, $C\underline{H_2}OH$); δ_C (100MHz): 1.5 (cpr CH_2), 7.1 (SnCH), 9.7 ($SnCH_2CH_2CH_2\underline{C}H_3$), 13.6 ($SnCH_2CH_2\underline{C}H_2CH_3$), 17.4 (cpr $\underline{C}HCH_2OH$), 27.3 ($SnCH_2\underline{C}H_2CH_2CH_3$), 29.0 ($Sn\underline{C}H_2CH_2CH_2CH_3$), 68.5 ($\underline{C}H_2OH$); MS (CI+, NH_3): *m/z* 72 (100%, MH^+-$SnBu_3$), tin isotope patterns observed in spectrum.

2-Tributylstannanyl cyclopropylcarbinol methyl ether (**116**)

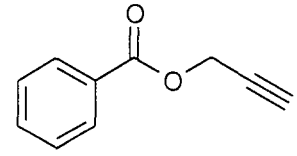
At room temperature, rapid additions of stannane cyclopropane (**115**)(0.63g in 2ml DMSO, 0.62mmol) followed by MeI (0.35g, 2.47mmol) were made to a stirred suspension of powdered KOH (0.8g in 43ml DMSO, 4.93mmol). After stirring for 16h, water was added and the aqueous mixture was extracted with DCM. The combined extracts were washed with water, dried over $MgSO_4$ and concentrated to yield the crude product (0.61g). FCC (petrol:ether, 9:1) provided the title compound as a colourless oil (0.60g, 66%). **Analysis (116)**: $^{\upsilon}$max (neat): 1107cm^{-1}; δ_H (250MHz): -0.01 (1H, m, cpr CH_2), 0.23 (1H, m, cpr CH_2), 0.60-1.70 (29H, m, $\underline{Bu_3}Sn$ + cpr $C\underline{H}CH_2C\underline{H}$), 3.08 (1H, m, $C\underline{H_2}OCH_3$), 3.29 (4H, m, $C\underline{H_2}O\underline{CH_3}$); δ_C (50MHz): -1.5 (cpr CH_2), 7.6 (cpr SnCH), 9.8 ($SnCH_2CH_2CH_2\underline{C}H_3$), 13.7 ($SnCH_2CH_2\underline{C}H_2CH_3$), 14.4 (cpr $\underline{C}HCH_2OCH_3$), 27.4 ($SnCH_2\underline{C}H_2CH_2CH_3$), 29.1 ($Sn\underline{C}H_2CH_2CH_2CH_3$), 58.3 ($OCH_3$), 77.8 ($\underline{C}H_2OCH_3$); MS (EI+): *m/z* 319 (100%, M^+-*n*-Bu), tin isotope patterns observed in spectrum.

Tetrahydro-2-(2-propynyloxy)-2H-pyran (**118**)[129]



TsOH (0.17g, 0.89mmol) was added to a solution of propargyl alcohol (5g, 89mmol) and 2,3-dihydropyran (18.75g, 223mmol) in DCM (250ml) at 0°C. After stirring at room temperature for 1h, the resultant purple solution was washed with aqueous brine / $NaHCO_3$ (200ml)(comprising 50ml sat. brine, 50ml sat. $NaHCO_3$ and 100ml water) and sat. brine, dried over $MgSO_4$ and concentrated to yield the crude product (18.86g). Distillation (22°C, 0.25mmHg) followed by FCC (petrol:ether, 9:1) provided 6.90g (55%) of the title compound as a colourless oil. **Analysis (118):** υmax (neat): 3290cm^{-1}; δ_H (400MHz): 1.44-1.91 (6H, m, C$\underline{H_2}$C$\underline{H_2}$C$\underline{H_2}$CH), 2.41 (1H, t, J=2.4, CH_2C≡C$\underline{H}$), 3.53 (1H, m, HCOC$\underline{H_2}$), 3.83 (1H, m, HCOC$\underline{H_2}$), 4.25 (2H, m, C$\underline{H_2}$C≡CH), 4.81 (1H, t, J=3.2, OC$\underline{H}$O); δ_C (100MHz): 19.0, 25.3, 30.2, 54.0 ($CH_2\underline{C}H_2O$), 62.0 ($\underline{C}H_2$C≡CH), 74.0 (CH_2C≡$\underline{C}$H), 79.7 ($CH_2\underline{C}$≡CH), 96.8 (OCHO); MS (EI+): *m/z* 140 (1%, M^+), 139 (1%, M^+-H), 55 (100%, $OCH_2C{\equiv}CH^+$).

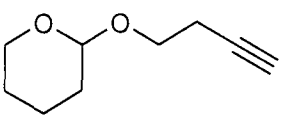
Benzoic acid prop-2-ynyl ester (**119**)



Benzoyl chloride (2.49ml, 21.43mmol) was added slowly to a solution of propargyl alcohol (1g, 17.86mmol), DMAP (0.22g, 1.79mmol) and triethylamine (3ml, 21.43mmol) in DCM (10ml) at 0°C. The reaction was then stirred at room temperature for 4h before water was added. The organic layer was separated, washed with HCl (aq)(1M) and water, dried over $MgSO_4$ and concentrated to yield the crude product (3.2g). FCC (petrol:ether, 9:1) delivered 2.11g (74%) of the desired alkyne as a colourless oil. **Analysis (119):** CHN: Found C, 74.88; H, 4.99%,

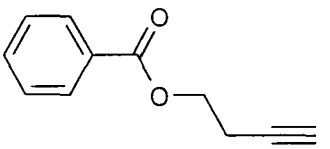
$C_{10}H_8O_2$ requires C, 74.99; H, 5.03%; υmax (neat): 1267, 1725, 3295cm^{-1}; δ_H (200MHz): 2.52 (1H, t, J=2.5, $CH_2C{\equiv}C\underline{H}$), 4.93 (2H, d, J=2.5, $C\underline{H_2}C{\equiv}CH$), 7.40-7.68 (3H, m, Ar), 8.05-8.17 (2H, m, Ar); δ_C (100MHz): 52.4 ($\underline{C}H_2C{\equiv}CH$), 75.0 ($CH_2C{\equiv}\underline{C}H$), 77.7 ($CH_2\underline{C}{\equiv}CH$), 128.4 (Ar), 129.4 (Ar), 129.8 (Ar), 133.3 (Ar), 151.0 (Ar), 165.8 (C=O); MS (EI+): *m/z* 160 (8%, M^+), 105 (100%, M^+-$OCH_2C{\equiv}CH$) 77 (64%, $C_6H_5^+$).

2-(3-Butynyloxy)tetrahydro-2H-pyran (**120**)[130]



TsOH (54mg, 0.28mmol) was added to a solution of 3-butyn-1-ol (2g, 28.54mmol) and 2,3-dihydropyran (6.5ml, 71.34mmol) in DCM (80ml) at 0°C. After stirring at room temperature for 2h, the resultant pink solution was washed with aqueous brine / $NaHCO_3$ (200ml)(comprising 50ml sat. brine, 50ml sat. $NaHCO_3$ and 100ml water) and sat. brine, dried over $MgSO_4$ and concentrated to yield the crude product (7.24g). FCC (petrol:ether, 9:1) provided 3.21g (73%) of the title compound as a colourless oil. **Analysis (120):** υmax (neat): 3293cm^{-1}; δ_H (400MHz): 1.45-1.88 (6H, m, $C\underline{H_2}C\underline{H_2}C\underline{H_2}CH$), 1.97 (1H, t, J=2.8, $CH_2C{\equiv}C\underline{H}$), 2.49 (2H, m, $C\underline{H_2}C{\equiv}CH$), 3.55 (2H, m, $HCOC\underline{H_2}$), 3.83 (2H, m, $C\underline{H_2}CH_2C{\equiv}CH$), 4.64 (1H, t, J=3.2, OCHO); δ_C (100MHz): 19.3, 19.9, 25.4, 30.5, 62.2, 65.5, 69.2, 81.4, 98.7; MS (CI+, NH_3): *m/z* 172 (27%, $M+NH_4^+$), 102 (100%, MH^+-$CH_2CH_2C{\equiv}CH$), 85 (70%, $C_5H_9O^+$).

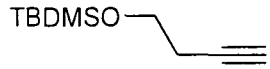
Benzoic acid but-3-ynyl ester (**121**)



Benzoyl chloride (1.84ml, 15.85mmol) was added slowly to a solution of 3-butyn-1-ol (1ml, 13.21mmol), DMAP (162mg, 1.32mmol) and triethylamine (4.4ml,

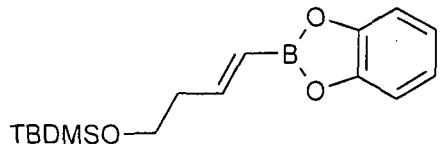
31.70mmol) in DCM (50ml) at 0°C. The reaction was then stirred at room temperature for 2h before water was added. The organic layer was separated, washed with HCl (aq)(1M) and water, dried over $MgSO_4$ and concentrated to yield the crude product (2.68g). Filtration through a pad of silica (petrol:ethyl acetate, 8:2) provided the title compound as a colourless oil (1.98g, 80%). **Analysis (121):** υmax (neat): 1274, 1716, 1789, 3298cm^{-1}; δ_H (200MHz): 2.04 (1H, t, J=3.1, C≡CH), 2.67 (2H, dt, J=3.1+6.7, $OCH_2C\underline{H_2}$), 4.43 (2H, t, J=6.7, $OC\underline{H_2}CH_2$), 7.38-7.72 (3H, m, Ar), 8.05-8.21 (2H, m, Ar); δ_C (63MHz): 19.8, 63.2, 70.7, 80.7, 129.1, 129.5, 130.3, 131.2, 133.8, 135.2, 167.0; MS (EI+): *m/z* 174 (1%, M^+), 105 (100%, M^+-$OCH_2CH_2C{\equiv}CH$), 77 (100%, $C_6H_5^+$).

Tert-butyldimethyl-but-3-ynyloxy silane (**122**)[131]



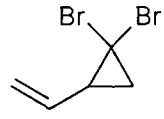
TBDMS-Cl (4.73g in 10ml DCM, 31.39mmol) was added slowly to a solution of 3-butyn-1-ol (2.0g, 28.54mmol), DMAP (0.14g, 1.14mmol) and triethylamine (4.80ml, 34.25mmol) in DCM (90ml) at 0°C. The reaction was then stirred at room temperature for 12h before water was added. The organic layer was separated, washed with HCl (aq)(1M) and water, dried over $MgSO_4$ and concentrated to yield the crude product (4.94g). FCC (petrol:ether, 9:1) provided the title compound as a colourless oil (4.19g, 80%). **Analysis (122):** υmax (neat): 1109, 3313cm^{-1}; δ_H (200MHz): 0.07 (6H, s, CH_3SiCH_3), 0.89 (9H, s, *t*-Bu), 1.96 (1H, t, J=2.7, C≡CH), 2.40 (2H, dt, J=2.7+7.1, $CH_2C\underline{H_2}C{\equiv}CH$), 3.74 (2H, t, J=7.1, $C\underline{H_2}CH_2C{\equiv}CH$); δ_C (50MHz): -5.3 (SiMe), 18.3, 22.8 (Si *t*-Bu), 25.9, 61.7, 69.6, 81.5; MS (CI+, NH_3): *m/z* 202 (100%, $M+NH_3^+$), 185 (80%, MH^+), 132 (80%, MH^+-$CH_2CH_2C{\equiv}CH$).

2-(4-*Tert*-butyldimethyloxy-but-1-enyl)-benzo[1,3,2]dioxaborolane (**123**)



Catecholborane (0.29ml, 2.72mmol) was added dropwise to substrate (**122**) (0.5g, 2.72mmol) at 0°C. The ice bath was then removed and the reaction was heated to 70°C. After 2h, the mixture (yellow) was subjected to Kugelrohr distillation (200°C, 0.1mmHg) which provided the desired title compound as an air/moisture sensitive colourless oil (0.47g, 57%). **123** was stored in the freezer under a blanket of argon prior to use. **Analysis (123):** δ_H (250MHz): 0.08 (6H, s, CH_3SiCH_3), 0.91 (9H, s, *t*-Bu), 2.51 (2H, dt, J=1.7+5.6, $CH_2C\underline{H}_2CH=CH$), 3.80 (2H, t, J=5.6, $C\underline{H}_2CH_2CH=CH$), 5.91 (1H, dt, J=1.7+16.7, C<u>H</u>=CH-B), 6.85 (1H, m, CH=C<u>H</u>-B), 6.95-7.34 (4H, m, Ar); MS (CI+, NH_3): *m/z* 322 (71%, $M+NH_4^+$), 305 (83%, MH^+), 132 (100%, $TBDMSOH^+$).

1,1-Dibromo-2-vinylcyclopropane (**125**)[86]



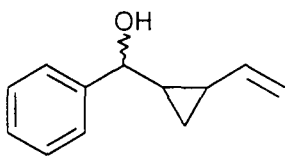
Bromoform (6.7ml, 76.72mmol) was added to a stirred suspension of 1,3-butdiene (100ml, 1151mmol) and potassium *t*-butoxide (18.94g, 169mmol) at -20°C. The addition (≈0.5h) was regulated as to ensure that the temperature did not rise above -10°C. After stirring for a further 2h, the resultant tan suspension was warmed to room temperature and excess diene was allowed to evaporate. The residue was diluted with pentane, filtered, washed rapidly with cold water and dried over Na_2SO_4. Distillation (34-38°C) followed by Kugelrohr distillation (70°C, 12mmHg) effected purification of the desired product, which was obtained as a colourless, air sensitive oil (11.4g, 66%). 1,1-dibromo-2-vinylcyclopropane (**125**) was stored in the freezer under a blanket of argon prior to use. **Analysis (125):** $^{\upsilon}$max (neat): 915, 1105,

1633cm^{-1}; δ_H (300MHz): 1.58 (1H, t, J=7.5, cpr CH_2), 1.97 (1H, m, cpr CH_2), 2.30 (1H, m, cpr C<u>H</u>CH=CH_2), 5.28-5.38 (2H, m, vinyl), 5.57 (1H, m, vinyl); δ_C (50MHz): 28.5, 30.2, 35.0, 119.5, 136.6; MS (EI+): *m/z* 226 (6%, M^+), 147 (29%, M^+-Br), 145 (29%, M^+-Br), 65 (100%, M^+-Br/HBr).

<u>1-Bromo-2-vinylcyclopropane (**126**)</u>[86]

Tri-*n*-butyltin hydride (10.2ml, 38.50mmol) was added to stirred dibromocyclopropane (**125**) (8.7g, 38.50mmol) at 35°C over 1h. After stirring for a further 12h at 33°C, the desired title cyclopropane was distilled (60°C, 68mmHg) directly from the reaction mixture and was collected as a colourless oil (1.83g, 32%). ^{1}H NMR analysis indicated the product to be a mixture of isomers (a:b, 1.5:1). **Analysis (126)** (two isomers, a and b): $^{\upsilon}$max (neat): 907, 985, 1263, 1637cm^{-1}; δ_H (300MHz): 0.92 (1Ha, m, cpr CH_2), 1.14 (1Hb, q, J=6.8, cpr CH_2), 1.26 (1Hb, m, cpr CH_2), 1.42 (1Ha, m, cpr CH_2), 1.68 (1Ha, m, cpr C<u>H</u>CH=CH_2), 1.88 (1Hb, m, cpr C<u>H</u>CH=CH_2), 2.80 (1Hb, m, cpr CHBr), 3.16 (1Ha, m, cpr CHBr), 4.98-5.30 (4H (2a/2b), m, vinyl), 5.38-5.52 (1Hb, m, vinyl), 5.57-5.70 (1Ha, m, vinyl); δ_C (50MHz): 16.4, 17.3, 20.5, 20.6, 23.0, 25.7, 114.8, 116.5, 137.3, 137.4; MS (EI+): *m/z* 148 (1%, M^+), 146 (1%, M^+), 81 (37%, Br^+), 79 (37%, Br^+), 67 (63%, M^+-Br), 39 (100%, $C_3H_3^+$), 28 (86%, $C_2H_4^+$).

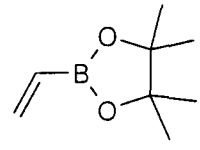
<u>Phenyl (2-vinylcyclopropyl)methanol (**127**)</u>[132]



1-Bromo-2-vinylcyclopropane (**126**) (100mg in 0.8ml of hexane/ether, 20:1, 0.68mmol) was added dropwise to *t*-BuLi (0.88ml, 1.7M in pentanes, 1.50mmol) at 0°C. After 5min, the resultant suspension was transferred *via* cannula to a flask

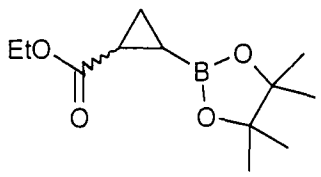
containing an ethereal solution of benzaldehyde (0.35ml in 2ml ether, 3.40mmol) at 0°C. The reaction was stirred at 0°C for 15min and room temperature for 0.5h before it was quenched with water and extracted with ether. The combined organic extracts were dried over $MgSO_4$ and concentrated to yield the crude product (375mg), which, after FCC (petrol:ethyl acetate, 5:1), provided 30mg (25%) of the title compound (colourless oil) as a mixture of diastereoisomers. Further chromatography enabled separation of the major isomer. **Analysis (127) major isomer:** $^{\upsilon}$max (neat): 3385cm^{-1}; δ_H (200MHz): 0.67 (1H, m, cpr CH_2), 1.01 (1H, m, cpr CH_2), 1.40 (1H, m, cpr C<u>H</u>CH=CH_2), 1.78 (1H, m, cpr C<u>H</u>CHOH), 4.29 (1H, d, J=11.2, C<u>H</u>OH), 5.13-5.39 (2H, m, vinyl), 5.76-5.97 (1H, m, vinyl), 7.26-7.50 (5H, m, Ar); δ_C (50MHz): 16.0, 21.0, 28.1, 66.5, 116.8, 126.5, 128.2, 129.1, 141.0; MS (EI+): *m/z* 174 (1%, M^+), 156 (58%, M^+-H_2O), 115 (87%, M^+-C_3H_5/H_2O), 91 (100%, tropylium).

<u>4,4,5,5-Tetramethyl-2-vinyl[1,3,2]dioxaborolane (**135**)</u>[92]



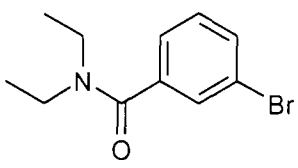
Vinyl magnesium bromide (100ml, 0.1M in THF, 100mmol) was added over 0.5h to a solution of trimethyl borate (12.62ml, 111mmol) in ether (90ml) at -78°C. The resultant white ppt was then warmed to 0°C and treated with HCl (aq) (44ml, 2.27M, 100mmol) dropwise. Additions of phenothiazine (52mg, 0.26mmol) and pinacol (13.13g, 111mmol) were subsequently made to the yellow two-phase solution at room temperature. After stirring for 12h, the aqueous layer was separated and extracted with ether. The combined organic extracts were washed with $NaHCO_3$ and dried over $MgSO_4$. Solvent was then removed by distillation at ambient temperature and Kugelrohr distillation of the residue (ambient temperature, 5mmHg) provided 7.6g (49%) of the title compound as a colourless oil. **Analysis (135):** δ_H (300MHz): 1.26 (12H, s, CH_3), 5.75-6.20 (3H, m, vinyl); δ_C (50MHz): 24.8 (CH_3), 83.3 (<u>C</u>CH_3), 137.0 (C<u>H</u>$_2$=CH); MS (EI+): *m/z* 154 (10%, M^+), 139 (68%, M^+-CH_3), 68 (100%, M^+-C_6H_{14}).

Ethyl 2-(4,4,5,5-tetramethyl[1,3,2]dioxaborolane) cyclopropanecarboxylate (**132**)



At room temperature, ethyl diazoacetate (6.4ml, 60.88mmol) was added to a solution of vinyl boronate (**135**) (7.5g, 48.70mmol) and palladium(II) acetate (1.1g, 4.90mmol) in ether (100ml) over 0.5h. When no more gas was evolved, another aliquot of palladium(II) acetate (1.1g, 4.90mmol) was added followed by additional ethyl diazoacetate (6.4ml, 60.88mmol) as previously. The reaction was then stirred for 5h, diluted with ether, filtered through a pad of celite, and concentrated to yield the crude product (16.37g). Kugelrohr distillation (110°C, 0.1mmHg) provided the title cyclopropane as a colourless oil (9.43g, 81%) which proved to be an inseparable mixture of diastereoisomers (a:b, 1:1). **Analysis** (**x**, two diastereoisomers, a and b): CHN: Found C, 59.74; H, 8.80%, $C_{12}H_{21}BO_2$ requires C, 59.54; H, 8.72%; $^{\upsilon}$max (neat): 1727cm^{-1}; δ_H (300MHz): 0.40 (1Ha, q, J=9.6, cpr CHB), 0.56 (1Hb, m, cpr CHB), 0.95-1.18 (4H (2a/2b), m, cpr CH_2), 1.23 (30H (15a/15b), m, CH_3 + $OCH_2\underline{CH_3}$), 1.70-1.90 (2H (1a/1b), m, cpr $CHCO_2Et$), 4.00-4.20 (4H (2a/2b), m, $O\underline{CH_2}CH_3$); δ_C (63MHz): 12.0, 13.7, 14.9, 18.4, 19.3, 25.4, 25.6, 61.2, 84.2, 175.0, 175.1; MS (EI+): *m/z* 240 (13%, M^+), 225 (62%, M^+-CH_3), 195 (63%,M^+-OEt) 41 (100%, $C_3H_5^+$).

3-Bromo-N,N-diethyl-benzamide (**133**)



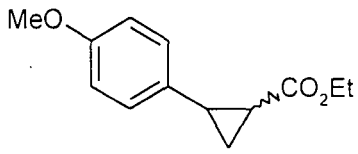
3-Bromobenzoyl chloride (50g, 228mmol) was added over 30 min to a solution of diethylamine (50g, 684mmol) in DCM (100ml) at 0°C. After stirring for 2h at 0°C and 12h at room temperature, water and additional DCM were added. The organic

layer was separated, washed with HCl (1M) and water, dried over $MgSO_4$ and concentrated yielding the title amide as an oil (57.32g, 98%). **Analysis (133):** CHN: Found C, 51.31; H, 5.22; N, 5.58%, $C_{11}H_{14}BrNO$ requires C, 51.58; H, 5.51; N, 5.47%; $^{\upsilon}$max (neat): 1633cm^{-1}; δ_H (360MHz): 1.12 (3H, broad s, $NCH_2C\underline{H}_3$), 1.24 (3H, broad s, $NCH_2C\underline{H}_3$), 3.25 (2H, broad s, NCH_2), 3.53 (2H, broad s, NCH_2), 7.20-7.60 (4H, m, Ar); δ_C (100MHz): 11.7 ($NCH_2\underline{C}H_3$), 13.1 ($NCH_2\underline{C}H_3$), 38.2 (NCH_2), 42.2 (NCH_2), 121.4 (CBr), 123.7 (Ar), 128.3 (Ar), 128.9 (Ar), 131.0 (Ar), 138.1 ($\underline{C}C=O$), 168.3 (NC=O); MS (EI+): *m/z* 257 (31%, M^+), 255 (31%, M^+), 185 (100%, M^+-NEt_2), 183 (100%, M^+-NEt_2).

Tetrakis(triphenylphosphine)palladium(0) (**139**)[94]

A mixture of palladium(II) chloride (1g, 5.67mmol) and triphenylphosphine (7.46g, 28.35mmol) in DMSO (60ml) was heated to 140°C until complete dissolution had occurred. The resultant orange solution was allowed to cool for 15min whereupon hydrazine hydrate (1.1ml, 22.68mmol) was added over 5min. After cooling to room temperature, the suspension was filtered, washed with ethanol and ether and dried under high vacuum to yield the title compound (5.82g, 89%) as a bright yellow, air sensitive solid. **139** was stored in the freezer under a blanket of argon prior to use. **Analysis (139):** Mpt: 100-102°C.

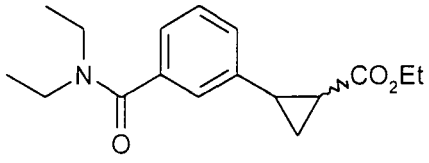
Ethyl 2-(4-methoxyphenyl)cyclopropanecarboxylate (**138**)



A solution of cyclopropylboronate ester (**132**) (100mg, 0.42mmol), 4-bromoanisole (0.047ml, 0.38mmol), tetrakis(triphenylphosphine)palladium(0) (**139**) (13mg, 0.01mmol) and pottasium phosphate (0.2g, 0.95mmol) in toluene/water (2ml, 3:1) was subjected to three cycles of freeze-thaw and purged with argon. The oxygen free reaction was heated to 100°C for 12h. The resultant dark solution was cooled and extracted with ether. The combined organic extracts were washed with water and

brine, dried over $MgSO_4$ and concentrated to yield the crude product (80mg). FCC (hexane:ether, 9:1) provided 35mg (38%) of the title compound as a mixture of diastereoisomers (1:1). Further chromatography enabled separation of one isomer, which was isolated as a white solid. **Analysis (138)**: Mpt: 82°C; CHN: Found C, 70.54; H, 7.17%, $C_{13}H_{16}O_3$ requires C, 70.89; H, 7.32%; $^{\upsilon}$max (neat): 1718cm^{-1}; δ_H (400MHz): 1.23 (1H, m, cpr CH_2), 1.29 (3H, t, J=8.0, $OCH_2C\underline{H}_3$), 1.56 (1H, m, cpr CH_2), 1.82 (1H, m, cpr $CHCO_2Et$), 2.48 (1H, m, cpr CHPh), 3.78 (3H, s, OCH_3), 4.16 (2H, q, J=8.0, $OC\underline{H}_2CH_3$), 6.81 (2H, d, J=8.7, Ar), 7.03 (2H, d, J=8.7, Ar); δ_C (100MHz): 13.2, 15.6, 22.8, 24.5, 26.6, 59.5, 64.7, 112.8, 126.3, 126.8, 131.0, 157.2, 172.5; MS (EI+): 220 (33%, M^+), 147 (100%, M^+-CO_2Et), 91 (29%, tropylium).

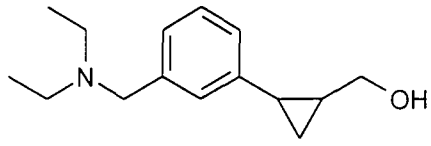
3-(2'-Ethylcyclopropylcarboxylate)-N,N diethyl benzamide (**140**)



A mixture of tetrakis(triphenylphosphine)palladium(0) (**139**) (0.95g, 0.82mmol), amide (**133**)(7g, 27.34mmol), cyclopropane (**132**)(7.22g, 30.07mmol) and potassium phosphate (14.51g, 68.35mmol) in toluene/water (150ml, 3:1) was purged with a stream of nitrogen for 10mins. The reaction was then heated to 100°C for 48h whereupon additional tetrakis(triphenylphosphine)palladium(0) (0.95g, 0.82mmol) was added. After further heating for 22h, the reaction was cooled and the aqueous layer was separated and extracted with ether. The combined organic portions were washed with water, dried over $MgSO_4$ and concentrated to yield the crude product as a tan oil (8.86g). FCC (petrol:ethyl acetate, 7:3) provided the title ester as a colourless oil (3.82g, 48%). The product was found to be a separable mixture of two diastereoisomers (1:1). **Analysis** (**140**, two diastereisomers): CHN: Found C, 69.92; H, 7.90; N, 4.89%, $C_{17}H_{23}NO_3$ requires C, 70.56; H, 8.01; N, 4.84%; $^{\upsilon}$max (neat): 1633, 1727cm^{-1}; MS (EI+): *m/z* 289 (17%, M^+), 217 (100%, M^+-NEt_2). **Analysis** (**140**, isomer one): δ_H (360MHz): 1.11-1.34 (10H, m, $C\underline{H}_3CH_2N$ (6) + cpr CH_2 + $C\underline{H}_3CH_2O$), 1.60 (1H, m, cpr CH_2), 1.91 (1H, m, cpr CHC=O), 2.53 (1H, m, cpr CHPh), 3.24 (2H, broad s, NCH_2), 3.54 (2H, broad s, NCH_2), 4.17 (2H, q, J=7.1,

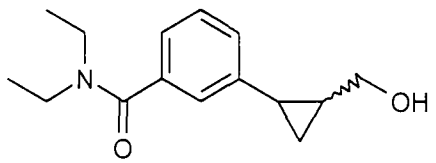
$CH_3C\underline{H}_2O$), 7.10-7.38 (4H, m, Ar); δ_C (90MHz): 12.9 ($NCH_2\underline{C}H_3$), 14.1 ($CO_2CH_2\underline{C}H_3$), 14.3 ($NCH_2\underline{C}H_3$), 16.7 (cpr), 23.00 (cpr), 25.8 (cpr), 39.1 ($N\underline{C}H_2CH_3$), 43.2 ($NCH_2\underline{C}H_3$), 60.6 ($CO_2\underline{C}H_2CH_3$), 124.01 (Ar), 124.03 (Ar), 126.9 (Ar), 128.3 (Ar), 137.4 (Ar), 140.4 (Ar), 170.9 (C=O), 173.0 (C=O). **Analysis (140,** isomer two): δ_H (360MHz): 1.00 (3H, t, J=7.1, $C\underline{H}_3CH_2O$), 1.10 (3H, broad s, $C\underline{H}_3CH_2N$), 1.23 (3H, broad s, $C\underline{H}_3CH_2N$), 1.35 (1H, m, cpr CH_2), 1.71 (1H, m, cpr CH_2), 2.10 (1H, m, cpr CHC=O), 2.57 (1H, q, J=8.6, cpr CHPh), 3.24 (2H, broad s, NCH_2), 3.53 (2H, broad s, NCH_2), 3.86 (2H, q, J=7.1, $CH_3C\underline{H}_2O$), 7.19-7.29 (4H, m, Ar).

3-(2'-Hydroxymethylcyclopropyl)-N,N diethyl benzamine (**141**)



Analysis (141): HRMS (EI+): Found M^+ 233.1776, $C_{15}H_{23}NO$ requires M^+ 233.1780; $^{\upsilon}$max (neat): 3342cm^{-1}; δ_H (360MHz): 0.88 (1H, q, J=5.6, cpr CH_2), 1.03 (7H, m, cpr CH_2 + $NCH_2C\underline{H}_3$), 1.48 (1H, m, cpr $C\underline{H}CH_2OH$), 2.28 (1H, m, cpr CHPh), 2.50 (4H, q, J=7.1, $NC\underline{H}_2CH_3$), 3.25 (1H, dd, J=8.4 + 11.7, $C\underline{H}_2OH$), 3.45 (1H, dd, J=6.3 + 11.7, $C\underline{H}_2OH$), 3.53 (2H, s, NCH_2Ph), 7.06-7.26 (4H, m, Ar); δ_C (50MHz): 7.3, 11.7, 20.7, 20.9, 46.7, 57.5, 62.9, 126.9, 127.1, 128.0, 129.4, 138.1, 139.9; MS (EI+): *m/z* 233 (13%, M^+), 143 (100%, M^+-NEt_2/H_2O).

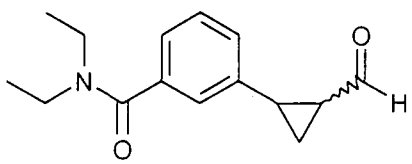
3-(2'-Hydroxymethylcyclopropyl)-N,N diethyl benzamide (**142**)



Lithium aluminium hydride (8.57ml, 1.0M in THF, 8.57mmol) was added dropwise over 0.75h to a stirred solution of ester (**140**)(3.3g, 11.42mmol) in THF (110ml) at

0°C. The reaction was maintained at 0°C for a further 1h after which time H_2O (0.33ml), NaOH (aq) (15%, 0.33ml) and further H_2O (1ml) were added sequentially. The resultant white ppt was filtered with the aid of Hyflo and washed with ethyl acetate. The combined washings were concentrated yielding the crude product as a brown oil (2.75g). FCC (ethyl acetate) provided the title alcohol as a colourless oil (1.36g, 48%). The product was found to be a separable mixture of two diastereoisomers (1:1). **Analysis** (**142**, two diastereoisomers): CHN: Found C, 72.56; H, 8.63; N, 5.41%, $C_{15}H_{21}NO_2$ requires C, 72.84; H, 8.56; N 5.66%; $^{\upsilon}$max (neat): 1614, 3410cm^{-1}; MS (EI+): *m/z* 247 (13%, M^+), 175 (100%, M^+-NEt_2). **Analysis** (**142**, isomer one): δ_H (360MHz): 0.96 (1H, m, cpr CH_2), 1.00-1.35 (7H, m, $NCH_2C\underline{H}_3$ (6) + cpr CH_2), 1.44 (1H, m, cpr $C\underline{H}CH_2OH$), 1.71 (1H, s, OH), 1.83 (1H, m, cpr CHPh), 3.25 (2H, broad s, NCH_2), 3.55 (2H, broad s, NCH_2), 3.61 (2H, d, J=4.9, $C\underline{H}_2OH$), 7.06-7.31 (4H, m, Ar); δ_C (90MHz): 12.9 ($NCH_2\underline{C}H_3$), 13.9 (cpr), 14.3 ($NCH_2\underline{C}H_3$), 21.1 (cpr), 25.5 (cpr), 39.3 ($N\underline{C}H_2CH_3$), 43.4 ($N\underline{C}H_2CH_3$), 65.5 (CH_2OH), 123.2 (Ar), 123.8 (Ar), 126.8 (Ar), 128.3 (Ar), 137.0 (Ar), 143.5 (Ar), 171.6 (C=O). **Analysis** (**142,** isomer two): δ_H (360MHz): 0.87 (1H, q, J=5.7, cpr CH_2), 1.00-1.30 (7H, m, $NCH_2C\underline{H}_3$ (6) + cpr CH_2), 1.50 (1H, m, cpr $C\underline{H}CH_2OH$), 1.73 (1H, s, OH), 2.30 (1H, dt, J=6.1 + 8.5, cpr CHPh), 3.24-3.55 (6H, m, $NC\underline{H}_2$ (4) + $C\underline{H}_2OH$), 7.06-7.33 (4H, m, Ar).

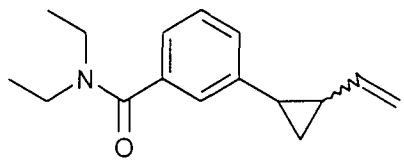
3-(2′-Cyclopropylcarboxaldehyde)-N,N diethyl benzamide (**143**)



To a stirred suspension of PCC on alumina (20%w/w) (11.35g, 10.53mmol) in DCM (30ml) at room temperature was added alcohol (**142**)(1.3g in 5ml DCM, 5.26mmol) rapidly *via* cannula. After 3h, the reaction was complete (tlc) (petrol:ethyl acetate, 1:1) and was diluted with ether, filtered and concentrated to yield the crude product as a brown oil (1.34g). FCC (hexane:ethyl acetate, 3:2) provided the title aldehyde (colourless oil) as an inseparable mixture of diastereoisomers (a:b, 1:1)(0.99g, 77%). **Analysis** (**143,** two diastereoisomers, a and b): $^{\upsilon}$max (neat): 1627, 1703cm^{-1}; δ_H

(360MHz): 1.11 (6H (3a/3b), broad s, $NCH_2C\underline{H}_3$), 1.26 (6H (3a/3b), broad s, $NCH_2C\underline{H}_3$), 1.51-1.63 (2H (1a/1b), m, cpr CH_2), 1.74 (1Ha, m, cpr CH_2), 1.89 (1Hb, m, cpr CH_2), 2.18 (2H (1a/1b), m, cpr $C\underline{H}CHO$), 2.63 (1Ha, m, cpr CHPh), 2.83 (1Hb, q, J=8.1, cpr CHPh), 3.23 (4H (2a/2b), broad s, $NC\underline{H}_2CH_3$), 3.54 (4H (2a/2b), broad s, $NC\underline{H}_2CH_3$), 7.09-7.34 (8H (4a/4b), m, Ar), 8.78 (1Hb, d, J=4.4, CHO), 9.35 (1Ha, d, J=4.4, CHO); δ_C (90MHz): 11.2 (cpr), 12.6 ($NCH_2\underline{C}H_3$), 13.9 ($NCH_2\underline{C}H_3$),15.9 (cpr), 25.7 (cpr), 26.1 (cpr), 29.4 (cpr), 33.4 (cpr), 39.0 ($N\underline{C}H_2CH_3$), 43.0 ($N\underline{C}H_2CH_3$), 123.9 (Ar), 124.1 (Ar), 124.6 (Ar), 126.7 (Ar), 126.8 (Ar), 128.2 (Ar), 128.3 (Ar), 129.7 (Ar), 135.0 (Ar), 137.0 (Ar), 137.2 (Ar), 140.5 (Ar), 170.5 (NC=O), 170.6 (NC=O), 199.0 (CHO), 200.1 (CHO); MS (EI+): *m/z* 245 (11%, M^+), 173 (100%, M^+-NEt_2).

3-(2'-Vinylcyclopropyl)-N,N diethyl benzamide (**131**)



To a suspension of methyl triphenylphosphonium iodide (2.23g, 5.51mmol) in THF (90ml) at 0°C was added *n*-BuLi (3.8ml, 1.6M in hexanes, 6.06mmol), followed, after 0.5h, by aldehyde (**143**)(0.9g in 5ml THF, 3.67mmol). The reaction was maintained at 0°C for 1h then warmed to room temperature and stirred for a further 1h before it was treated with sat. NH_4Cl (aq). The aqueous layer was separated and extracted with ether. The combined organic extracts were washed with water and brine, dried over $MgSO_4$ and concentrated to yield the crude product (1.58g). FCC (hexane:ethyl acetate, 7:3) provided 0.66g (74%) of the title compound (colourless oil) as an inseparable mixture of diastereoisomers (a:b, 1:1). **Analysis (131,** two diastereoisomers, a and b): HRMS (EI+): Found M^+ 243.1622, $C_{16}H_{21}NO$ requires M^+ 243.1623; $^{\upsilon}$max (neat): 1633cm^{-1}; δ_H (400MHz): 1.0-1.35 (16H (8a/8b), m, $NCH_2C\underline{H}_3$ + cpr CH_2), 1.70 (1Ha, m, cpr $C\underline{H}CH{=}CH_2$), 1.85-1.96 (1Ha, m, cpr CHPh / 1Hb, m, cpr $C\underline{H}CH{=}CH_2$), 2.35 (1Hb, m, cpr CHPh), 3.24 (4H (2a/2b), broad s, $NC\underline{H}_2$), 3.54 (4H (2a/2b), broad s, $NC\underline{H}_2$), 4.83-5.15 (5H, m, olefinic), 5.53 (1H, m, olefinic), 7.06-7.31 (8H (4a/4b), m, Ar); δ_C (90MHz): 11.6 (cpr), 12.8

($NCH_2\underline{C}H_3$), 14.2 ($NCH_2\underline{C}H_3$), 16.7 (cpr), 22.8 (cpr), 23.1 (cpr), 25.0 (cpr), 27.3 (cpr), 39.2 (NCH_2), 43.2 (NCH_2), 112.7, 114.3, 123.3, 123.5, 123.8, 126.5, 126.9, 128.0, 128.2, 129.9, 136.9, 137.3, 137.6, 139.0, 140.2, 142.7, 171.26 (C=O), 171.29 (C=O); MS (EI+): *m/z* 243 (17%, M^+), 171 (100%, M^+-NEt_2).

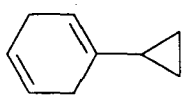
4.3. Birch Reductions

Lithium Reductions with the Absence of H^+ (Series 1 and 3 Reductions)

General procedure:

Ammonia (200ml per 1g Li) was distilled into a cooled (-78°C) 3-necked round-bottom flask equipped with a Dewar condenser (s.CO_2/acetone, fitted with a Drierite drying tube). The ammonia inlet system was then replaced with a thermometer. An ethereal solution of the substrate was subsequently added followed by sufficient ether to ensure a homogeneous solution. To this vigorously stirred solution, lithium (10eq., cut into small pieces) was added portion-wise. The resultant deep blue solution was maintained at 78°C for 2h after which time ethanol was added and the cooling bath removed. After the ammonia had evaporated (fume-cupboard!), standard aqueous work-up provided the products which were purified by FCC.

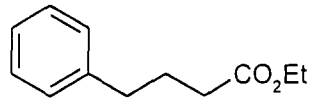
1-Cyclopropyl-1,4-cyclohexadiene (**102**)[57] from phenylcyclopropane (**81**)



The reduction of phenylcyclopropane (**81**) (1g, 8.48mmol) using lithium (0.59g, 84.75mmol), l.NH_3 (120ml) and ether (20ml) gave a crude yield of 0.53g. Partial purification was achieved by FCC (petrol). ^1H NMR analysis indicated the product (0.22g) to be a 1:2.5 (i.e. 72%wt **102**) mixture of phenylcyclopropane and 1-cyclopropyl-1,4-cyclohexadiene (**102**, 15%). **Analysis (102):** δ_H (200MHz): 0.50 (4H, m, cpr CH_2), 1.61 (1H, m, cpr CH), 2.48-2.78 (4H, m, ch CH_2), 5.45 (1H, m, ch

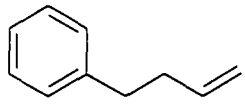
C=C<u>H</u>), 5.72 (2H, m, ch C<u>H</u>=C<u>H</u>); MS (EI+): *m/z* 120 (19%, M^+), 91 (97%, tropylium), 71 (100%, M^+-C_3H_5).

Ethyl 4-phenylbutanoate (**103**)[133] from ethyl 2-phenylcyclopropanecarboxylate (**83**)



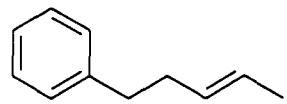
The reduction of ester (**83**) (0.80g, 4.21mmol) using lithium (0.30g, 42.10mmol), l.NH_3 (60ml) and ether (40ml) gave a crude yield of 0.65g. FCC (petrol:ether, 9:1) provided ethyl 4-phenylbutanoate (**103**) (0.21g, 26%). **Analysis (103):** $^{\upsilon}$max (neat): 1731cm^{-1}; δ_H (200MHz): 1.26 (3H, t, J=7.1, $OCH_2C\underline{H}_3$), 1.96 (2H, p, J=7.5, $PhCH_2C\underline{H}_2$), 2.33 (2H, t, J=7.5, CH_2CO_2Et), 2.66 (2H, t, J=7.5, $PhCH_2$), 4.12 (2H, q, J=7.1, $OC\underline{H}_2CH_3$), 7.10-7.14 (5H, m, Ar); δ_C (63MHz): 14.2, 26.5, 33.6, 35.1, 60.3, 125.9, 128.2, 128.4, 142.1, 170.1; MS (EI+): *m/z* 192 (15%, M^+), 104 (58%, M^+-CH_2CO_2Et), 91 (100%, tropylium).

4-Phenyl but-1-ene (**104**) from 2-phenyl cyclopropylcarbinol methyl ether (**85**)



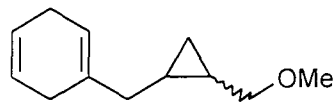
The reduction of **85** (0.50g, 3.09mmol) using lithium (0.22g, 30.90mmol), l.NH_3 (44ml) and ether (4ml) gave a crude yield of 0.21g. FCC (petrol) provided 4-phenyl but-1-ene (**104**) (90mg, 22%). **Analysis (104):** HRMS (EI+): Found M^+ 132.0941, $C_{10}H_{12}$ requires M^+ 132.0939; δ_H (250MHz): 2.53 (2H, m, $PhCH_2C\underline{H}_2$), 2.88 (2H, t, J=8.4, $PhCH_2$), 5.13-5.25 (2H, m, $CH=C\underline{H}_2$), 6.02 (1H, m, $C\underline{H}=CH_2$), 7.10-7.40 (5H, m, Ar); MS (EI+): *m/z* 132 (35%, M^+), 104 (33%, M^+-C_2H_4), 91 (100%, tropylium).

1-Phenyl pent-3-ene (**105**)[134] from 2-phenyl-vinylcyclopropane (**84**)



The reduction of **84** (0.50g, 3.47mmol) using lithium (0.24g, 34.70mmol), l.NH_3 (48ml) and ether (4ml) gave a of crude yield of 0.49g. FCC (petrol) provided 1-phenyl pent-3-ene (**105**) (0.29g, 57%). **Analysis (105)**: $^{\upsilon}$max (neat): 2854, 2931, 3026, 3063cm^{-1}; δ_H (250MHz): 1.77 (3H, m, CH_3), 2.43 (2H, m, $PhCH_2C\underline{H}_2$), 2.78 (2H, t, J=7.3, $PhCH_2$), 5.63 (2H, m, olefinic), 7.20-7.40 (5H, m, Ar); δ_C (50MHz): 17.9 (CH_3), 34.5 ($PhCH_2\underline{C}H_2$), 36.1 ($PhCH_2$), 124.3, 125.3, 125.7, 128.2, 128.4, 130.7; MS (EI+): *m/z* 146 (19%, M^+), 91 (100%, tropylium).

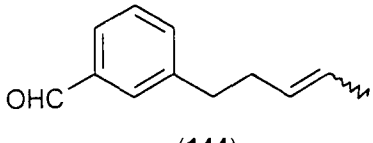
2-(Methylcyclohexa-1.4-diene)cyclopropylcarbinol methyl ether (**106**) from 2-benzyl cyclopropylcarbinol methyl ether (**87**)



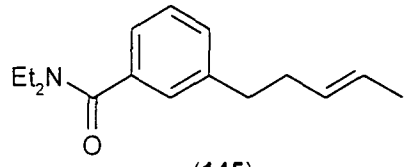
The reduction of **87** (0.5g, 2.84mmol) using lithium (0.20g, 28.40mmol), l.NH_3 (40ml) and ether (8ml) gave a crude yield of 0.49g. FCC (petrol:ethyl acetate, 9:1) provided **106** (100mg, 20%) as a mixture of diastereoisomers (a:b, 1:2.5) together with recovered starting material (**87**) (0.12g, 24%). **Analysis (106,** two diastereoisomers, a and b): HRMS (EI+): Found M^+ 178.1358, $C_{12}H_{18}O$ requires M^+ 178.1358; $^{\upsilon}$max (neat): 1106cm^{-1}; δ_H (250MHz): 0.08 (1Ha, m, cpr CH_2), 0.30-0.50 (2Ha, m, cpr CH_2 + cpr $C\underline{H}CH_2OCH_3$ / 1Hb, m, cpr CH_2), 0.60-1.25 (1Ha, m, cpr $CH{=}CCH_2C\underline{H}$ / 3Hb, m, cpr CH_2 + cpr $C\underline{H}CH_2OCH_3$ + cpr $CH{=}CCH_2C\underline{H}$), 1.75-1.90 (2H (1a/1b), m, $CH{=}CC\underline{H}_2$), 1.95 (1Hb, dd, J=8.1+18.8, $CH{=}CC\underline{H}_2$), 2.18 (1Ha, dd, J=8.1+18.8, $CH{=}CC\underline{H}_2$), 2.55-2.80 (8H (4a/4b), m, ch CH_2), 3.15-3.50 (10H (5a/5b), m, OCH_3 + $C\underline{H}_2OCH_3$), 5.48-5.60 (2H (1a/1b), m, olefinic), 5.65-5.83 (4H (2a/2b), m, olefinic); δ_C (50MHz): 10.0, 10.3, 13.8, 15.0, 15.3, 18.0, 26.7, 29.25,

29.31, 36.2, 41.3, 58.2, 58.3, 72.8, 77.6, 118.1, 118.2, 124.19, 124.23, 124.3, 134.8; MS (EI+): *m/z* 178 (1%, M^+), 91 (100%, tropylium).

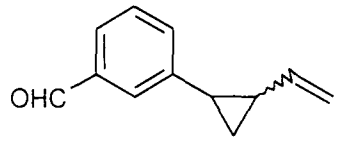
3-(Pent-2-ene)-benzaldehyde (**144**), 3-(pent-3-ene)-N,N-diethyl benzamide (**145**) and 3-(2′-vinylcyclopropyl)-benzaldehyde (**146**) from 3-(2′-vinylcyclopropyl)-N,N-diethyl benzamide (**131**)



(**144**)



(**145**)



(**146**)

The reduction of **131** (0.1g, 0.41mmol) using lithium (29mg, 4.10mmol), l.NH_3 (6.0ml) and ether (1.0ml) gave a crude yield of 76mg. FCC (hexane:ether, 20:1 gradient to hexane:ethyl acetate, 5:1) provided 3-(pent-2-ene)-benzaldehyde (**144**) (20mg, 28%), 3-(pent-3-ene)-N,N-diethyl benzamide (**145**) (8mg, 8%), 3-(2′-vinylcyclopropyl)-benzaldehyde (**146**) (29mg, 41% crude yield) and recovered starting material (**131**) (10mg, 10%). Aldehyde **146** was derivatised with 2,4 DNPH for full characterisation. ^{1}H NMR analysis indicated that (**145**) had been isolated as a single isomer and that (**144**) and (**146**) were mixtures of isomers in the ratios 2:1 (a:b), 1.2:1 (a:b) respectively.

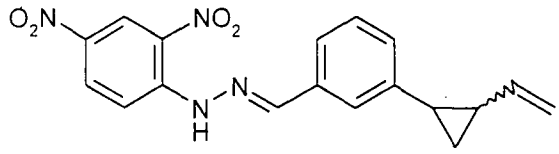
Analysis (144, two isomers, a and b): HRMS (EI+): Found M^+ 174.1045, $C_{12}H_{14}O$ requires M^+ 174.1045; $^{\upsilon}$max (neat): 1702cm^{-1}; δ_H (360MHz): 1.54 (3Ha, d, J=6.2, CH_3), 1.64 (3Hb, d, J=3.4, CH_3), 2.32 (2Ha, m, $PhCH_2C\underline{H_2}$), 2.39 (2Hb, m, $PhCH_2C\underline{H_2}$), 2.74 (4H (2a/2b), m, $PhCH_2$), 5.45 (4H (2a/2b), m, olefinic), 7.45 (4H (2a/2b), m, Ar), 7.70 (4H (2a/2b), m, Ar), 10.00 (2H (1a/1b), s, CHO). δ_C (90MHz): 12.7, 17.9, 28.5, 34.2, 35.4, 35.7, 125.1, 126.1, 127.6, 127.7, 128.9, 129.5, 129.9,

134.8, 136.6, 143.2, 192.6; MS (EI+): *m/z* 174 (47%, M^+), 119 (100%, M^+-C_4H_7), 91 (41%, tropylium), 55 (41%, $C_4H_7^+$).

Analysis (145): HRMS (EI+): Found M^+ 245.1788, $C_{16}H_{23}NO$ requires M^+ 245.1780; $^{\upsilon}$max (neat): 1632cm^{-1}; δ_H (360MHz): 1.12 (3H, broad s, $NCH_2C\underline{H}_3$), 1.24 (3H, broad s, $NCH_2C\underline{H}_3$), 1.55 (3H, d, J=6.0, CH_3), 2.36 (2H, q, J=7.4, $PhCH_2C\underline{H}_2$), 2.68 (2H, t, J=7.4, $PhCH_2$), 3.25 (2H, broad s, $NC\underline{H}_2CH_3$), 3.54 (2H, broad s, $NC\underline{H}_2CH_3$), 5.43 (2H, m, olefinic), 7.16-7.31 (5H, m, Ar); δ_C (90MHz): 12.5 (CH_3), 13.0 ($NCH_2\underline{C}H_3$), 14.4 ($NCH_2\underline{C}H_3$), 28.4 ($PhCH_2\underline{C}H_2$), 35.4 ($PhCH_2$), 39.1 (NCH_2), 43.7 (NCH_2), 123.4, 124.5, 126.1, 128.0, 129.0, 129.1, 137.0, 142.2, 171.3 (NC=O); MS (EI+): *m/z* 245 (29%, M^+), 191 (80%, M^+-C_4H_6), 173 (100%, M^+-NEt_2), 91 (28%, tropylium).

Analysis (146, two diastereoisomers, a and b): δ_H (360MHz): 1.09-1.43 (2Ha, m, cpr CH_2), 1.74 (1Hb, m, cpr $C\underline{H}CH=CH_2$), 1.92-2.03 (1Ha, m, cpr $C\underline{H}CH=CH_2$ / 1Hb, m, cpr PhCH), 2.39 (1Ha, m, cpr PhCH), 4.86-5.17 (3Ha, m, olefinic / 2Hb, m, olefinic), 5.56 (1Hb, m, olefinic), 7.34-7.71 (8H (4a/4b), m, Ar), 9.99 (1Hb, s, CHO), 10.00 (1Ha, s, CHO).

[3-(2′-Vinylcyclopropyl)-benzaldehyde]-2,′′4′′-dinitrophenylhydrazone (**147**)



A stock solution of 2,4-DNPH reagent was prepared from 2,4-DNPH (0.6g, 33% water), concentrated HCl (2ml), water (3ml) and ethanol (10ml).

Warmed 2,4-DNPH stock solution (1ml) was treated with 3-(2′-vinylcyclopropyl)-benzaldehyde (**146**) (29mg in 0.25ml EtOH, 0.17mmol). The resultant ppt was filtered and dried under high vacuum (80°C, 0.1mmHg) to yield the title compound as a red solid (20mg, 34% from **131**). **Analysis (147,** two diastereoisomers, a and b): Mpt: 124-125°C; HRMS (EI+): Found M^+ 352.1166, $C_{18}H_{16}N_4O_4$ requires M^+

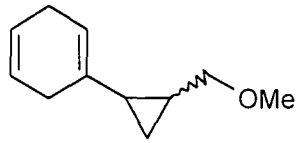
352.1172; $^{\upsilon}$max (neat): 1330, 1615, 3286cm^{-1}; δ_H (360MHz): 1.10 (1Ha, m, cpr CH_2), 1.18 (1Hb, m, cpr CH_2), 1.24-1.38 (2H, (1a/1b). m, cpr CH_2), 1.76 (1Hb, m, cpr C<u>H</u>CH=CH_2), 1.91-2.04 (1Ha, m, cpr C<u>H</u>CH=CH_2 / 1Hb, m, cpr PhCH), 2.41 (1Ha, m, cpr PhCH), 4.88-5.17 (3Ha, m, olefinic / 2Hb, m, olefinic), 5.55 (1Hb, m, olefinic), 7.14-7.60 (10H (5a/5b) m, Ar), 8.10 (4H (2a/2b) m, nitro-Ar 5+6), 8.36 (2H (1a/1b), m, NH), 9.15 (1Ha, s, N=CH), 9.16 (1Hb, m, N=CH), 11.31 (2H (1a/1b)m, nitro-Ar 3); δ_C (75MHz): 11.8, 16.9, 23.0, 23.1, 25.0, 27.6, 113.1, 114.7, 116.8, 123.5, 124.8, 125.2, 125.4, 128.2, 128.4, 128.7, 129.0, 129.4, 130.0, 131.9, 132.9, 133.1, 137.5, 138.2, 139.9, 140.1, 143.4, 144.78, 144.80, 148.0, 148.1; MS (EI+): *m/z* 352 (79%, M^+), 128 (100%, M^+-$(NO_2)_2$ArNHN=CH/CH_3), 115 (93%, M^+-$(NO_2)_2$ArNHN=CH/C_2H_4).

Lithium reductions in the presence of H^+ (Series 2 Reductions)

General procedure:

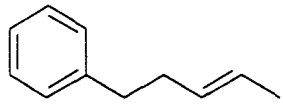
Ammonia (200ml per 1g Li) was distilled into a cooled (-78°C) 3-necked round-bottom flask equipped with a Dewar condenser (s.CO_2/acetone, fitted with a Drierite drying tube). The ammonia inlet system was then replaced with a thermometer. An ethereal solution of the substrate was subsequently added followed ethanol by sufficient ether to ensure a homogeneous solution. To this vigorously stirred solution, lithium (10eq., cut into small pieces) was added portion-wise. The resultant deep blue solution was maintained at 78°C for 2h (unless otherwise stated) after which time ethanol was added and the cooling bath removed. After the ammonia had evaporated (fume-cupboard!), standard aqueous work-up provided the products which were purified by FCC.

2-(Cyclohexa-1,4-diene)cyclopropylcarbinol methyl ether (**107**) from 2-phenyl cyclopropylcarbinol methyl ether (**85**)



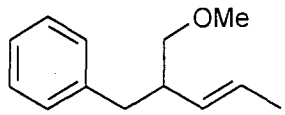
The reduction of **85** (0.50g, 3.09mmol) using lithium (0.22g, 30.90mmol), ethanol (0.54ml, 9.27mmol), l.NH_3 (44ml) and ether (4ml) gave a crude yield of 0.30g. FCC (petrol:ether, 9:1) provided **107** (0.19g, 38%) as a mixture of diastereoisomers (a:b, 1:1). **Analysis** (**107**, two diastereoisomers, a and b): HRMS (EI+): Found M^+ 164.1201, $C_{11}H_{16}O$ requires M^+ 164.1201; $^{\upsilon}$max (neat): 1108cm^{-1}; δ_H (200MHz): 0.50 (2H (1a/1b), m, cpr CH_2), 0.75 (2H (1a/1b), m, cpr CH_2), 1.19 (4H (2a/2b), m, cpr C<u>H</u>CH_2OCH_3 + cpr CH=CC<u>H</u>), 2.45-2.75 (8H (4a/4b), m, ch CH_2), 3.15-3.45 (10H (5a/5b), m, O<u>C</u>H_3 + C<u>H_2</u>OCH_3), 5.38-5.49 (2H (1a/1b), m, olefinic), 5.60-5.78 (4H (2a/2b), m, olefinic); δ_C (63MHz): 9.9, 15.0, 17.1, 18.1, 22.2, 23.3, 24.0, 27.4, 28.5, 31.4, 59.0, 72.9, 76.8, 118.3, 124.7, 125.0, 126.5, 129.0, 135.0; MS (CI+, NH_3): *m/z* 182 (11%, $M+NH_4^+$), 165 (100%, MH^+), 133 (85%, M^+-OCH_3).

1-Phenyl pent-3-ene (**105**)[134] from 2-phenyl-vinylcyclopropane (**84**)



The reduction of **84** (0.50g, 3.47mmol) using lithium (0.24g, 34.70mmol), ethanol (0.61ml, 10.41mmol), l.NH_3 (48ml) and ether (4ml) gave a crude yield of 0.50g. FCC (petrol) provided **105** (0.41g, 81%). For analysis see page 151.

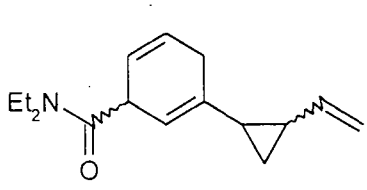
1-Phenyl-2-methoxymethyl pent-3-ene (**108**) from 2-methoxymethyl-3-phenyl vinylcyclopropane (**88**)



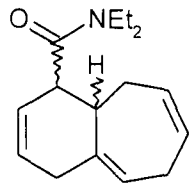
The reduction of **88** (42mg, 0.22mmol) using lithium (15mg, 2.20mmol), ethanol (0.04ml, 0.66mmol), l.NH_3 (3ml) and ether (2ml) gave a crude yield of 47mg. FCC (petrol:ether, 18:1) provided **108** (27mg, 64%). The reaction proved to be self-quenching after 45min. **Analysis (108)**: HRMS (EI+): Found M^+ 190.1359, $C_{13}H_{18}O$ requires M^+ 190.1358; $^{\upsilon}$max (neat): 1119cm^{-1}; δ_H (200MHz): 1.64 (3H, d, J=4.7, $CHC\underline{H}_3$), 2.58 (2H, m, $PhCH_2$), 2.76 (1H, m, $C\underline{H}CH_2OCH_3$), 3.20-3.45 (5H, m, OCH_3 + $C\underline{H}_2OCH_3$), 5.30-5.50 (2H ,m, olefinic), 7.10-7.38 (5H, m, Ar); δ_C (50MHz): 18.1 ($CH\underline{C}H_3$), 38.2 ($PhCH_2$), 44.3 ($\underline{C}HCH_2OCH_3$), 58.8 (OCH_3), 75.6 ($\underline{C}H_2OCH_3$), 125.7 (olefinic), 126.3 (olefinic), 128.0 (Ar), 129.3 (Ar), 132.0 (Ar), 140.2 (Ar); MS (EI+): *m/z* 190 (1%, M^+), 91 (100%, tropylium).

Potassium Reductions in the Presence of H^+ (Series 4 Reductions)

3-(2′-Vinylcyclopropyl)-N,N-diethyl-cyclohexa-2,5-dienyl-amide (**151**) and 1-N,N-diethylamide bicyclo[5.4.0]-1,4,7-decatriene (**152**) from 3-(2′-vinylcyclopropyl)-N,N-diethyl benzamide (**131**)



(**151**)

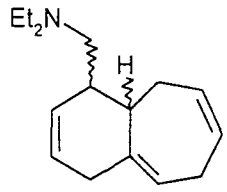


(**152**)

Amide (**131**) (0.4g in 2ml THF, 1.65mmol), *t*-BuOH (0.16ml, 1.65mmol) and THF (10ml) were added to ammonia (24ml) at -78°C. Potassium (160mg, 4.13mmol)(small pieces, washed in petrol) was then added portion-wise whereupon

the reaction turned blue. After a few minutes the colour faded to green and finally deep yellow. The resultant solution was stirred at -78°C for 2h when it was quenched with sat. NH_4Cl (aq). The cooling bath was then removed and after the ammonia had evaporated (≈4h), water was added and the solution was extracted with ether. The combined organic extracts were washed with water, dried over $MgSO_4$ and concentrated to yield the crude product (380mg). FCC (petrol:ethyl acetate, 7:3) provided the colourless oils **151** (120mg, 30%) and **152** (180mg, 45%) as inseparable 1:1 mixtures of diastereoisomers. **Analysis** (**151**, two diastereoisomers, a and b): HRMS (EI+): Found M^+ 245.1777, $C_{16}H_{23}NO$ requires M^+ 245.1780; $^{\upsilon}$max (neat): 1636cm^{-1}; δ_H (500MHz): 0.74 (2H (1a/1b), m, cpr CH_2), 1.00 (2H (1a/1b), m, cpr CH_2), 1.07-1.23 (12H (6a/6b), m, $NCH_2C\underline{H}_3$), 1.39-1.59 (4H (2a/2b), m, cpr $C\underline{H}CH=CH_2$ + cpr $C\underline{H}CHCH=CH_2$), 2.48-2.70 (4H (2a/2b), m, ch CH_2), 3.37 (8H (4a/4b), m, NCH_2), 3.95 (2H (1a/1b), m, CHC=O), 4.87 (2H (1a/1b), d, both J=13.5, olefinic), 5.05 (2H (1a/1b), m, olefinic), 5.40 (4H (2a/2b), m, olefinic), 5.65 (2H (1a/1b), m, olefinic), 5.91 (2H (1a/1b), m, olefinic); δ_C (126MHz): 12.4, 12.6, 12.9, 14.8, 22.4, 22.7, 26.9. 27.0, 27.6, 27.8, 40.4, 40.5, 41.6, 41.7, 112.1, 112.2, 116.2, 116.3, 123.1, 125.9, 136.4, 141.1, 172.0; MS (EI+): *m/z* 245 (10%, M^+), 91 (81%, tropylium), 72 (100%, NEt_2^+). **Analysis (152):** $^{\upsilon}$max (neat): 1643cm^{-1}; MS (EI+): *m/z* 245 (10%, M^+), 100 (100%, $Et_2NC=O^+$), 91 (35%, tropylium), 72 (66%, M^+-NEt_2).

1-N,N-Diethylmethylamine bicyclo[5.4.0]-1,4,7-decatriene (**153**)



Lithium aluminium hydride (0.2ml, 1.0M in THF, 0.20mmol) was added to a stirred solution of amide (**152**) (50mg, 0.20mmol) in ether (2ml) at room temperature. The reaction was then stirred for 18h whereupon H_2O (0.008ml) was added. The resultant white ppt was filtered with the aid of celite and washed with ethyl acetate. The combined washings were concentrated to yield the product as a colourless oil

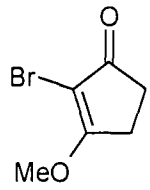
(42mg, 89%) which proved to be an inseparable mixture of two diastereoisomers (a:b, 1:1). **Analysis (153**, two diastereoisomers, a and b): HRMS (CI+, NH_3): Found MH^+ 232.2070, $C_{16}H_{26}N$ requires MH^+ 232.2065; $^{\upsilon}$max (neat): 1067, 2967, 3028cm^{-1}; δ_H (500MHz): 0.93 (12H (6a/6b), m, $NCH_2C\underline{H}_3$), 1.97-2.96 (28H (14a/14b), m, NCH_2 + allylic), 5.41-5.88 (10H (5a/5b), m, vinyl); δ_C (125MHz): 11.5, 11.7, 26.0, 26.3, 28.4, 28.8, 34.9, 36.9, 38.7, 39.4, 40.2, 40.4, 47.36, 47.43, 55.7, 57.1, 119.7, 122.1, 125.9, 126.0, 129.6, 130.17, 130.21, 131.2, 131.7, 131.9, 139.4, 141.1; MS (CI+, NH_3): *m/z* 232 (84%, MH^+), 86 (61%, $CH_2NEt_2^+$), 74 (100%, C_5N^+).

4.5 Synthetic Work Towards Ingenol

(Z)-1,2-*Bis*-tributylstannanyl-ethene (**157**)[100]

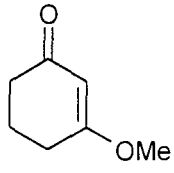
To a solution of hexa-*n*-butylditin (1.75ml, 3.48mmol) in THF (3.5ml) at -20°C was added *n*-butyl lithium (1.39ml, 2.5M in hexanes, 3.48mmol) followed after 15min by methyl lithium (2.18m, 1.6M in ether, 3.48mmol). After a further 2min, the solution was added *via* canulla to a flask containing a solution of copper(II) cyanide (312mg, 3.48mmol) in THF (3.5ml) at -20°C. The reaction was then stirred for 15min before being cooled to -78°C whereupon acetylene (passed through Dreshler bottles containing concentrated H_2SO_4 (x2) and Drierite) was blown over the surface of the solution for 0.75h. An addition of tri-*n*-butyltin chloride (0.94ml, 3.48mmol) was then made and the reaction was stirred for 0.5h at -78°C and 0.75h at 0°C before it was treated with sat.NH_4Cl (aq) and extracted with ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and concentrated to yield the product (3.4g). Both FCC and distillation techniques failed to effect purification. The product was found (^{1}H NMR spectrum) to be a 68% w/w mixture of the title Z-*bis*-stannane (**157**, 92%) and tetrabutyltin. **Analysis (157):** δ_H (200MHz): 0.75-1.71 (54H, m, $SnBu_3$), 7.34 (2H, s, vinyl); MS (EI+): *m/z* 291 (22%, $SnBu^+$), 41 (100%, $C_3H_5^+$).

2-Bromo-3-methoxycyclopent-2-enone (**159**)



A suspension of NBS (0.45g, 2.55mmol) and 1,3-cyclopentadione (0.25g, 2.55mmol) in chloroform (17ml) was refluxed for 2h. After cooling and removal of chloroform *in vacuo*, additions of TsOH (25mg, 0.13mmol) and methanol (17ml) were made and the resultant solution was refluxed for 12h. The reaction was then poured into water and extracted with DCM. The combined extracts were dried over $MgSO_4$ and concentrated yielding the crude solids (0.36g). Recrystallisation (ether:ethyl acetate, 4:1) afforded the title compound as white crystals (0.18g, 40%). **Analysis (159):** Mpt: 118-119°C; HRMS (EI+): Found M^+ 189.9629, $C_6H_7BrO_2$ requires M^+ 189.9630; υmax (KBr): 1688cm^{-1}; δ_H (200MHz): 2.60 (2H, m, $C\underline{H}_2COCH_3$), 2.78 (2H, m, $C\underline{H}_2C{=}O$), 4.08 (3H, s, $OC\underline{H}_3$); δ_C (63MHz): 25.2 ($\underline{C}H_2OCH_3$), 31.8 ($\underline{C}H_2C{=}O$), 57.0 (OCH_3), 97.0 ($C{=}\underline{C}OCH_3$), 183.9 ($C{=}\underline{C}Br$), 196.9 (C=O); MS (EI+): *m/z* 190 (100%, M^+), 192 (100%, M^+).

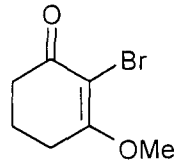
3-Methoxy cyclohex-2-enone (**167**)[105]



Using Dean and Stark apparatus, a solution of 1,3-cyclohexadione (**166**)(2g, 17.84mmol), methanol (10ml, 247mmol) and TsOH (85mg, 0.45mmol) in benzene (35ml) was refluxed until 20ml of solvent had been removed (≈12h). After cooling, the residue was diluted with benzene, washed with NaOH (aq)(3M saturated with NaCl) and water, dried over $MgSO_4$ and concentrated to yield the crude product (1.97g). Kugelrohr distillation (0.05mmHg, 65°C) provided 1.86g (83%) of the desired enone as a colourless oil. **Analysis (167):** υmax (neat): 1379, 1605, 1646,

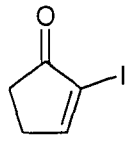
1665cm^{-1}; δ_H (250MHz): 1.95 (2H, m, C<u>H</u>$_2$CH$_2$C=O), 2.32 (2H, t, J=6.5, CH$_2$COCH$_3$), 2.38 (2H, t, J=6.3, C<u>H</u>$_2$C=O), 3.66 (3H, s, OCH$_3$), 5.34 (1H, s, C=CH); δ_C (50MHz): 21.2 (<u>C</u>H$_2$CH$_2$C=O), 28.8 (<u>C</u>H$_2$COCH$_3$), 36.7 (<u>C</u>H$_2$C=O), 55.5 (OCH$_3$), 102.3 (C=<u>C</u>H), 178.6 (CH=<u>C</u>OCH$_3$), 199.6 (C=O); MS (EI+): *m/z* 126 (40%, M$^+$), 98 (37%, M$^+$-CO), 68 (100%, M$^+$-C$_3$H$_6$O).

<u>2-Bromo-3-methoxy-2-cyclohexen-1-one (**161**)</u>



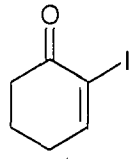
NBS (0.71g, 3.97mmol) was added to a solution of 3-methoxy cyclohex-2-enone (**167**) (0.5g, 3.97mmol) in 1,2 DCE (5ml) at 0°C over 2h. After stirring for a further 12h at room temperature, the reaction was filtered and concentrated. The residue was diluted with toluene (10ml), washed with water and dried over $MgSO_4$. The solution was then concentrated at ambient temperature to 1/5 volume, cooled in the freezer (24h) and filtered. The white crystalline solid obtained was dried under vacuum to yield the desired product (90mg, 11%). **Analysis (161):** Mpt: 92-93°C; HRMS (EI+): Found M$^+$ 203.9786, $C_7H_9BrO_2$ requires M$^+$ 203.9786; $^{\upsilon}$max (KBr): 1323, 1595, 1655cm^{-1}; δ_H (250MHz): 2.08 (2H, m, C<u>H</u>$_2$CH$_2$C=O), 2.55 (2H, t, J=6.0, C<u>H</u>$_2$COCH$_3$), 2.70 (2H, t, J=6.0, C<u>H</u>$_2$C=O), 3.95 (3H, s, OCH$_3$); δ_C (100MHz): 20.4 (<u>C</u>H$_2$CH$_2$C=O), 26.7 (<u>C</u>H$_2$COCH$_3$), 36.6 (<u>C</u>H$_2$C=O), 56.4 (OCH$_3$), 102.9 (C=<u>C</u>Br), 173.0 (CH=<u>C</u>OCH$_3$), 191.0 (C=O); MS (EI+): *m/z* 206 (20%, M$^+$), 204 (20%, M$^+$), 164 (94%, M$^+$-CH$_2$C=O), 162 (95%, M$^+$-CH$_2$C=O), 55 (100%, C$_3$H$_3$O$^+$), 42 (100%, CH$_2$C=O$^+$).

2-Iodo-2-cyclopenten-1-one (**176**)



Iodine (3.09g in 20ml pyridine/DCM (1:1), 12.18mmol) was added to a solution of 2-cyclopenten-1-one (**178**) (0.5g, 6.09mmol) in pyridine/DCM (20ml, 1:1) at 0°C over 1h. After stirring for a further 12h at room temperature, the reaction was washed with water, HCl (aq)(1M), further water, sat. NaS_2O_3, dried over $MgSO_4$ and concentrated to yield the crude product as a tan solid (0.92g). FCC (petrol:ether, 6:1) delivered the desired α-iodoenone as white crystals (0.54g, 43%). **Analysis (176):** Mpt: 71°C; CHN: Found C, 28.76; H, 2.15%, C_5H_5IO requires C, 28.87; H, 2.42%; $^{\upsilon}$max (KBr): 1660, 1752cm^{-1}; δ_H (300MHz): 2.48 (2H, m, cpn CH_2), 2.76 (2H, m, cpn CH_2), 8.00 (1H, t, J=3.0, CH=CI); δ_C (75MHz): 31.2, 31.5, 103.1 (CH=CI), 169.9 (CH=CI), 204.3 (C=O); MS (EI+): *m/z* 208 (71%, M^+), 127 (34%, I^+), 53 (100%, $C_4H_5^+$).

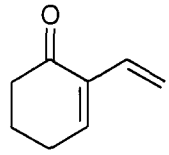
2-Iodo-2-cyclohexen-1-one (**177**)[107]



Iodine (2.65g in 20ml pyridine/DCM (1:1), 10.42mmol) was added to a solution of 2-cyclohexen-1-one (**179**) (0.5g, 5.21mmol) in pyridine/DCM (20ml, 1:1) at 0°C over 0.5h. After stirring for a further 2h at room temperature, the reaction was washed with water, HCl (aq)(1M), further water, sat. NaS_2O_3, dried over $MgSO_4$ and concentrated to yield the crude product as a tan solid (1.12g). FCC (petrol:ether, 4:1) delivered the desired α-iodoenone as white crystals (0.66g, 57%). **Analysis (177):** Mpt: 47-49°C; $^{\upsilon}$max (golden gate): 1672cm^{-1}; δ_H (300MHz): 2.09 (2H, m, ch CH_2), 2.43 (2H, m, ch CH_2), 2.67 (2H, t, J=6.6, ch CH_2), 7.77 (1H, t, J=4.2, CH=CI); δ_C

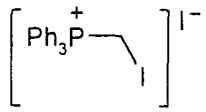
(75MHz): 23.5, 30.6, 37.9, 104.5 (CH=CI), 160.1 (CH=CI), 192.8 (C=O); MS (EI+): *m/z* 222 (100%, M^+), 194 (79%, M^+-CO), 95 (35%, M^+-I).

2-Vinyl-cyclohex-2-enone (**181**)[106]



To a solution of α-iodoenone (**177**) (172mg, 0.78mmol), bis(benzonitrile)palladium(II) chloride (15mg, 0.04mmol), copper(I) iodide (15mg, 0.08mmol) and triphenylarsine (24mg, 0.08mmol) in N-methyl pyrrolidinone (6ml) at room temperature was added tri-*n*-butylvinyl stannane (0.23ml, 0.78mmol). After stirring for 12h, the reaction was diluted with ether and stirred vigorously with KF (aq) (1.0M) for 0.5h. The ether layer was then separated, filtered, washed with water, dried over $MgSO_4$ and concentrated (ambient temperature) to yield the crude product (0.38g). FCC (petrol:ether, 5:1) delivered 18mg (19%) of the title compound as an thermally unstable colourless oil. **Analysis (181):** δ_H (300MHz): 2.00 (2H, m, CH_2CH_2C=O), 2.44 (4H, m, CH_2C=O + CH_2CH=C), 5.18 (1H, d, J=12.0, CH=CH_2), 5.67 (1H, d, J=18.0, CH=CH_2), 6.55 (1H, dd, J=12.0 + 18.0, CH=CH_2), 7.03 (1H, t, J=4.8, CH_2CH=C).

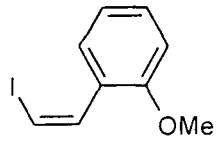
Iodomethyltriphenylphosphonium iodide (**186**)



A mixture of triphenylphosphine (30g, 114mmol) and diiodomethane (12ml, 148mmol) in benzene (30ml) was heated to reflux for 18h. The resultant precipitate was filtered, washed with benzene and dried under vacuum to yield the pure product as a white solid (33g, 54%). **Analysis (186):** Mpt: 229-230°C (turns yellow at

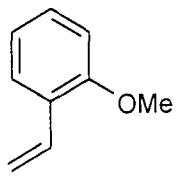
200°C); CHN: Found C, 43.09; H, 3.19%, $C_{19}H_{17}I_2P$ requires C, 43.05; H, 3.23%; $^{\upsilon}$max (neat): 507, 1438, 2849, 2918, 3042cm^{-1}.

1-(2'-Iodo-vinyl)-2-methoxy-benzene (**182**)

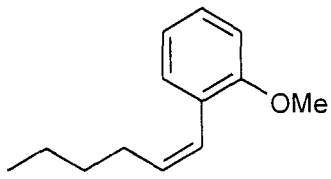


Potassium hexamethyldisilazide (20.7ml, 1M in THF, 20.70mmol) was added to a suspension of Wittig salt (**186**)(10.97g, 20.70mmol) in THF (50ml) at room temperature. After stirring for 0.5h, the temperature was firstly reduced to –60°C whereupon HMPA (6.34ml, 36.43mmol) was added and then to –78°C, when *o*-anisaldehyde (2ml, 16.56mmol) was added. The reaction was maintained for 1h at –78°C then allowed to warm to room temperature before water and ether were added. The organic layer was separated and washed with water, dried over $MgSO_4$ and concentrated to yield the crude product as a tan semi-solid (8.2g). Gross quantities of triphenylphosphine oxide were removed by trituation of an ether solution followed by filtration. The filtrate was concentrated and subjected to Kugelrohr distillation (150°C, 0.1mmHg) which provided the desired product as a yellow oil (3.16g, 73%). **Analysis (182):** CHN: Found C, 40.30; H, 3.21%, C_9H_9IO requires C, 41.56; H, 3.49%; $^{\upsilon}$max (neat): 751, 2834, 3061cm^{-1}; δ_H (400MHz): 3.81 (3H, s, OCH_3), 6.56 (1H, d, J=8.5, CH=C<u>H</u>I), 6.88 (1H, d, J=8.8, Ar), 6.97 (1H, m, Ar), 7.31 (1H, m, Ar), 7.39 (1H, d, J=8.8, Ar), 7.73 (1H, d, J=8.5, C<u>H</u>=CHI); δ_C (100MHz): 57.55 (OCH_3), 82.92 (CH=<u>C</u>HI), 112.62, 121.99, 122.76, 130.97, 131.51, 137.08, 158.85; MS (EI+): *m/z* 260 (45%, M^+), 133 (96%, M^+-I), 118 (75%, M^+-I/CH_3, 105 (100%, M^+-CHI/CH_3).

1-Ethenyl-2-methoxy-benzene (**187**)[135] and Z-1-(2'-methoxyphenyl)-hex-1-ene (**188**)[136]



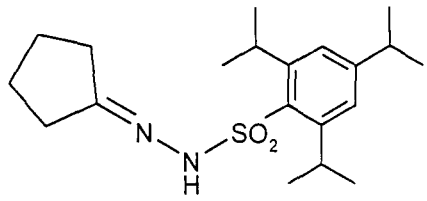
(**187**)



(**188**)

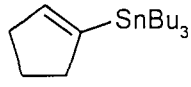
n-BuLi (2.9ml, 1.6M in hexanes, 4.64mmol) was added to a solution of vinyl iodide (**182**)(1g, 3.85mmol) in THF (30ml) at -78°C over 5min. After stirring at -78°C for 0.5h and room temperature for 15min, the resultant yellow solution was re-cooled to -78°C and cyclopentanone (0.34ml, 3.85mmol) was added dropwise. The reaction was then allowed to warm to room temperature, and after 1.5h, quenched with sat. NH_4Cl (aq) and extracted with ether. The combined extracts were washed with water and brine, dried over $MgSO_4$ and concentrated to yield the crude product (795mg). FCC (petrol:ethyl acetate, 4:1) followed by Kugelrohr distillation (145/175°C, 0.1mmHg) effected purification of the 2 major components, **187** (70mg, 14%) and **188** (180mg, 26%). **Analysis (187):** δ_H (300MHz): 3.85 (3H, s, OCH_3), 5.27 (1H, dd, J=1.5 + 11.1, CH=C$\underline{H}_2$), 5.74 (1H, dd, J=1.5 + 17.7, CH=C$\underline{H}_2$), 6.80-7.00 (2H, m, Ar), 7.06 (1H, dd, J=11.1 + 17.7, C$\underline{H}$=CH_2), 7.20-7.30 (1H, m, Ar), 7.48 (1H, m, Ar); MS (EI+): *m/z* 134 (68%, M^+), 119 (62%, M^+-Me), 91 (100%, tropylium). **Analysis (188):** $^{\upsilon}$max (neat): 3016, 3076cm^{-1}; δ_H (500MHz): 0.93 (3H, t, J=9.8, $CH_2CH_2C\underline{H}_3$), 1.39 (2H, m, $CH_2C\underline{H}_2CH_3$), 1.49 (2H, m, $C\underline{H}_2CH_2CH_3$), 2.30 (2H, m, CH=CHC$\underline{H}_2$), 3.86 (3H, s, OCH_3), 5.77 (1H, dt, J=6.1 + 12.2, CH=C$\underline{H}CH_2$), 6.54 (1H, d, J=12.2, C$\underline{H}$=$CHCH_2$), 6.89-7.00 (2H, m, Ar), 7.25-7.34 (2H, m, Ar); δ_C (125MHz): 14.00 ($CH_2CH_2\underline{C}H_3$), 22.4 ($CH_2\underline{C}H_2CH_3$), 28.4 ($\underline{C}H_2CH_2CH_3$), 32.1 (CH=CH$\underline{C}H_2$), 55.4 (OCH_3), 110.3, 119.9, 124.0, 126.5, 127.9, 130.0, 133.0, 156.9; MS (EI+): *m/z* 190 (52%, M^+), 147 (100%, M^+-C_3H_7), 91 (46%, tropylium).

Cyclopetanone 2,4,6-triisopropylbenzenesulfonylhydrazone (**190**)



Cyclopentanone (5.95ml, 67mmol) was added to a stirred suspension of 2,4,6–triisopropylbenzenesulfonylhydrazide (20g, 67mmol) in methanol (70ml) at room temperature. The resulting solution was treated with conc. HCl (0.7ml) followed by stirring at room temperature for 3h. The reaction was then cooled in the freezer for 24h and filtered. The white solid obtained was washed with cold methanol and dried under vacuum to yield the desired product (14.58g, 60%). **Analysis (190):** Mpt: 164-166°C; CHN: Found C, 65.89; H, 8.67; N, 7.90; S, 8.92%, $C_{20}H_{32}N_2O_2S$ requires C, 65.89; H, 8.85; N, 7.68; S, 8.80%; $^{\upsilon}$max (neat): 1600, 1656, 3239cm^{-1}. δ_H (360MHz): 1.27 (18H, m, CH_3), 1.69 (2H, p, J=7.0, C$\underline{H}_2$CH$_2$C=N), 1.80 (2H, p, J=7.0, C$\underline{H}_2$CH$_2$C=N), 2.17 (2H, t, J=7.4, C$\underline{H}_2$C=N), 2.33 (2H, t, J=7.4, C$\underline{H}_2$C=N), 2.91 (1H, h, J=6.9, *p*-C$\underline{H}$(CH$_3$)$_2$), 4.27 (2H, h, J=6.7, *o*-C$\underline{H}$(CH$_3$)$_2$), 7.17 (2H, s, Ar), 7.39 (1H, s, N$\underline{H}$); δ_C (90MHz): 23.3, 24.5, 24.5, 24.6, 27.4, 29.7, 33.1, 33.9, 123.5, 131.4, 151.1, 152.8, 166.0 (C=N); MS (ESI): *m/z* 365 (100%, MH$^+$).

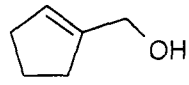
Tri-*n*-butyl (1-cyclopenten-1-yl) stannane (**189**)[113]



To a suspension of hydrazone (**190**)(7g, 19.23mmol) in pentane/TMEDA (74ml, 1:1) at -78°C was added *s*-BuLi (31.06ml, 1.3M in hexanes, 40.38mmol). After stirring for 2h, the temperature was allowed to rise to 0°C at which point effervescence was observed. When no more gas was evolved, the temperature was reduced again to -78°C and tri-*n*-butyltin chloride (5.22ml, 19.23mmol) was added. The reaction was stirred for 0.25h at -78°C, 0.5h at 0°C and 1h at room temperature before it was quenched with sat. NH_4Cl (aq) and diluted with hexane. The organic layer was

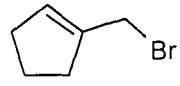
separated and washed with water, KF (aq) (10%) and brine, dried over $MgSO_4$ and concentrated to yield the crude product as an orange oil (11.47g). Purification was achieved by Kugelrohr distillation (0.2mmHg, 150°C) which provided the title stannane as yellow oil (1.5g, 22%). **Analysis (189):** δ_H (360MHz): 0.89 (9H, t, J=7.5, $Sn(CH_2)_3C\underline{H}_3$), 1.2-1.6 (18H, m, $Sn(C\underline{H}_2)_3CH_3$), 3.40 (6H, m, cyclopentene), 5.87 (1H, m, SnC=CH).

Cyclopent-1-enyl-methanol (**195**)



To a solution of methyl(cyclopent-1-ene)carboxylate (**194**) (14.46g, 115mmol) in hexane (350ml) at -78°C was added DIBAL-H (252ml, 1M in hexanes, 252mmol) over 3h. After stirring for a further 1h, the reaction was allowed to warm to 0°C whereupon MeOH (37ml, 917mmol) and water (16.5ml, 917mmol) were added. The resultant white slurry was filtered with the aid of Hyflo and washed with ethyl acetate. The combined filtrate was washed with water, dried over $MgSO_4$ and concentrated to yield the desired alcohol as a pale yellow oil (9.17g, 82%). **Analysis (195):** δ_H (360MHz): 1.47 (1H, s, OH), 1.89 (2H, m, cpn CH_2), 2.32 (4H, m, cpn CH_2), 4.19 (2H, s, $C\underline{H}_2OH$), 5.62 (1H, m, CH=C).

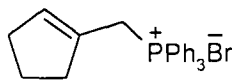
1-Bromomethyl-cyclopentene (**196**)



To a solution of allylic alcohol (**195**)(6.5g, 66.33mmol) and pyridine (1.34ml, 16.59mmol) in pentane at -40°C was added PBr_3 (4.37ml, 46.44mmol) dropwise over 0.5h. After stirring for 15min, the reaction was allowed to warm to 0°C and stirred for a further 0.75h. After this time, ice/water was added and the aqueous layer was extracted with ether. The combined extracts were washed with sat. $NaHCO_3$ (aq) (until no more gas was evolved) and brine, dried over $MgSO_4$ and

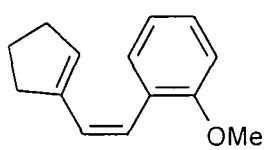
concentrated at ambient temperature to yield a brown oil (8.8g). The crude product was filtered through a short column of alumina and the title bromide was collected as an unstable yellow oil (8.6g, 81%). **Analysis (196):** δ_H (360MHz): 1.96 (2H, m, cpn CH_2), 2.37 (4H, m, cpn CH_2), 4.07 (2H, s, $C\underline{H}_2Br$), 5.78 (1H, s, CH=C); δ_C (90MHz): 23.5, 31.6, 32.9, 33.3, 130.9 (<u>C</u>H=C), 140.4.(CH=<u>C</u>).

<u>(1-Cyclopentenylmethyl)triphenylphosphonium bromide (**193**)</u>



A mixture of triphenylphosphine (8.31g, 31.68mmol) and allyl bromide (**196**)(5.10g, 31.68mmol) in toluene (40ml) was heated to reflux for 0.5h. The temperature was then reduced to 50°C and stirring was continued for a further 12h whereupon the reaction was cooled, diluted with ether and filtered. The crude solids were washed with hot ether and dried under vacuum to yield the product as a white solid (11.89g, 89%). **Analysis (193):** Mpt: >230°C; CHN: Found C, 68.01; H, 5.57%, $C_{21}H_{24}BrP$ requires C, 68.09; H, 5.71%; $^{\upsilon}$max (neat): 1435, 1485, 2870, 3047cm^{-1}; δ_H (360MHz): 1.72 (2H, p, J=7.5, cpn CH_2), 2.00 (2H, m, cpn CH_2), 2.22 (2H, m, cpn CH_2), 4.76 (1H, s, $C\underline{H}_2P$), 4.80 (1H, s, $C\underline{H}_2P$), 5.67 (1H, m, CH=C), 7.69-7.87 (15H, m, Ar); δ_C (90MHz): 23.2, 26.9 (d, J=49.2), 32.7 (d, J=3.0), 36.6 (d, J=2.4), 118.4 (d, J=85.4), 129.6 (d, J=10.2), 130.3 (d, J=12.6), 133.8 (d, J=9.9), 135.0 (d, J=2.9), 136.1 (d, J=11.2); MS (ESI): *m/z* 343 (100%, M^+-Br).

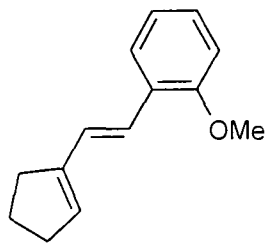
<u>Z-1- (Cyclopent-1-ene)-2-(2′-methoxyphenyl)ethene (**185**)</u>



NaHMDS (48ml, 1.0M in THF, 48mmol) was added to a solution of wittig salt (**193**)(18.5g, 43.74mmol) in THF (160ml) at 0°C. After stirring at room temperature for 0.5h, the resultant red suspension was cooled to -78°C and *o*-anisaldehyde (6.55g

in 10ml THF, 48mmol) was added *via* cannula. The reaction was then stirred for 1h at -78°C, 1h at 0°C and 1h at room temperature before water was added. The aqueous layer was separated and extracted with ether. The combined extracts were washed with water and brine, dried over $MgSO_4$ and concentrated to yield the crude product (26.5g). Gross quantities of triphenylphosphine oxide were removed by tritiation of an ether solution followed by filtration. The filtrate was concentrated and subjected to FCC (hexane:ether, 20:1) which provided the title Z-diene as a colourless oil (6.7g, 77%). **Analysis (185):** HRMS (EI+): Found M^+ 200.1202, $C_{14}H_{16}O$ requires M^+ 200.1201; υmax (neat): 1244, 3010cm^{-1}; δ_H (400MHz): 1.73 (2H, p, J=7.4, cpn CH_2), 2.05 (2H, m, cpn CH_2), 2.29 (2H, m, cpn CH_2), 3.79 (3H, s, OCH_3), 5.80 (1H, m, C=C<u>H</u>CH_2), 6.42 (2H, s, C<u>H</u>=C<u>H</u>), 6.79-6.88 (2H, m, Ar), 7.13-7.23 (2H, m; Ar); δ_C (100MHz): 24.9, 32.6, 34.3, 55.8 (OCH_3), 110.3, 120.1, 125.0, 128.0, 128.2, 128.7, 131.7, 134.5, 142.6, 157.5; δ_H (360MHz) (C_6D_6): 1.62 (2H. q, J=7.4, cpn CH_2), 2.20 (4H, m, cpn CH_2), 3.32 (3H, s, OCH_3), 5.74 (1H, m, C=C<u>H</u>CH_2), 6.64 (1H. d. J=12.4, PhCH=C<u>H</u>), 6.68 (1H, d, J=8.4, Ar), 6.87 (1H, d, J=12.4, PhC<u>H</u>=CH), 6.97 (1H, t, J=7.5, Ar), 7.24 (1H, dt, J=1.0 + 7.5, Ar), 7.44 (1H, d, J=7.1, Ar); MS (EI+): *m/z* 200 (100%, M^+), 171 (98%, M^+-C_2H_5), 47 (35%, tropylium).

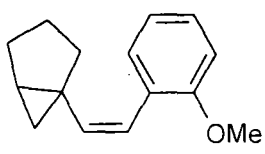
<u>E-1-(Cyclopent-1-ene)-2-(2'-methoxyphenyl)ethene (**197**)</u>



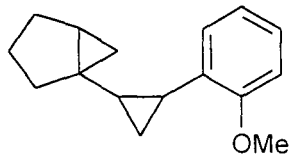
Analysis (197): υmax (neat): 1240, 3001, 3047cm^{-1}; δ_H (360MHz): 1.96 (2H, m, cpn CH_2), 2.46 (2H, m, cpn CH_2), 2.58 (2H, m, cpn CH_2), 3.84 (3H, s, OCH_3), 5.83 (1H, s, C=C<u>H</u>CH_2), 6.75 (1H, d, J=16.2, PhCH=C<u>H</u>), 6.85 (1H, d, J=8.15, Ar), 6.91 (1H, m, Ar), 7.02 (1H, d, J=16.2, PhC<u>H</u>=CH), 7.18 (1H, m, Ar), 7.48 (1H, m, Ar); δ_C (90MHz): 23.0, 31.1, 32.8, 55.3 (OCH_3), 110.7, 120.5, 123.1, 126.0, 126.2, 126.7,

127.9, 131.2, 143.3, 156.5; MS (EI+): *m/z* 200 (100%, M^+), 171 (91%, M^+-C_2H_5), 91 (35%, tropylium).

1-(Bicyclo[3.1.0]hexyl)-2-(2'methoxyphenyl)ethene (**198**) and
1-(bicyclo[3.1.0]hexyl)-2-(2'methoxyphenyl)cyclopropane (**199**)



(**198**)

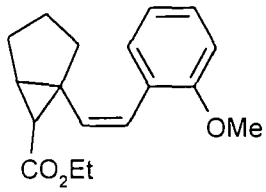


(**199**)

Diiodomethane (0.61ml, 7.50mmol) was added over 12h to a refluxing solution of diene (**185**)(0.5g, 2.50mmol) and diethyl zinc (5ml, 1M in hexanes, 5.0mmol) in benzene (2.5ml). The reaction was then cooled to room temperature, quenched with HCl (aq)(1M) and extracted with ether. The combined organic extracts were washed with sat. $NaHCO_3$ (aq), water and brine, dried over $MgSO_4$ and concentrated to yield the crude product as a pale green oil (0.61g). FCC (hexane:ether, 20:1) effected purification of the two products (colourless oils), **198** (16mg, 3%) and **199** (200mg, 35%) as a 1:1 mixture of diastereoisomers. **Analysis (198):** HRMS (EI+): Found M^+ 214.1357, $C_{15}H_{18}O$ requires M^+ 214.1358; $^{\upsilon}$max (neat): 752, 1244, 2951, 3062cm^{-1}; δ_H (360MHz): 0.43 (1H, m, cpr CH_2), 0.58 (1H, t, J=4.6, cpr CH_2), 1.18 (2H, m, cpr CH + cpn CH_2), 1.50-1.84 (5H, m, cpn CH_2), 3.82 (3H, s, OCH_3), 5.83 (1H, d, J=11.6, PhCH=C<u>H</u>), 6.48 (1H. d, J=11.6, PhC<u>H</u>=CH), 6.84 (1H, d, J=7.5, Ar), 6.91 (1H, t, J=7.5, Ar), 7.21 (1H, m, Ar), 7.41 (1H, m, Ar); δ_C (90MHz): 15.2, 21.5, 27.5, 28.5, 28.7, 32.3, 55.4, 110.0, 119.7, 124.3, 126.9, 127.9, 131.0, 135.5, 156.8; MS (EI+): *m/z* 214 (79%, M^+), 171 (100%, M^+-C_3H_7), 91 (67%, tropylium). **Analysis** (**199**, two diastereoisomers, a and b): HRMS (EI+): Found M^+ 228.1511, $C_{16}H_{20}O$ requires M^+ 228.1514; $^{\upsilon}$max (neat): 1242, 1494, 3032cm^{-1}; δ_H (500MHz): 0.17, 0.60-1.00, 1.10-1.70, 2.20 (26H (13a/13b), m, cpr/cpn), 3.88 (3Ha, s, OCH_3), 3.89 (3Hb, s, OCH_3), 6.80-7.20 (8H (4a/4b), m, Ar); δ_C (90MHz): 6.6, 6.7, 10.6, 11.3, 17.4, 17.8, 20.9, 21.3, 21.7, 22.5, 22.5, 23.0, 26.7, 26.9, 27.0, 27.6, 31.1, 32.3, 55.1, 55.1, 109.4, 109.5, 119.6, 119.7, 126.4, 126.4, 127.8, 128.4, 128.8, 129.0,

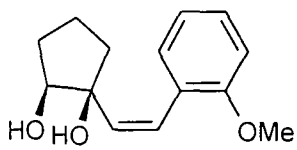
159.2, 159.3; MS (EI+): *m/z* 228 (8%, M^+), 121 (85%, M^+-ArOMe), 91 (100%, tropylium).

1-(6'Carboethoxy-bicyclo[3.1.0]hexyl)-2-(2''-methoxyphenyl)ethene (**200**)



Ethyl diazoacetate (0.48ml in 0.5ml DCM, 4.57mmol) was added over 12h to a solution of diene (**185**)(1g, 5.00mmol) and copper(I) triflate (100mg, 90% benzene complex, 0.20mmol) in DCM (1ml) at room temperature. The reaction was then diluted with DCM and washed with water. The organic portion was separated, dried over $MgSO_4$ and concentrated to yield the crude product (1.8g). Repeated FCC (hexane:ether, 9:1) provided the title compound as a clear colourless oil (25mg, 2%). **Analysis (200)**: HRMS (EI+): Found M^+ 286.1550, $C_{18}H_{22}O_3$ requires M^+ 286.1569; υmax (neat): 1726cm^{-1}; δ_H (200MHz): 1.00-1.30 (4H, m, cpr $CH_2C\underline{H}$ + $OCH_2C\underline{H}_3$), 1.40-1.92 (6H, m, cpn CH_2), 2.02 (1H, m, cpr $CH_2CHC\underline{H}$), 3.82 (3H, s, OCH_3), 4.01 (2H, m, $OC\underline{H}_2CH_3$), 5.93 (1H, d, J=12.2, PhCH=C$\underline{H}$), 6.65 (1H, d, J=12.2, PhC$\underline{H}$=CH), 6.80-7.00 (2H, m, Ar), 7.18-7.42 (2H, m, Ar); δ_C (50MHz): 14.3, 20.9, 27.2, 29.7, 333.0, 35.7, 38.2, 55.4, 60.2, 110.1, 119.9, 126.9, 127.7, 128.2, 130.1, 130.3, 156.9, 171.7; MS (EI+). *m/z* 286 (14%, M^+), 213 (100%, M^+-CO_2Et).

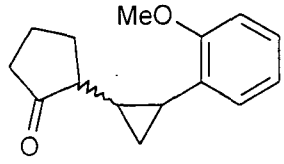
1-(1',2'-Dihydroxycyclopentyl)-2-(2''methoxyphenyl)ethene (**201**)



OsO_4 (68mg, 0.27mmol) was added to a solution of diene (**185**)(17g, 85mmol) and Me_3N-O.H_2O (9.44g, 85mmol) in pyridine/water/*t*-butanol (227ml, 1:7:25) at room temperature. After heating to reflux for 12h, the reaction was quenched with sat.

Na_2SO_3 and *t*-butanol was removed under high vacuum. The aqueous residue was then saturated with NaCl and extracted with ether. The combined extracts washed with sat. brine, dried with $MgSO_4$ and concentrated to yield the crude product (16.8g). FCC (petrol:ethyl acetate, 3:2) provided the title diol as a cream semi-solid (13.51, 68%). **Analysis (201):** HRMS (EI+): Found M^+ 234.1260, $C_{14}H_{18}O_3$ requires M^+ 234.1256; $^{\upsilon}$max (neat): 3080-3630cm^{-1}; δ_H (500MHz): 1.31 (1H, m, cpn CH_2), 1.63 (1H, m, cpn CH_2), 1.72-1.95 (4H, m, cpn CH_2), 2.56 (1H, s, OH), 2.74 (1H, s, OH), 3.85 (3H, s, OCH_3), 3.89 (1H, t, J=9.2, C<u>H</u>OH), 5.81 (1H, d, J=12.5, PhCH=C<u>H</u>), 6.54 (1H, d, J=12.5, PhC<u>H</u>=CH), 6.90 (1H, d, J=8.0, Ar), 6.96 (1H, t, J=8.0, Ar), 7.26 (1H, t, J=8.0, Ar), 7.33 (1H, d, J=8.0, Ar); δ_C (75MHz): 19.1, 30.2, 36.3, 55.3, 78.6, 80.4, 110.3, 120.2, 126.2, 126.3, 128.4, 130.5, 135.3, 155.9; MS (EI+): *m/z* 234 (21%, M^+), 216 (27%, M^+-H_2O), 121 (100%, $C_8H_9O^+$) 91 (39%, tropylium).

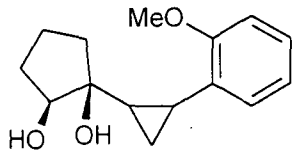
<u>1-(2'Ketocyclopentyl)-2-(2''methoxyphenyl)cyclopropane (**202**)</u>



Diiodomethane (0.27ml in 1ml toluene, 3.33mmol) was added over 12h to a solution of diol (**201**) (0.26g, 1.11mmol) and diethyl zinc (2.22ml, 1M in hexanes, 2.22mmol) in toluene (1.5ml) at 80°C. The reaction was then cooled to room temperature, quenched with water and extracted with ether. The combined organic extracts were washed with water and brine, dried over $MgSO_4$ and concentrated to yield the crude product (330mg). FCC (petrol:ethyl acetate, 5:1) provided the product (130mg, 51%) as an inseparable mixture of four diastereoisomers (1:1:1:1). **Analysis (202)** (four diastereoisomers): HRMS (EI+): Found M^+ 230.1311, $C_{15}H_{18}O_2$ requires M^+ 230.1307; $^{\upsilon}$max (neat): 1737cm^{-1}. δ_H (500MHz): 0.78-2.35 (44H, m, cpr/cpn), 3.85-3.88 (12H , 4 s, OCH_3), 6.80-7.20 (16H, m, Ar); δ_C (75MHz): 6.6, 7.6, 11.2, 12.6, 14.5, 14.8, 15.2, 16.5, 18.4, 20.1, 20.3, 20.4, 20.5, 20.6, 20.7, 21.7, 28.0, 29.2, 29.3, 29.9, 37.8, 38.1, 38.2, 38.3, 47.5, 48.6, 50.4, 52.5, 55.0, 55.2, 55.4, 109.5, 109.9, 110.0, 110.1, 119.7, 119.9, 120.3, 120.4, 125.4, 125.5, 126.3, 126.4, 127.1, 127.15,

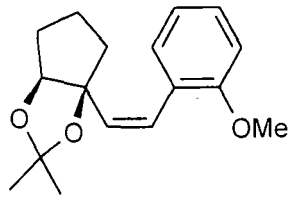
127.24, 127.3, 128.6, 128.8, 130.7, 130.9, 158.0 (C=O), 158.2 (C=O), 159.0 (C=O), 159.4 (C=O); MS (EI+): *m/z* 230 (16%, M^+), 147 (99%, M^+-C_5H_7O), 134 (100%, M^+-C_5H_7O/CH), 91 (52%, tropylium).

1-(1′,2′-Dihydroxycyclopentyl)-2-(2″methoxyphenyl)cyclopropane (**204**)



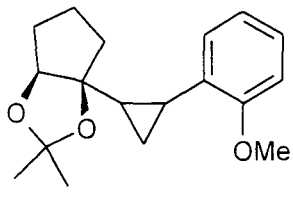
A suspension of diiodomethane (34ml, 0.43mol) and zinc-copper couple (28g, 0.43mol) in monoglyme (400ml) was heated to reflux until initiation was observed (purple colour evident). After cooling to room temperature, additions of N-ethyldiisopropylamine (75ml, 0.43mol) and diol (**201**) (5.0g, 21.37mmol) were made. The reaction was then stirred for 24h at room temperature before sat. NH_4Cl (aq) was added. The quenched mixture was filtered through a pad of celite and extracted with ether. The organic extracts were washed with water, dried over $MgSO_4$ and concentrated to yield the crude product (7.66g). FCC (petrol:ethyl acetate, 1:1) provided 3.46g of an oil which was found (^{1}H NMR) to be a inseparable mixture of starting material and product. This material was subjected to the conditions described above for a second time to yield 2.1g (40%) of the title compound as an unstable pale yellow oil. Crude ^{1}H NMR indicated the product to be a 1:2 mixture of diastereoisomers. **Analysis (204) major isomer:** CHN: Found C, 72.28; H, 7.84%, $C_{15}H_{20}O_3$ requires C, 72.17; H, 7.94%; υmax (neat): 3150-3600cm^{-1}; δ_H (300MHz): 1.05 (1H, m, cpr CH_2), 1.20 (1H, m, cpr CH_2), 1.33-1.90 (8H, m, cpr/cpn), 2.00 (1H, s, COH), 2.14 (1H, d, J=6.0, CHOH), 3.48 (1H, m, CHOH), 3.90 (3H, s, OCH_3), 6.91 (2H, m, Ar), 7.23 (2H, m, Ar); δ_C (75MHz): 5.0, 16.0, 19.7, 26.4, 32.4, 37.7, 55.3, 76.7, 79.9, 110.3, 121.0, 127.2, 128.1, 129.8, 159.0; MS (CI+, NH_3): *m/z* 249 (11%, MH^+), 231 (99%, MH^+-H_2O), 213 (100%, MH^+-$2H_2O$).

1-(3',3'-Dimethyl-2',4'-dioxabicyclo[3.3.0]octyl)-2-(2''methoxyphenyl)ethene (**205**)



A solution of diol (**201**) (0.5g, 2.14mmol), 2,2-dimethoxypropane (1ml, 8.56mmol) and TsOH (19mg, 0.1mmol) in DMF (15ml) was stirred at room temperature for 24h. Water was then added and the aqueous mixture was extracted with ether. The combined extracts were washed with water, dried over $MgSO_4$ and concentrated to yield the crude product (0.62g). Filtration through a plug of silica (petrol:ethyl acetate, 9:1) provided the title compound as a colourless oil (0.5g, 59%). **Analysis (205):** CHN: Found C, 74.19; H, 8.13%, $C_{17}H_{22}O_3$ requires C, 74.42; H, 8.08%; ν_{max} (neat): 1249cm^{-1}; δ_H (300MHz): 1.22-1.30 (4H, m, CH_3CCH_3 + cpn CH), 1.34 (3H, s, CH_3CCH_3), 1.51 (2H, m, cpn CH_2), 1.70 (2H, m, cpn CH_2), 1.98 (1H, m, cpn CH), 3.82 (3H, s, OCH_3), 4.41 (1H, d, J=4.8, OCH), 5.98 (1H, d, J=12.3, olefinic), 6.48 (1H, d, J=12.3, olefinic), 6.80-6.95 (2H, m, Ar), 7.20-7.40 (2H, m, Ar); δ_C (50MHz): 23.5, 25.3, 26.7, 33.3, 40.6, 55.3, 87.0, 91.2, 108.8, 109.9, 119.8, 125.1, 126.6, 128.5, 131.2, 136.7, 156.7; MS (CI+, NH_3): *m/z* 292 (29%, $M+NH_4^+$), 275 (86%, MH^+), 274 (100%, M^+), 259 (63%, M^+-CH_3).

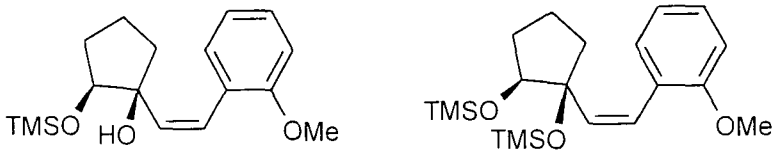
1-(3',3'-Dimethyl-2',4'-dioxabicyclo[3.3.0]octyl)-2-(2''methoxyphenyl)cyclopropane (**206**)



To a vigorously stirred solution of diethyl zinc (7.0ml, 1M in hexanes, 7.0mmol) in 1,2 DCE (10ml) at 0°C was added chloroiodomethane (1.0ml, 14mmol) dropwise, followed, after 10min, by alkene (**205**) (0.48g, 1.75mmol). After a further 10min, cooling was removed and the reaction was stirred at room temperature for 12h.

NH_4Cl was then added and the reaction was extracted with DCM. The combined extracts were washed with water, dried over $MgSO_4$ and concentrated to yield the crude product (0.52g). FCC (petrol:ether, 9:1) delivered 0.2g (40%) of the title cyclopropane (colourless oil) as a single diastereoisomer. **Analysis (206):** CHN: Found C, 74.90; H, 8.46%, $C_{18}H_{24}O_3$ requires C, 74.97; H, 8.39%; υmax (neat): 749, 1241, 1495cm^{-1}; δ_H (500MHz): 0.84-1.00 (2H, m, cpr CH_2), 1.06 (1H, m, cpr C<u>H</u>CHPh), 1.19 (2H, m, cpn CH_2), 1.29 (1H, m, cpn CH_2), 1.34 (3H, s, $CH_3CC\underline{H}_3$), 1.45 (3H, s, $C\underline{H}_3CCH_3$), 1.59 (3H, m, cpn CH_2), 2.18 (1H, m, cpr CHPh), 3.86 (3H, s, OCH_3), 4.50 (1H, d, J=4.0, OCH), 6.78-6.89 (2H, m, Ar), 7.15 (2H, m, Ar); δ_C (125MHz): 6.1, 16.5, 22.6, 26.4, 27.4, 27.5, 32.8, 36.8, 55.0, 87.0, 91.7, 109.0, 109.3, 119.8, 126.8, 127.1, 129.4, 159.1; MS (EI+): *m/z* 288 (8%, M^+), 154 (41%, M^+-$C_9H_{10}O$), 134 (100%, $C_9H_{10}O^+$), 91 (51%, tropylium).

<u>1-(1'-Hydroxy-2'-trimethylsilyloxycyclopentyl)-2-(2''methoxyphenyl)ethene (**207**) and 1-(1', 2'-*bis*-trimethylsilyloxycyclopentyl)-2-(2''methoxyphenyl)ethene (**208**)</u>

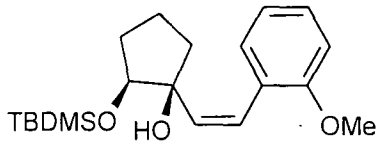


(**207**) (**208**)

A solution of TMS-Cl (0.16ml, 1.29mmol), diol (**201**) (0.2g, 0.86mmol) and triethylamine (0.18ml, 1.29mmol) in DMF (10ml) was stirred at room temperature until all the starting material had been consumed (3h) (tlc, petrol:ethyl acetate, 1:1). Water was then added and the aqueous mixture was extracted with ether. The combined ethereal extracts were washed with brine, dried over $MgSO_4$ and concentrated to yield the crude product (300mg). FCC (petrol:ethyl acetate, 18:1 gradient to 8:2) provided 140mg (54%) of **207** and 65mg (20%) of **208** as colourless oils. **Analysis (207):** CHN: Found C, 66.59; H, 8.56%, $C_{17}H_{26}O_3Si$ requires C, 66.62; H, 8.55%; υmax (neat): 3545cm^{-1}; δ_H (500MHz): 0.00 (9H, s, $SiCH_3$), 1.30 (1H, m, cpn CH_2), 1.47 (2H, m, cpn CH_2), 1.58-1.76 (3H, m, cpn CH_2), 2.63 (1H, s, OH), 3.69 (3H, s, OCH_3), 3.78 (1H, t, J=9.5, CHOTMS), 5.53 (1H, d, J=12.5, olefinic), 6.44 (1H, d, J=12.5, olefinic), 6.68-6.75 (2H, m, Ar), 7.08 (1H, m, Ar),

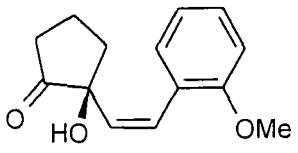
7.43 (1H, m, Ar); δ_C (125MHz): 0.0, 19.4, 30.9, 35.4, 55.3, 79.4, 80.1, 109.9, 119.7, 126.5, 126.7, 128.2, 130.9, 135.2, 156.5; MS (EI+): *m/z* 306 (1%, M^+), 288 (8%, M^+-H_2O), 216 (47%, MH^+-TMS/H_2O), 73 (100%, TMS^+). **Analysis (208):** CHN: Found C, 63.46; H, 9.13%, $C_{20}H_{34}O_3Si_2$ requires C, 63.44; H, 9.05%; $^{\upsilon}$max (neat): 753, 841, 1249cm^{-1}; δ_H (500MHz): 0.05 (9H, s, $SiCH_3$), 0.15 (9H, s, $SiCH_3$), 1.37-1.55 (2H, m, cpn CH_2), 1.60-1.78 (3H, m, cpn CH_2), 1.95 (1H, m, cpn CH_2), 3.84 (4H, m, CHOTMS + OCH_3), 5.82 (1H, d, J=13.0, olefinic), 6.58 (1H. d, J=13.0, olefinic), 6.83-6.95 (2H, m, Ar), 7.23 (1H, m, Ar), 7.82 (1H, m, Ar); δ_C (125MHz): 0.0, 2.3, 18.2, 29.5, 35.7, 55.1, 79.6, 82.2, 109.4, 119.6, 126.0, 126.2, 128.1, 132.0, 134.7, 156.5; MS (EI+): *m/z* 378 (1%, M^+), 288 (M^+-TMSOH), 73 (100%, TMS^+).

1-(1′-Hydroxy-2′-*tert*-butyldimethylsilyloxycyclopentyl)-2-(2″methoxyphenyl)ethene (**209**)



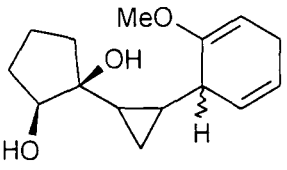
A solution of TBDMS-Cl (0.16g, 1.05mmol), diol (**201**) (50mg, 0.21mmol), triethylamine (0.15ml, 1.05mmol) and DMAP (15mg, 0.13mmol) in DMF (5ml) was stirred at room temperature for 12h. Water was then added and the reaction was extracted with ether. The combined extracts were washed with water, dried over $MgSO_4$ and concentrated to yield the crude product (0.1g). FCC (petrol:ether, 9:1) provided the title silyl ether as a colourless oil (64mg, 86%). **Analysis (209):** CHN: Found C, 68.78; H, 9.33%, $C_{20}H_{32}O_3Si$ requires C, 68.92; H, 9.25%; $^{\upsilon}$max (neat): 3545cm^{-1}; δ_H (500MHz): 0.08 (3H, s, $SiCH_3$), 0.10 (3H, s, $SiCH_3$), 0.92 (9H, s, *t*-Bu), 1.40-1.90 (6H, m, cpn CH_2), 2.87 (1H, s, OH), 3.83 (3H, s, OCH_3), 3.95 (1H, t, J=10.8, OCH), 5.69 (1H, d, J=12.5, olefinic), 6.58 (1H, d, J=12.5, olefinic), 6.80-6.95 (2H, m, Ar), 7.23 (1H, m, Ar), 7.59 (1H, m, Ar); δ_C (125MHz): -4.8, -4.5, 18.1, 19.5, 25.8, 31.1, 35.2, 55.3, 80.1, 80.2, 109.9, 119.8, 126.78, 126.81, 128.3, 131.3, 135.3, 156.6; MS (CI+, NH_3): *m/z* 348 (1%, M^+), 331 (87%, MH^+-H_2O), 201 (100%, MH^+-TBDMSO/H_2O/CH_3).

1-(1′-Hydroxy-2′-ketocyclopentyl)-2-(2″methoxyphenyl)ethene (**211**)



To a stirred solution of oxalyl chloride (0.22ml, 2.57mmol) in DCM (14ml) at -78°C was added DMSO (0.36ml in 3ml of DCM, 5.14mmol) followed, after 10min, by diol (**201**) (0.5g, 2.14mmol). After a further 10min, the resultant white ppt was treated with triethylamine (1.43ml, 10.27mmol) and the reaction was allowed to warm to room temperature. After stirring for 12h, water was added and the aqueous mixture was extracted with DCM. The organic extracts were washed with water, dried over $MgSO_4$ and concentrated to yield the crude product (0.52g). FCC (petrol:ethyl acetate, 7:3) followed by Kugelrohr distillation (0.1mmHg, 250°C) afforded the title compound (100mg, 20%) as a colourless oil. **Analysis (211)**: HRMS (EI+): Found M^+ 232.1094, $C_{14}H_{16}O_3$ requires M^+ 232.1100; $^{\upsilon}$max (neat): 3150-3650cm^{-1}; δ_H (300MHz): 1.80-2.31 (6H, m, cpn CH_2), 2.95 (1H, s, OH), 3.84 (3H, s, OCH_3), 5.76 (1H, d, J=12.6, olefinic), 6.73 (1H, d, J=12.6, olefinic), 6.83-7.00 (2H, m, Ar), 7.20-7.50 (2H, m, Ar); δ_C (63MHz): 17.2, 34.5, 36.9, 55.4, 79.4, 110.4, 120.3, 125.5, 129.2, 129.3, 129.9, 130.2, 156.6, 217.0; MS (EI+): *m/z* 232 (10%, M^+), 214 (80%, M^+-H_2O), 115 (100%, M^+-C_8H_5O), 91 (79%, tropylium).

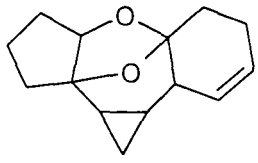
1-(1′,2′-Dihydroxycyclopentyl)-2-(2″methoxycyclohexa-2,5-dienyl)cyclopropane (**212**)



Cyclopropane (**204**) (2g in 20ml ether, 8.07mmol), ethanol (1.42ml, 24.21mmol) and ether (20ml) were added to ammonia (100ml) at -78°C. Lithium (0.57g, 80.70mmol) (small pieces, washed in petrol) was then added partition-wise resulting in a deep

blue solution. After stirring for 2h at -78°C, the reaction was quenched with ethanol and the ammonia was allowed to evaporate (≈4h). Water was then added and solution was extracted with ether. The combined organic extracts were washed with water, dried over $MgSO_4$ and concentrated to yield the crude product (1.76g). FCC (petrol:ethyl acetate, 1:1) provided the title compound (1.0g, 50%) as a mixture of diastereoisomers (2:1). Further chromatography enabled separation of the major isomer as a white waxy solid. **Analysis (212) major isomer:** CHN: Found C, 71.73; H, 9.09%, $C_{15}H_{20}O_3$ requires C, 71.97; H, 8.86%; $^{\upsilon}$max (neat): 1212, 3360, 3420, 3485cm^{-1}; δ_H (500MHz) (C_6D_6): 0.34 (1H, m, cpr CH_2), 0.45 (1H, m, cpr CH_2), 0.65 (1H, m, cpr C<u>H</u>CHCOCH$_3$), 0.86 (1H, m, cpr C<u>H</u>COH), 1.38 (1H, m, cpn CH_2), 1.79 (4H, m, cpn CH_2), 2.10 (1H, m, cpn CH_2), 2.50-2.70 (3H, m, ch CH_2 + OH), 3.06 (3H, s, OCH_3), 3.13 (1H, m, ch CH=CHC<u>H</u>), 3.70 (1H, m, C<u>H</u>OH), 3.93 (1H, s, OH), 4.34 (1H, m, ch C<u>H</u>=COCH$_3$), 5.61 (1H, m, ch CH$_2$C<u>H</u>=CH), 5.75 (1H, m, ch CH$_2$CH=C<u>H</u>); δ_C (126MHz) (C_6D_6): 22.2 (cpr CH_2), 37.2 (cpn CH_2), 40.2 (cpr <u>C</u>HCHCOCH$_3$), 43.0 (cpr <u>C</u>HCOH), 43.4 (ch CH_2), 50.1 (cpn CH_2), 53.3 (ch CH=CH<u>C</u>H), 56.9 (cpn CH_2), 70.0 (OCH_3), 93.0 (CHOH), 96.3 (COH), 108.3 (ch <u>C</u>H=COCH$_3$), 139.9 (ch CH$_2$<u>C</u>H=CH), 145.9 (ch CH$_2$CH=<u>C</u>H), 172.6 (ch CH=<u>C</u>OCH$_3$); MS (EI+): *m/z* 250 (5%, M^+), 214 (92%, M^+-2H$_2$O), 121 (89%, $C_8H_9O^+$), 91 (100%, tropylium).

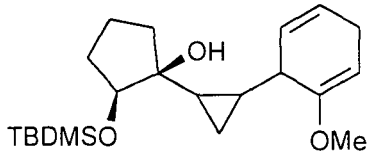
<u>6,16-Dioxahexacyclo[1(5,11),0(5,15),0(7,11),0(12,14)]pentadec-1-ene (**214**)</u>



Analysis (214): CHN: Found C, 77.21; H, 8.19%, $C_{14}H_{18}O_2$ requires C, 77.03; H, 8.31%; $^{\upsilon}$max (neat): 1031, 1086, 1442, 3017cm^{-1}; δ_H (400MHz): 0.62 (1H, m, cpr CH_2), 0.63 (1H, m, cpr CH=CHCHC<u>H</u>), 0.76 (1H, m, cpr CH_2), 1.47 (3H, m, cpr OCCH + cpn OCHCH$_2$C<u>H</u>$_2$), 1.59 (1H, m, cpn OCCH$_2$), 1.78 (3H, m, ch CH=CHCH$_2$C<u>H</u>$_2$ + cpn OCHC<u>H</u>$_2$), 2.00 (1H, m, cpn OCCH$_2$), 2.07 (1H, m, ch CH=CHC<u>H</u>$_2$), 2.12 (2H, m, ch CH=CHC<u>H</u>$_2$ + cpn OCHC<u>H</u>$_2$), 2.32 (1H, m, ch CH=CHC<u>H</u>), 4.04 (1H, m, cpn OCH), 5.45 (1H, m, vinyl), 5.68 (1H, m, vinyl). δ_C

(100MHz): 12.8 (cpr CH_2), 13.7 (cpr CH=CHCH<u>C</u>H), 18.0 (cpr OC<u>C</u>H), 23.2 (cpn OC<u>C</u>H_2), 23.8 (ch CH=CH<u>C</u>H_2), 32.2 (cpn OCHCH$_2$<u>C</u>H_2), 32.6 (ch CH=CHCH$_2$<u>C</u>H_2), 34.8 (cpn OCH<u>C</u>H_2), 39.4 (ch CH=CH<u>C</u>H), 81.7 (cpn O<u>C</u>HCH$_2$), 90.6 (cpn O<u>C</u>CH_2), 106.5 (ch OCO), 125.7 (vinyl), 131.1 (vinyl). MS (EI+): *m/z* 218 (7%, M^+), 79 (100%, $C_6H_7^+$).

<u>1-(1'-Hydroxy-2'-*tert*-butyldimethylsilyloxycyclopentyl)-2-(2''methoxycyclohexa-2,5-dienyl)cyclopropane (**216**)</u>



A solution of TBDMS-Cl (0.60g, 4.0mmol), diol (**212**) (0.2g, 0.8mmol), triethylamine (0.56ml, 4.0mmol) and DMAP (60mg, 0.48mmol) in DMF (20ml) was stirred at room temperature for 12h. Water was then added and the reaction was extracted with ether. The combined extracts were washed with water, dried over $MgSO_4$ and concentrated to yield the crude product (0.34g). FCC (petrol:ether, 18:1 gradient to 9:1) provided the title silyl ether (225mg, 77%) as a separable mixture of diastereoisomers (2:1). **Analysis (216) major isomer:** CHN: Found C, 69.47; H, 10.23%, $C_{21}H_{36}O_3Si$ requires C, 69.18; H, 9.95%; $^{\upsilon}$max (neat): 3528cm^{-1}; δ_H (300MHz): 0.08 (3H, s, $SiCH_3$), 0.09 (3H, s, $SiCH_3$), 0.40 (1H, m, cpr CH_2), 0.50 (1H, m, cpr CH_2), 0.58-0.85 (2H, m, cpr C<u>H</u>CHCOCH$_3$ + cpr C<u>H</u>COH), 0.91 (9H, s, *t*-Bu), 1.57 (2H, m, cpn CH_2), 1.82 (3H, m, cpn CH_2), 2.10 (1H, m, cpn CH_2), 2.79 (3H, m, ch CH_2 + OH), 3.15 (1H, m, CHOSi), 3.54 (3H, s, OCH_3), 3.89 (1H, t, J=7.9, CH=CHC<u>H</u>), 4.63 (1H, m, C<u>H</u>=COCH$_3$), 5.69 (2H, m, C<u>H</u>=C<u>H</u>); δ_C (126MHz) (C_6D_6): -4.2 ($SiCH_3$), -3.7 ($SiCH_3$), 3.8 (cpr CH_2), 18.1 (SiC), 20.4 (cpn CH_2), 22.4 (cpr <u>C</u>HCHCOCH$_3$), 25.8 (cpr <u>C</u>HCOH), 25.9 (C(<u>C</u>H$_3$)$_3$), 27.1 (ch CH_2), 32.8 (cpn CH_2), 35.1 (CH=CH<u>C</u>H), 36.5 (cpn CH_2), 53.2 (OCH_3), 78.6 (COH), 81.4 (CHOSi), 90.2 (<u>C</u>H=COCH$_3$), 122.9 (CH$_2$<u>C</u>H=CH), 130.0 (CH$_2$CH=<u>C</u>H), 158.0 (CH=<u>C</u>OCH$_3$); MS (EI+): *m/z* 364 (1%, M^+), 346 (10%, M^+-H_2O), 214 (74%, M^+-TBDMSOH/H_2O), 121 (67%, $C_8H_9O^+$), 75 (100%, $(CH_3)_2Si{=}OH^+$). **Analysis (216) minor isomer:** CHN: Found C, 69.21; H, 10.03%, $C_{21}H_{36}O_3Si$ requires C, 69.18; H, 9.95%; δ_H (300MHz): 0.07 (3H, s, $SiCH_3$), 0.08 (3H, s, $SiCH_3$), 0.27 (1H, m, cpr CH_2), 0.66

(1H, m, cpr CH_2), 0.75-0.97 (11H, m, cpr C<u>H</u>CHCOCH$_3$ + cpr C<u>H</u>COH + *t*-Bu), 1.31 (1H, m, cpn CH_2), 1.50 (2H, m, cpn CH_2), 1.79 (3H, m, cpn CH_2), 2.65-2.84 (3H, m, ch CH_2 + CHOSi), 3.59 (3H, s, OCH_3), 3.62 (1H, s, OH), 3.94 (1H, t, J=7.5, CH=CHC<u>H</u>), 4.72 (1H, m, C<u>H</u>=CCH$_3$), 5.71 (2H, m, C<u>H</u>=C<u>H</u>); δ_C (126MHz): -4.3, -4.2, 5.9, 18.6, 18.8, 23.9, 24.5, 26.3, 26.7, 30.3, 34.2, 36.6, 54.2, 79.6, 80.2, 91.7, 123.5, 128.9, 156.0.

5.0 References

[1] See the Botanical Dermatology Database at: http://bodd.cf.ac.uk.

[2] For a review of the constituents of these plants see: *Naturally Occuring Phorbol Esters*, F.J. Evans (Ed.), CRC Press, Florida, 1986.

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APPENDIX

Requirements for the Board of Studies

The board of Studies in Chemistry requires that each postgraduate research thesis contains an appendix listing:

i, all research colloquia, seminars and lectures arranged by the Department of Chemistry during the period of the author's residence as a postgraduate student;

ii, lectures organised by Durham University Chemical Society

iii, details of first year postgraduate induction courses completed by the author; and

iv, all research conferences attended and papers presented by the author during the period when research for the thesis was carried out.

University of Durham

Board of Studies in Chemistry

POSTGRADUATE COLLOQUIA, LECTURES AND SEMINARS FROM INVITED SPEAKERS

1996

October 9	Professor G. Bowmaker, University Aukland, NZ Coordination and Materials Chemistry of the Group 11 and Group 12 Metals : Some Recent Vibrational and Solid State NMR Studies
October 14	Professor A. R. Katritzky, University of Gainesville,University of Florida, USA Recent Advances in Benzotriazole Mediated Synthetic Methodology
October 16	Professor Ojima, Guggenheim Fellow, State University of New York at Stony Brook Silylformylation and Silylcarbocyclisations in Organic Synthesis
October 22	Professor Lutz Gade, Univ. Wurzburg, Germany Organic transformations with Early-Late Heterobimetallics: Synergism and Selectivity
October 22	Professor B. J. Tighe, Department of Molecular Sciences and Chemistry, University of Aston Making Polymers for Biomedical Application - can we meet Nature's Challenge? Joint lecture with the Institute of Materials

October 23 Professor H. Ringsdorf (Perkin Centenary Lecture), Johannes Gutenberg-Universitat, Mainz, Germany
Function Based on Organisation

October 29 Professor D. M. Knight, Department of Philosophy, University of Durham.
The Purpose of Experiment - A Look at Davy and Faraday

October 30 Dr Phillip Mountford, Nottingham University
Recent Developments in Group IV Imido Chemistry

November 6 Dr Melinda Duer, Chemistry Department, Cambridge
Solid-state NMR Studies of Organic Solid to Liquid-crystalline Phase Transitions

November 12 Professor R. J. Young, Manchester Materials Centre, UMIST
New Materials - Fact or Fantasy?
Joint Lecture with Zeneca & RSC

November 13 Dr G. Resnati, Milan
Perfluorinated Oxaziridines: Mild Yet Powerful Oxidising Agents

November 18 Professor G. A. Olah, University of Southern California, USA
Crossing Conventional Lines in my Chemistry of the Elements

November 19 Professor R. E. Grigg, University of Leeds
Assembly of Complex Molecules by Palladium-Catalysed Queueing Processes

November 20 Professor J. Earnshaw, Deptartment of Physics, Belfast
Surface Light Scattering: Ripples and Relaxation

November 27 Dr Richard Templer, Imperial College, London
Molecular Tubes and Sponges

December 3 Professor D. Phillips, Imperial College, London
"A Little Light Relief" –

December 4 Professor K. Muller-Dethlefs, York University
Chemical Applications of Very High Resolution ZEKE Photoelectron Spectroscopy

December 11 Dr Chris Richards, Cardiff University
Stereochemical Games with Metallocenes

1997

January 15 Dr V. K. Aggarwal, University of Sheffield
Sulfur Mediated Asymmetric Synthesis

January 16 Dr Sally Brooker, University of Otago, NZ
Macrocycles: Exciting yet Controlled Thiolate Coordination Chemistry

January 21 Mr D. Rudge, Zeneca Pharmaceuticals
High Speed Automation of Chemical Reactions

January 22	Dr Neil Cooley, BP Chemicals, Sunbury Synthesis and Properties of Alternating Polyketones
January 29	Dr Julian Clarke, UMIST What can we learn about polymers and biopolymers from computer-generated nanosecond movie-clips?
February 4	Dr A. J. Banister, University of Durham From Runways to Non-metallic Metals - A New Chemistry Based on Sulphur
February 5	Dr A. Haynes, University of Sheffield Mechanism in Homogeneous Catalytic Carbonylation
February 12	Dr Geert-Jan Boons, University of Birmingham New Developments in Carbohydrate Chemistry
February 18	Professor Sir James Black, Foundation/King's College London My Dialogues with Medicinal Chemists
February 19	Professor Brian Hayden, University of Southampton The Dynamics of Dissociation at Surfaces and Fuel Cell Catalysts
February 25	Professor A. G. Sykes, University of Newcastle The Synthesis, Structures and Properties of Blue Copper Proteins
February 26	Dr Tony Ryan, UMIST Making Hairpins from Rings and Chains
March 4	Professor C. W. Rees, Imperial College Some Very Heterocyclic Chemistry.
March 5	Dr J. Staunton FRS, Cambridge University Tinkering with biosynthesis: towards a new generation of antibiotics
March 11	Dr A. D. Taylor, ISIS Facility, Rutherford Appleton Laboratory Expanding the Frontiers of Neutron Scattering
March 19	Dr Katharine Reid, University of Nottingham Probing Dynamical Processes with Photoelectrons
October 8	Professor E Atkins, Department of Physics, University of Bristol Advances in the control of architecture for polyamides: from nylons to genetically engineered silks to monodisperse oligoamides
October 15	Dr R M Ormerod, Department of Chemistry, Keele University Studying catalysts in action
October 21	Professor A F Johnson, IRC, Leeds Reactive processing of polymers: science and technology
October 22	Professor R J Puddephatt (RSC Endowed Lecture), University of Western Ontario Organoplatinum chemistry and catalysis

October 23 Professor M R Bryce, University of Durham, Inaugural Lecture
New Tetrathiafulvalene Derivatives in Molecular, Supramolecular and Macromolecular
Chemistry: controlling the electronic properties of organic solids

October 29 Professor R Peacock, University of Glasgow
Probing chirality with circular dichroism

October 28 Professor A P de Silva, The Queen's University, Belfast
Luminescent signalling systems"

November 5 Dr M Hii, Oxford University
Studies of the Heck reaction

November 11 Professor V Gibson, Imperial College, London
Metallocene polymerisation

November 12 Dr J Frey, Department of Chemistry, Southampton University
Spectroscopy of liquid interfaces: from bio-organic chemistry to atmospheric chemistry

November 19 Dr G Morris, Department of Chemistry, Manchester Univ.
Pulsed field gradient NMR techniques: Good news for the Lazy and DOSY

November 20 Dr L Spiccia, Monash University, Melbourne, Australia
Polynuclear metal complexes

November 25 Dr R Withnall, University of Greenwich
Illuminated molecules and manuscripts

November 26 Professor R W Richards, University of Durham, Inaugural Lecture
A random walk in polymer science

December 2 Dr C J Ludman, University of Durham
Explosions

December 3 Professor A P Davis, Department. of Chemistry, Trinity College Dublin.
Steroid-based frameworks for supramolecular chemistry

December 10 Sir G Higginson, former Professor of Engineering in Durham and retired Vice-Chancellor of Southampton Univ.
1981 and all that.

December 10 Professor M Page, Department of Chemistry, University of Huddersfield
The mechanism and inhibition of beta-lactamases

October 27 Professor W Roper FRS. University of Auckland, New Zealand

1998

January 14 Professor D Andrews, University of East Anglia
Energy transfer and optical harmonics in molecular systems

January 20 Professor J Brooke, University of Lancaster
What's in a formula? Some chemical controversies of the 19th century

January 21	Professor D Cardin, University of Reading Sorry title missing.
January 27	Professor R Jordan, Dept. of Chemistry, Univ. of Iowa, USA. Cationic transition metal and main group metal alkyl complexes in olefin polymerisation
January 28	Dr S Rannard, Courtaulds Coatings (Coventry) The synthesis of dendrimers using highly selective chemical reactions
February 3	Dr J Beacham, ICI Technology The chemical industry in the 21st century
February 4	Professor P Fowler, Department of Chemistry, Exeter University Classical and non-classical fullerenes
February 11	Professor J Murphy, Dept of Chemistry, Strathclyde University
February 17	Dr S Topham, ICI Chemicals and Polymers Perception of environmental risk; The River Tees, two different rivers
February 18	Professor G Hancock, Oxford University Surprises in the photochemistry of tropospheric ozone
February 24	Professor R Ramage, University of Edinburgh The synthesis and folding of proteins
February 25	Dr C Jones, Swansea University Low coordination arsenic and antimony chemistry
March 4	Professor T C B McLeish, IRC of Polymer Science Technology, Leeds University The polymer physics of pyjama bottoms (or the novel rheological characterisation of long branching in entangled macromolecules)
March 11	Professor M J Cook, Dept of Chemistry, UEA How to make phthalocyanine films and what to do with them.
March 17	Professor V Rotello, University of Massachusetts, Amherst The interplay of recognition & redox processes - from flavoenzymes to devices
March 18	Dr J Evans, Oxford University Materials which contract on heating (from shrinking ceramics to bullet proof vests
October 7	Dr S Rimmer, Ctr Polymer, University of Lancaster New Polymer Colloids
October 9	Professor M F Hawthorne, Department Chemistry & Biochemistry, UCLA, USA RSC Endowed Lecture
October 21	Professor P Unwin, Department of Chemistry, Warwick University Dynamic Electrochemistry: Small is Beautiful

October 23 Professor J C Scaiano, Department of Chemistry, University of Ottawa, Canada
In Search of Hypervalent Free Radicals, RSC Endowed Lecture

October 26 Dr W Peirs, University of Calgary, Alberta, Canada
Reactions of the Highly Electrophilic Boranes HB(C6F5)2 and B(C6F5)3 with Zirconium and Tantalum Based Metallocenes

October 27 Professor A Unsworth, University of Durham
What's a joint like this doing in a nice girl like you?
In association with The North East Polymer Association

October 28 Professor J P S Badyal, Department of Chemistry, University of Durham
Tailoring Solid Surfaces, Inaugural Lecture

November 4 Dr N Kaltscoyannis, Department of Chemistry, UCL, London
Computational Adventures in d & f Element Chemistry

November 3 Dr C J Ludman, Chemistry Department, University of Durham
Bonfire night Lecture

November 10 Dr J S O Evans, Chemistry Department, University of Durham
Shrinking Materials

November 11 Dr M Wills, Department of Chemistry, University of Warwick
New Methodology for the Asymmetric Transfer Hydrogen of Ketones

November 12 Professor S Loeb, University of Windsor, Ontario, Canada
From Macrocycles to Metallo-Supramolecular Chemistry

November 17 Dr J McFarlane
Nothing but Sex and Sudden Death!

November 18 Dr R Cameron, Department of Materials Science & Metallurgy, Cambridge University
Biodegradable Polymers

November 24 Dr B G Davis, Department of Chemistry, University of Durham
Sugars and Enzymes

December 1 Professor N Billingham, University of Sussex
Plastics in the Environment - Boon or Bane
In association with The North East Polymer Association.

December 2 Dr M Jaspers, Department of Chemistry, University of Aberdeen
Bioactive Compounds Isolated from Marine Inverterates and Cyanobacteria

December 9 Dr M Smith Department. of Chemistry, Warwick University
Multinuclear solid-state magnetic resonance studies of nanocrystalline oxides and glasses

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January 19 Dr J Mann, University of Reading
The Elusive Magic Bullet and Attempts to find it?

January 20	Dr A Jones, Department of Chemistry, University of Edinburgh Luminescence of Large Molecules: from Conducting Polymers to Coral Reefs
January 27	Professor K Wade, Department of Chemistry, University of Durham Foresight or Hindsight? Some Borane Lessons and Loose Ends
February 3	Dr C Schofield, University of Oxford Studies on the Stereoelectronics of Enzyme Catalysis
February 9	Professor D J Cole-Hamilton, St. Andrews University Chemistry and the Future of life on Earth
February 10	Dr C Bain, University of Oxford Surfactant Adsorption and Marangoni Flow at Expanding Liquid Surfaces
February 17	Dr B Horrocks, Department of Chemistry, Newcastle University Microelectrode techniques for the Study of Enzymes and Nucleic Acids at Interfaces
February 23	Dr C Viney, Heriot-Watt Spiders, Slugs And Mutant Bugs
February 24	Dr. A-K Duhme, University of York Bioinorganic Aspects of Molybdenum Transport in Nitrogen-Fixing Bacteria
March 3	Professor B Gilbert, Department of Chemistry, University of York Biomolecular Damage by Free Radicals: New Insights through ESR Spectroscopy
March 9	Dr Michael Warhurst, Chemical Policy issues, Friends of the Earth Is the Chemical Industry Sustainable?
March 10	Dr A Harrison, Department of Chemistry, The University of Edinburgh Designing model magnetic materials
March 17	Dr J Robertson, University of Oxford Recent Developments in the Synthesis of Heterocyclic Natural Products
May 11	Dr John Sodeau, University of East Anglia Ozone Holes and Ozone Hills
May 12	Dr Duncan Bruce, Exeter University The Synthesis and Characterisation of Liquid-Crystalline Transition Metal Complexes

First Year Induction Courses

Advanced nuclear magnetic resonance spectroscopy	Dr. A. M. Kenwright
Advanced mass spectroscopy	Dr. M. Jones
Synthetic aspects of organotransition chemistry	Prof. D. Parker

Conferences Attended

RSC, Stereochemistry at Sheffield, University of Sheffield, December, 1996 to 1999

8th SCI Graduate Symposium, Novel Organic Chemistry, Aberdeen University, 10 April, 1997

21st Century Heterocyclic Chemistry, University of Sunderland, 7 May, 1997
RSC, Perkin division, 15th International Symposium, Synthesis in Organic Chemistry, St. Catherine's College, Oxford, 22-24 July, 1997

9th Scottish Graduate Symposium on Novel Organic Chemistry, Edinburgh University, 27 March, 1998

RSC, National Congress. University of Durham, 6-9 April, 1998

BOSS 7, Louvain-la-Neuve, Belgium, 5-9 July, 1998

10th Scottish Graduate Symposium on Novel Organic Chemistry, University of Glasgow, 26 March, 1999