# New routes to highly functionalised compounds from vinylcyclopropanes

# NEW ROUTES TO HIGHLY FUNCTIONALISED COMPOUNDS FROM VINYLCYCLOPROPANES

By

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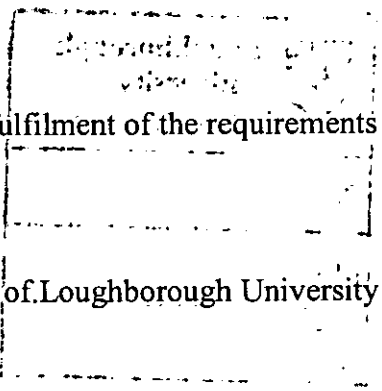
A Doctoral Thesis



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# Abstract

**Elisabeth J. Wyatt** **PhD**
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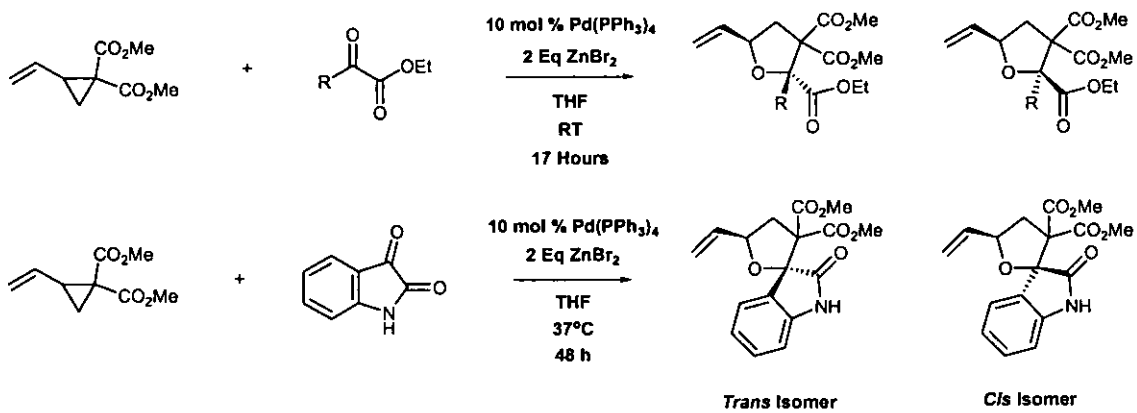
**New Routes to Highly Functionalised Heterocyclic Compounds From Vinylcyclopropanes**

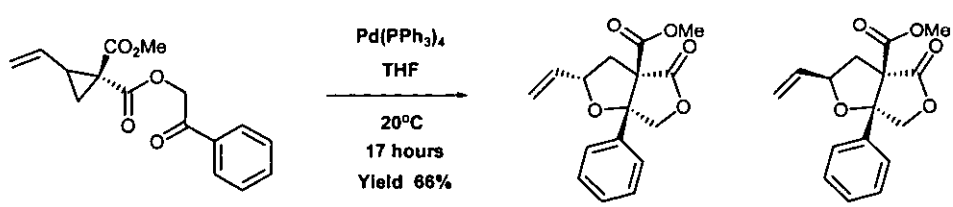
**Keywords: Palladium catalyzed [3+2] cycloaddition activated cyclopropanes and carbonyl moieties tetrahydrofurans.**

Studies towards the development of a novel methodology have been achieved. A palladium catalyzed [3 + 2] cycloaddition is described herein. Doubly activated vinylcyclopropanes have been ring opened with palladium (0) and the resulting zwitterionic π-allyl palladium species have participated in a nucleophilic addition with activated carbonyl moieties to construct tetrahydrofurans as a mixture of diastereoisomers. The palladium catalyzed [3 + 2] cycloaddition has shown to be successful with ketone moieties activated by an adjacent electron-withdrawing group such as ethyl esters in a range of α-keto esters, and amides in a range of substituted isatins (**scheme 1**). The reaction boasts good yields and the stereochemical preference of the reaction has shown to be dependant on the choice of reaction solvent.




**Scheme 1**

The reaction has shown to be successful on application to the intramolecular mode to form a bicyclic heterocycle (**scheme 2**).




**Scheme 2**

The methodology has been successfully incorporated towards the synthesis of the natural product monocerin.

# Table of Contents

# 2. Results and Discussion

# Acknowledgements

Firstly I would like to take this opportunity to thank my supervisor. A great big thank you goes to Dr Gareth Pritchard for his steady stream of patience, encouragement, guidance and support throughout my studies. Thank you for everything Gaz. I feel I have been very fortunate to work for you.

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Thank you to my family who have always supported me emotionally and financially; thank you, this is for you. Love you all.

# Abbreviations

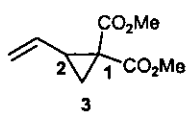
| | |
|---|---|
| $[\alpha]_D$ | specific rotation (degml/gdm) |
| Ac | acetyl |
| ACN | acetonitrile |
| ACP | alkylidenecyclopropanes |
| Approx | approximately |
| aq. | aqueous |
| Ar | aryl |
| Bn | benzyl |
| BOC | N-*tert*-butoxycarbonyl |
| br | broad |
| *n*BuLi | butyllithium |
| $^t$Bu | *tert*-butyl |
| cat. | catalytic |
| CI | chemical ionisation |
| conc. | concentration |
| Cp | cyclopentadienyl |
| CsOH | cesium hydroxide |
| d | doublet |
| D | deuterium (NMR spectroscopy) |
| dba | dibenzylideneacetone |
| DCCI | dicyclohexylcarbodiimide |
| DCE | dichloroethane |
| d.e. | diastereomeric excess |
| DEPT | distortionless enhancement by polarisation transfer |
| DIBAL | diisobutylaluminium hydride |
| DMAP | 4-(dimethylamino)pyridine |
| DME | dimethoxy ethane |
| DMF | *N*,*N*-dimethyl formamide |
| DMSO | dimethyl sulfoxide |

| | |
|---|---|
| DPPE | 1,2-bis(diphenylphosphino)ethane |
| EDCI | 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide |
| e.e. | enantiomeric excess |
| EI | electron ionisation |
| Eq | equivalent(s) |
| Et | ethyl |
| EtOAc | ethyl acetate |
| EtOH | ethanol |
| EWG | electron-withdrawing group |
| FAB | fast atom bombardment |
| HCl | hydrochloric acid |
| Het | heterocycle |
| HMPA | hexamethylphosphoramide |
| hr | hour |
| Hz | hertz |
| i | iso |
| IR | infra-red |
| L | ligand |
| LiOH | lithium hydroxide |
| liq. | Liquid |
| lit. | literature |
| *J* | coupling constant (NMR spectroscopy) |
| KOH | potassium hydroxide |
| LDA | lithium diisopropyl amide |
| LiOH | lithium hydroxide |
| *m* | *meta* |
| MCP | methylenecyclopropane |
| Me | methyl |
| MeOH | methanol |
| MgSO4 | magnesium sulfate |
| mins | minutes |
| mol. | Molecular |

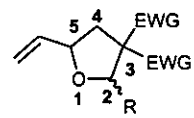
| | |
|---|---|
| m.p. | melting point |
| *m/z* | mass to charge ratio |
| NaOH | sodium hydroxide |
| $NaHCO_3$ | saturated sodium bicarbonate |
| $Na_2SO_4$ | sodium sulfate |
| $Na_2S_2O_3$ | sodium thiosulfate |
| $NH_4Cl$ | ammonium chloride |
| NMR | nuclear magnetic resonance |
| nOe | nuclear Overhauser effect |
| *o* | *ortho* |
| *p* | *para* |
| P.E. 40-60 | petrol ether (40-60) |
| Ph | phenyl |
| q | quartet |
| RDS | rate determining step |
| $R_f$ | retention factor |
| RT | room temperature |
| s | strong (ir spectroscopy) or singlet (NMR spectroscopy) |
| $S_N2$ | bimolecular nucleophilic substitution |
| str | stretch |
| t | triplet |
| TBAF | tetrabutylammonium fluoride |
| Temp. | temperature |
| *tert* | tertiary |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| TLC | thin layer chromatography |
| TMS | trimethylsilyl |
| $ZnBr_2$ | zinc bromide |
| w | weak |

# Compound Numbering

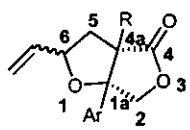
**Vinylcyclopropanes**




**Tetrahydrofurans**




**Fused Bicyclic Heterocycles**




**NMR Assignment**

Where a mixture of diastereoisomers is isolated:

- The carbons for the *trans*-isomer will be represented as C

- The carbons for the *cis*-isomer will be represented as C'

# 1. Introduction

## 1.1 Transition Metal Assisted Cycloadditions

A major focus of research activity in organic chemistry is the discovery and the development of new chemical reactions. The development of new strategies for the synthesis of molecules with interesting molecular architectures is a high priority for organic chemists. Reactions addressing the issues of stereo and enantiomeric control and are compatible with a variety of functional groups are found to have the broadest applicability in organic chemistry. Reactions constructing multiple bonds, rings and/or stereocentres are particularly important tools for the organic chemist and of the methods currently available, cycloaddition reactions reserve a prominent and powerful position.[1]

Cycloaddition reactions can be activated by various external factors such as light, heat, Lewis acids, high pressure or sonication and the presence of polarized functional groups in the substrate are often encouraged to facilitate the transformation.[1] Metal catalysts provide new opportunities for selective cycloaddition reactions via complexation or reaction of the metal to an olefin, which in turn significally modifies and improves its reactivity of this moiety, opening the way for improved reactivity and novel chemistry.

Retrosynthetically, the Diels-Alder reaction[2] and Robinson annelation[3] can be employed for the crucial carbon-carbon bond construction of six membered rings. Complex organic molecules can efficiently be constructed from relatively simple building blocks in one pot.

This summary will detail some of the recent approaches to five membered carbocycles and heterocycles using cycloaddition strategies, employing the use of transition metal catalysts, mainly palladium. A complete overview of transition metal catalyzed heterocyclic synthesis has recently been reported by Itaru Nakamura and Yoshinori Yamamoto.[4]

# 1.2 Palladium Catalyzed [3 + 2] Cycloaddition Reactions Using Methylenecyclopropane

## 1.2.1 Synthesis of Methylenecyclopentanes

Methylenecyclopropanes, **2**, are now accepted as being very versatile building blocks for organic synthesis. Despite being a highly strained carbocyclic ring,[5] they are stable at ambient temperatures and are even present in some naturally occurring compounds for example hypoglycin A (**figure 1**).[6]

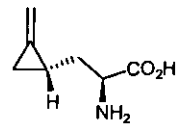



**Figure 1**

The exocyclic double bond enforces additional strain on the three membered ring, which is apparent in the lengthening of the C(2)-C(3) bond (when compared to cyclopropane **1**) to 1.5415(3) A, and an increase of the C(2)-C(1)-C(3) angle to 63.9° (**figure 2**). [7]

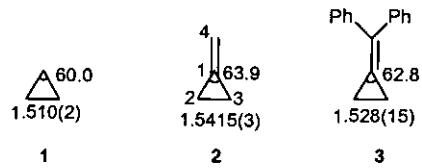


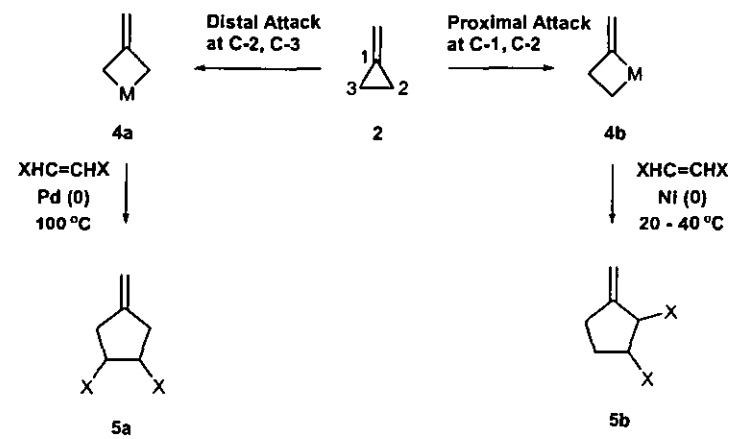

**Figure 2**

Methylenecyclopropanes participate in reactions, that are characteristic of reactive olefins, for example electrophilic additions,[8] radical additions,[9] additions of carbenes and nitrenes[10] and various types of cycloadditions initiated thermally[11] or in the

presence of strongly electron withdrawing subsituents.[12] Cycloaddition reactions involving methylenecyclopropanes are of great interest to the organic chemist as they construct two new C-X bonds (X = C, N, O). They can be achieved using relatively mild conditions, in good yields by employing the use of a suitable transition metal such as $Pd^0$ and $Ni^0$.

Initial studies in this field, were carried out independently by Noyori and Binger.[13, 14]

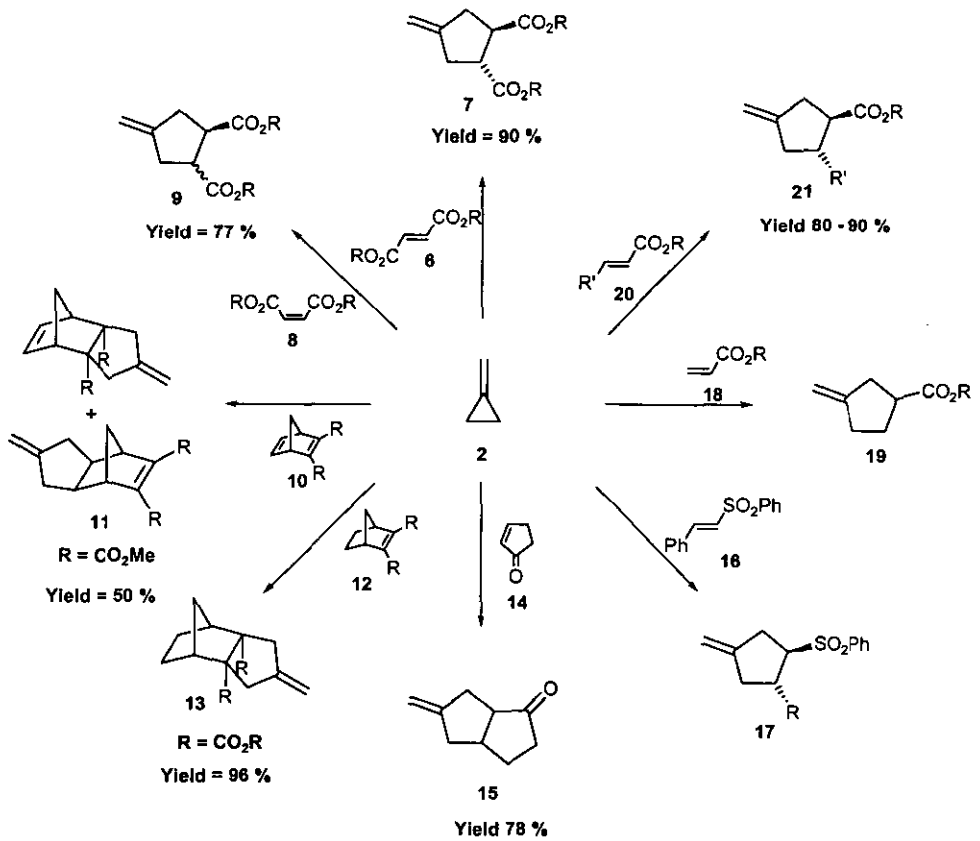
There are two reaction pathways in which a metal-catalyzed cycloaddition between methylenecyclopropane **2** and a double bond can proceed to afford regioisomeric products (**scheme 1**).[13] The transition metal can oxidatively insert into the distal bond, C-2, C-3 to afford metallocyclobutane **4a**. Subsequent carbometalation onto the double bond and reductive elimination results in the cyclopentane **5a** being formed in which the $C_2$ unit has been introduced in the distal position to the exocyclic double bond. Alternatively, proximal bond cleavage between C-1 and C-3 leads to the isomeric metallacyclobutane **4b** and subsequently the isolation of the cyclopentane **5b** where the $C_2$ unit has been introduced in the proximal position to the exocyclic double bond. The formalistic mechanism is detailed in **scheme 1**.[7]




**Scheme 1**

Both the regio-isomeric cyclopentanes **5a** and **5b** can be isolated in the presence of Ni (0) catalysts whereas for the reaction catalyzed by palladium (0), the distal bond is exclusively cleaved leading to cycloadducts of type **5a**. [14]

Binger and co-workers, following work described for nickel catalysis[13, 15] in the early 1980s reported that palladium catalyzed cycloadditions between methylenecyclopropane and some electron deficient alkenes were highly successful **(scheme 2)**.[16, 7]



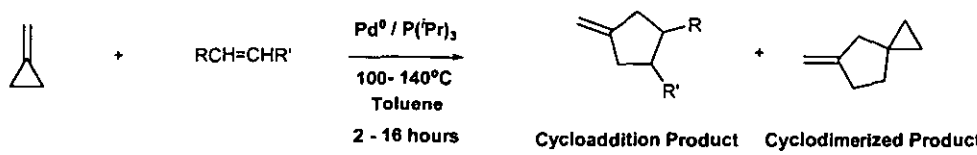

**Reagents and Conditions**

**(i) 1 mmol $Pd_2(dba)_3$/ 1 mmol $P(^iPr)_3$, toluene, 100 - 140°C, 2 - 16 hours.**

**Scheme 2**

Binger stipulated that the cyclization reaction between dialkyl fumarate **6** occurred selectively at the distal position and the addition of the (*E*)-olefin was highly stereoselective, whereas the reaction with dialkyl maleate **8** resulted in a scrambling of stereochemistry. It is believed that the addition of the (*Z*)-olefin was accompanied by a metal-catalyzed (*Z*) to (*E*) isomerization of the starting olefin, hence a mixture of *cis* / *trans* stereoisomers was isolated. The cycloaddition reaction with 2,3-dimethoxycarbonylnorbornadiene **10** was reported to be highly stereoselective with only the exo-isomer being isolated. The cycloaddition of methylenecyclopropane with 2-cycloalkenones was only successful with 2-cyclopentenone **14** affording **15**.[7, 16] Again the cycloaddition using the co-substrate vinylsulphones **16** was restricted to *trans*-2-phenylvinyl-phenylsulphone to give **17**. It was rationalized that other vinylsulphones had too strong a binding affinity with the metal, preventing any further reaction between the metal and methylenecyclopropane. Alkyl acrylates **20** were proven to be a good substrate for the cycloaddition with methylenecyclopropane **2**.

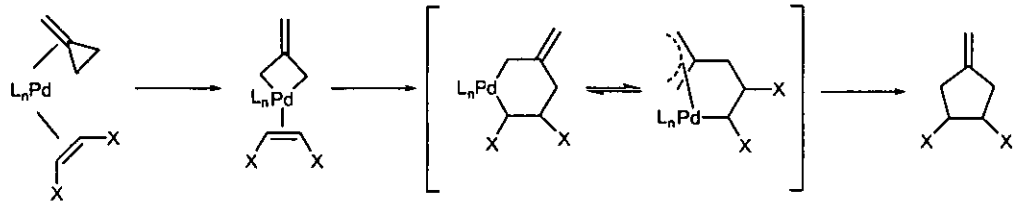
Binger was then able to conclude that these cycloaddition reactions were dependant on the degree of π-bond strength of the electron deficient olefins to the palladium. Alkenes that are able to complex strongly may hinder the metal from further interactions with the methylenecyclopropane, such as maleic anhydride, acrolein and acrylonitrile.[7, 16] Conversely, alkenes that bind to the metal too loosely may result in cyclodimerization of the methylenecyclopropane as opposed to cycloaddition (**scheme 3**).




**Scheme 3**

Binger and co-workers proposed that the mechanism in operation involved pre-coordination of both the olefin and the exocyclic double bond of the methylenecyclopropane to the metal **22a**. This in turn initiated distal ring opening by

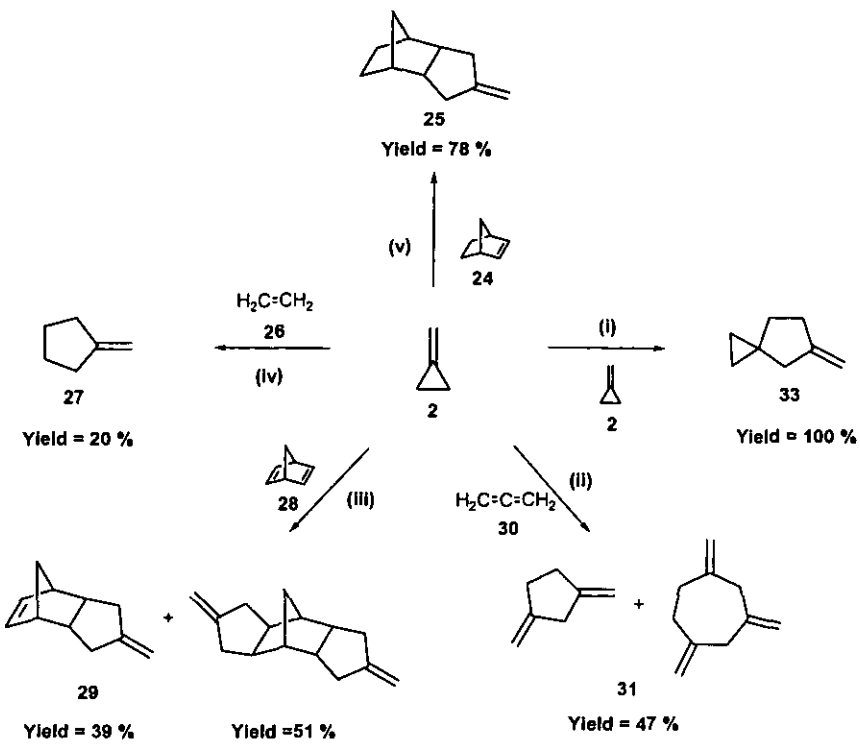
oxidative addition of the palladium into the cyclopropyl σ-bond **22b**. It was then postulated that the σ-allyl complex **22c** was in rapid equilibrium with the isomeric σ-allyl complex **22d** (**scheme 4**) and on reductive elimination of the palladium, the desired cyclopentane was isolated.




**22a** **22b** **22c** **22d** **23**

**Scheme 4**

Binger and co-workers went on to attempt the cyclization with non-activated alkenes (**scheme 5**).[16] This was due to the surprising success of the cyclization with 2,3-dimethoxycarbonylnorbornadiene **10** with methylenecyclopropane **2**.




**Reagents and Conditions**

(i) 1 mmol $Pd_2(dba)_3$ / 1 mmol $P(^iPr)_3$, benzene, 80°C, 42 hours
(ii) 1 mmol $Pd_2(dba)_3$ / 1 mmol $P(^iPr)_3$, benzene, 115°C, 20 hours
(iii) 1 mmol $Pd_2(dba)_3$ / 1 mmol $P(^iPr)_3$, benzene, 100°C, 2 hours
(iv) 1 mmol $Pd_2(dba)_3$ / 1 mmol $P(^iPr)_3$ / 2 mmol $Et_2AlOEt$, benzene, 100°C, 3 hours
(v) 1 mmol $Pd_2(dba)_3$ / 1 mmol $P(^iPr)_3$, benzene, 100°C, 4 hours

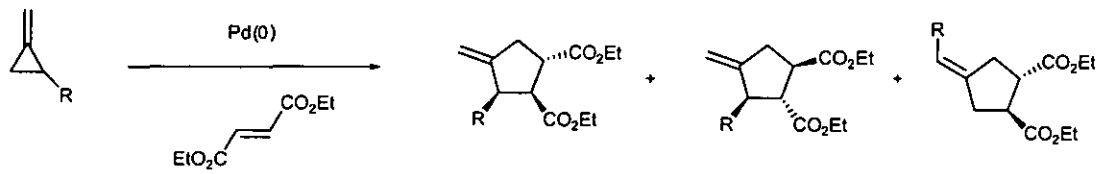
**Scheme 5**

Norbornene **24**, ethylene **26**, norbornadiene **28**, and allene **30** and methylenecyclopropane **2** were successfully cyclized in the presence of $Pd_2(dba)_3/P(^iPr)_3$ (**scheme 5**). Again these alkenes were not too strongly complexed to the metal to prevent further interaction of the metal with methylenecyclopropane **2**, but are not so weakly bound that cyclodimerization of the methylenecyclopropane is faster than cycloaddition of the two substrates.

### 1.2.2 Synthesis of Substituted Methylenecyclopentanes and Alkylidenecyclopentanes

The use of substituted methylenecyclopropanes (ring substitution) and alkylidenecyclopropanes (exocyclic double bond substitution) was a natural progression from the work described previously.[17] It was hoped that substitution, both on the ring and the exocyclic double bond, would reduce the reactivity of the double bond and hence slow down the competing metal catalyzed cyclodimerization, and in turn make the [3 + 2] cycloaddition path more favourable.

For the substituted methylenecyclopropanes, the isolation of regioisomers complicated the issue (**scheme 6**).

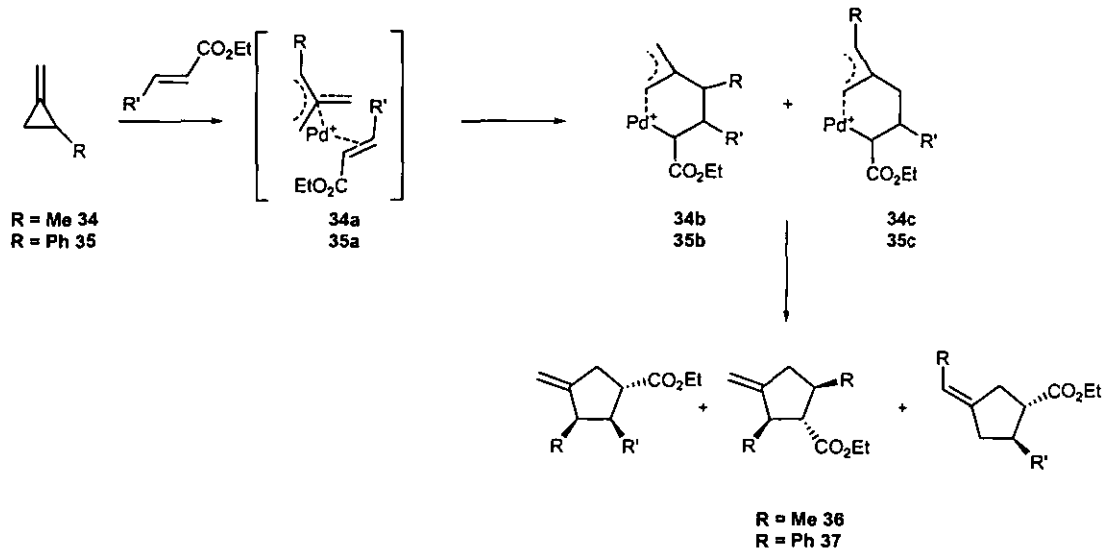



| | | | | | | |
|---|---|---|---|---|---|---|
| R = Me 34 | R = Me, 36, yield = 83 % | 1.7 | : | 1 | : | 4 |
| R = Ph 35 | R = Ph, 37, yield = 85 % | 1 | : | 1.2 | : | 5.5 |

**Scheme 6**

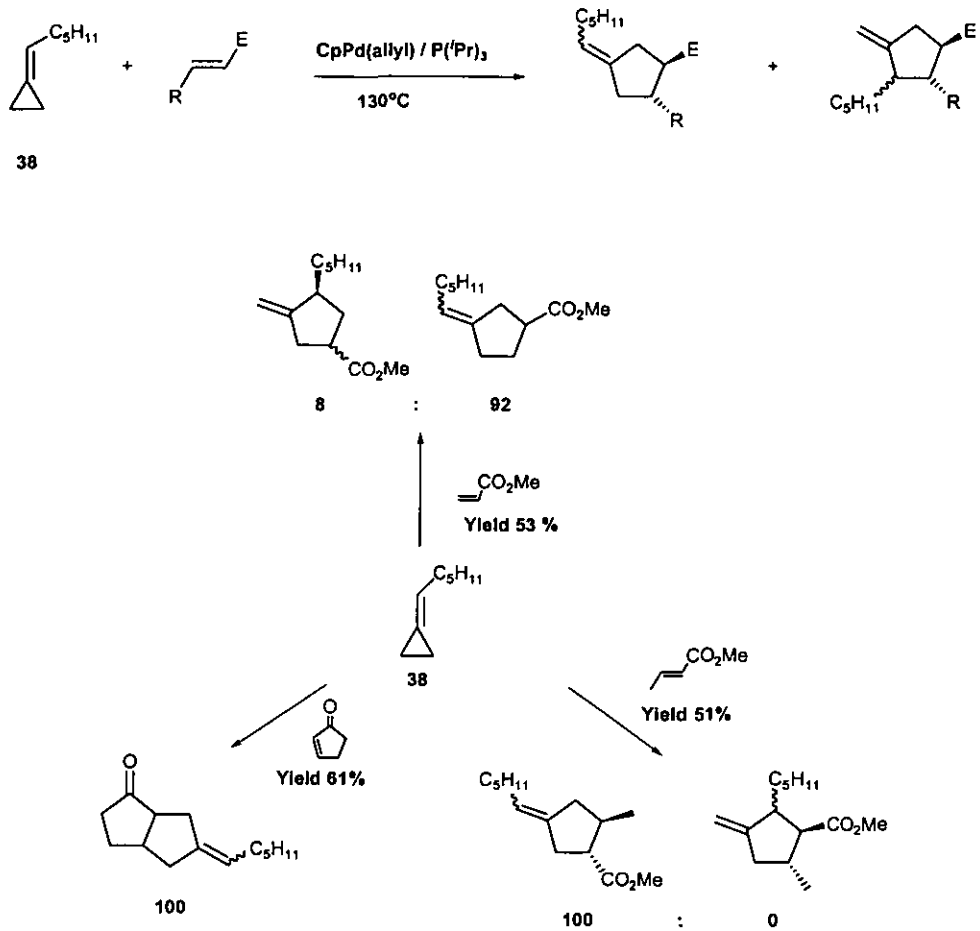
Again palladium oxidatively inserts into the distal bond of the substituted methylenecyclopropane **34** and co-ordinates to the olefin. It was then believed that the isomerization occurred in the metal complex intermediate **34a** to afford the

regioisomers **34b** and **34c**, and on reductive elimination the mixture of regioisomers **36** was isolated (**scheme 7**).



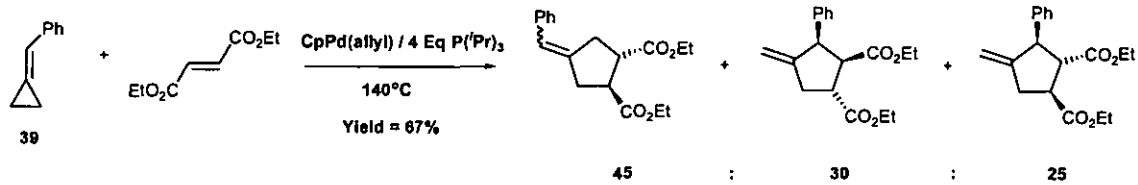

**Scheme 7**

Binger and co-workers went on to report that the methylenecyclopropanes substituted at the exo-double bond gave more promising results than for the unsubstituted methylenecyclopropanes. The substitution at this position did in fact relieve the distal ring opening and hence reduced the cyclodimerization of the methylenecyclopropane. With the change of reactivity of the cyclopropane now available, milder reaction conditions could now be employed and co-substrates that were previously unsuccessful with the parent unsubstituted methylenecyclopropane could now be successfully cyclized.[18,19] Binger did note that when using triisopropylphosphane/ Pd(0) as the catalyst, the alkyldienecyclopentanes were formed almost exclusively. The successful cycloadditions with hexylidenecyclopropane **38** and electron deficient alkenes are described below (**scheme 8**).



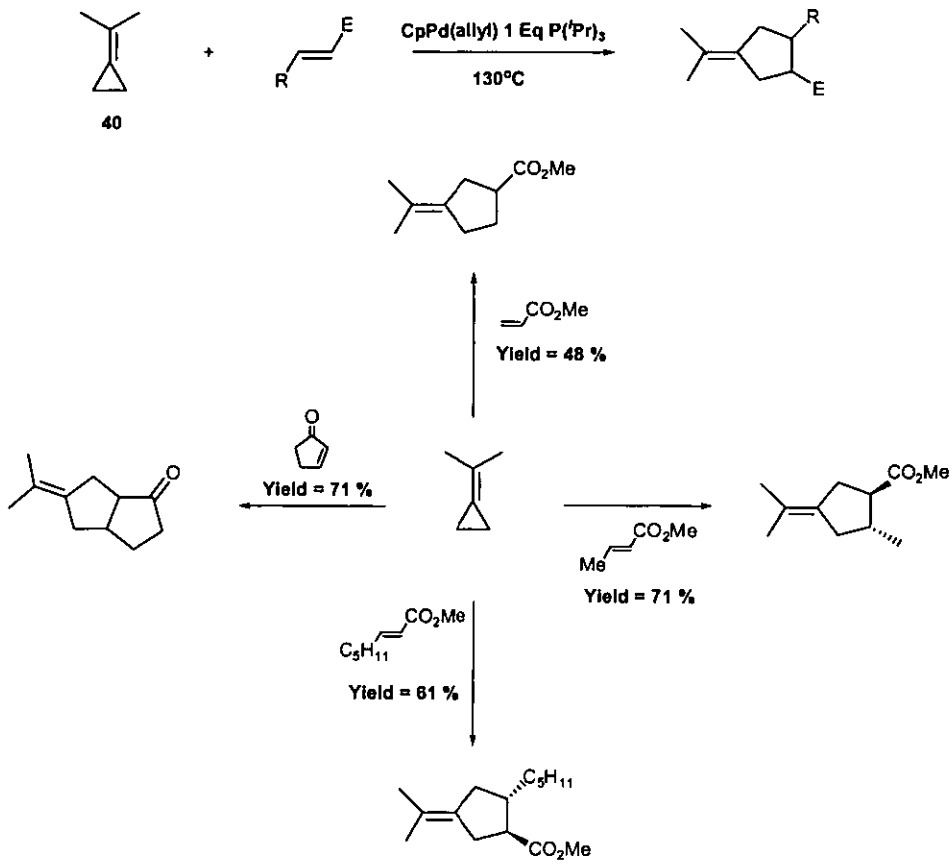

**Scheme 8**

Only one example of the successful cyclization of (phenylmethylene)cyclopropane **39** with an electron deficient olefin was reported (**scheme 9**). [18]



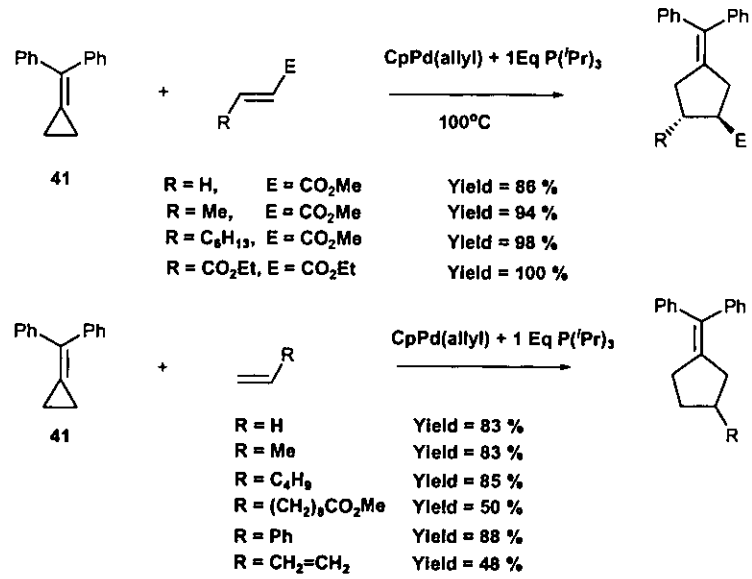

**Scheme 9**

The successful cyclizations using isopropylidenecyclopropane **40** and electron deficient olefins have also been described (**scheme 10**). [18]




**Scheme 10**

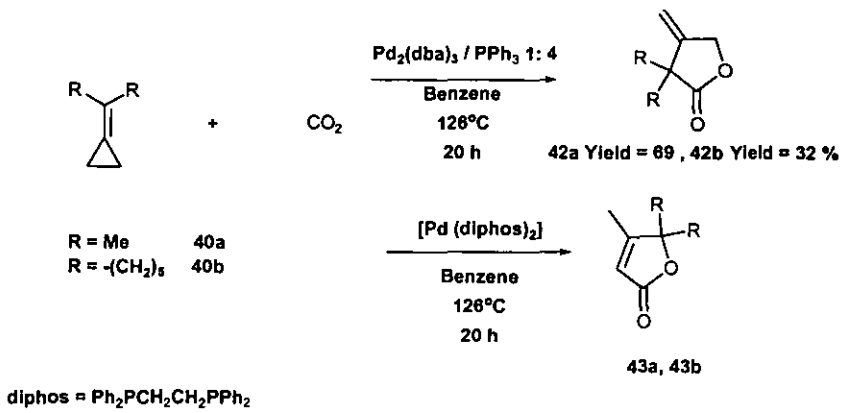
The following details the results obtained for the [3 + 2] cycloaddition between (diphenylmethylene)cyclopropane **41** and electron deficient olefins (**scheme 11**).




**Scheme 11**

### 1.2.3 Synthesis of Substituted Heterocycles.[7, 20, 21]

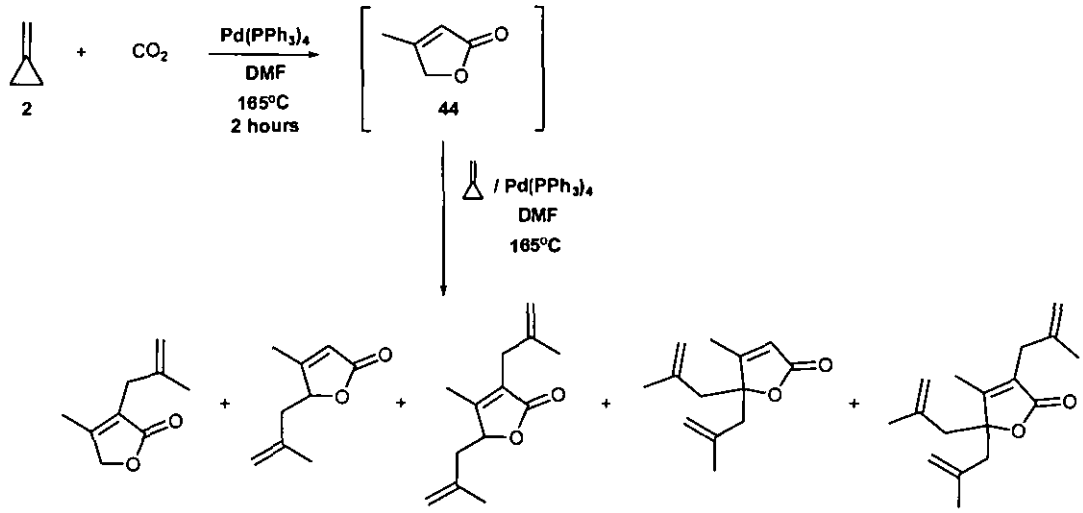
The work in this area was established by Inoue and co-workers. They reported the opening of methylenecyclopropane **2** with carbon dioxide under palladium catalyzed conditions to give five membered lactones (**scheme 12**).[22]




**Scheme 12**

They subjected isopropylidenecyclopropane **40a** and the cyclopropane **40b** to high pressures of carbon dioxide to afford the desired lactones. They found that the regioselectivity of the reaction could be manipulated by the choice of palladium ligand. The basicity of the phosphine ligand appeared to be the determining factor as to which regioisomer was isolated. A less basic phosphine ligand such as $PPh_3$, afforded the isomers **42a** and **b** as opposed to **43a** and **b**.

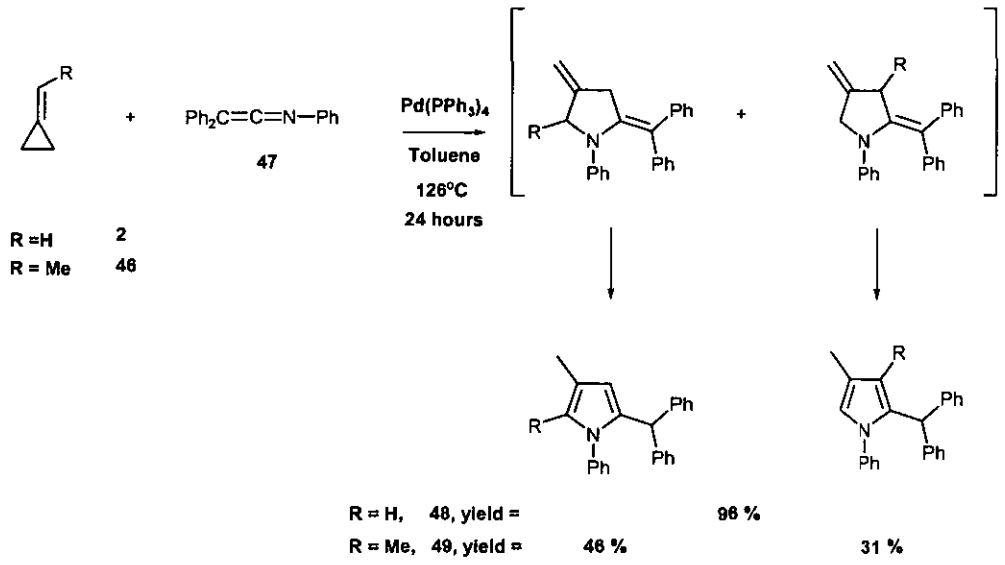
Further studies, in this area were completed by Binger and co-workers. They reported difficulties encountered for the cycloaddition of unsubstituted methylenecyclopropanes and carbon dioxide due to the co-oligomerization of the resulting butenolides cycloadduct and further methylenecyclopropane (**scheme 13**).




**Scheme 13**

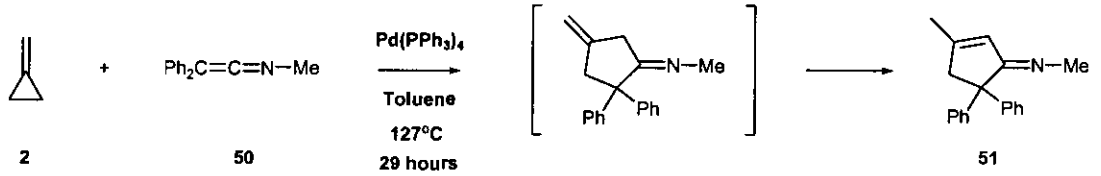
The isolation of the co-oligomers described in **scheme 13** was a problem for this methodology and was attributed to the presence of acidic protons in the butenolid **44** and hence on its formation, further reaction with methylenecyclopropane occurred. This problem was tackled by employing ($\eta^3$-allyl)-($\eta^5$-cyclopentadienyl)Pd/$PPh_3$ catalyst, DMF as a solvent at a temperature of 165°C under 40 bar of carbon dioxide.[23] Nevertheless, the formation of the co-oligomers was a major deterrent for this reaction to have a useful application in organic synthesis.

Binger and co-workers also described their work on palladium [3 + 2] cycloadditions between substituted methylenecyclopropanes and the double bond of the triphenylketeneimine **47** to afford substituted pyrrolines **48** and **49** (**scheme 14**). [24]




**Scheme 14**

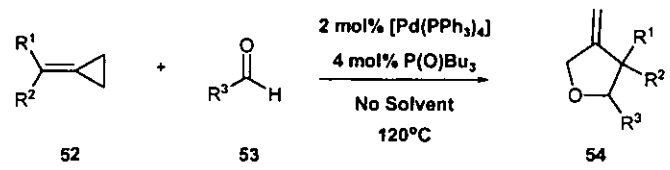
It seems that this cyclization is limited to this type of keteneimine. On switching the keteneimine to the more reactive diphenylketene-*N*-methylimine **50**, the cycloaddition occurred at the carbon carbon double bond to afford the cyclopentane **51 (scheme 15)**.




**Scheme 15**

Recently there has been a great deal of interest in this area. Yamamoto and co-workers have described in detail their work on a novel and elegant route into methylenetetrahydrofuran and methylenepyrrolidine skeletons employing an intermolecular [3 + 2] palladium catalyzed cycloaddition strategy. [25]

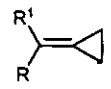
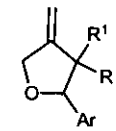
Yamamoto reported that alkylidenecyclopropanes **52** participate in a palladium catalyzed [3 + 2] cycloaddition with the carbon-oxygen double bond of an aldehyde **53** to afford the desired substituted methylenetetrahydrofurans, **54 (scheme 16)**. [25]




**Scheme 16**

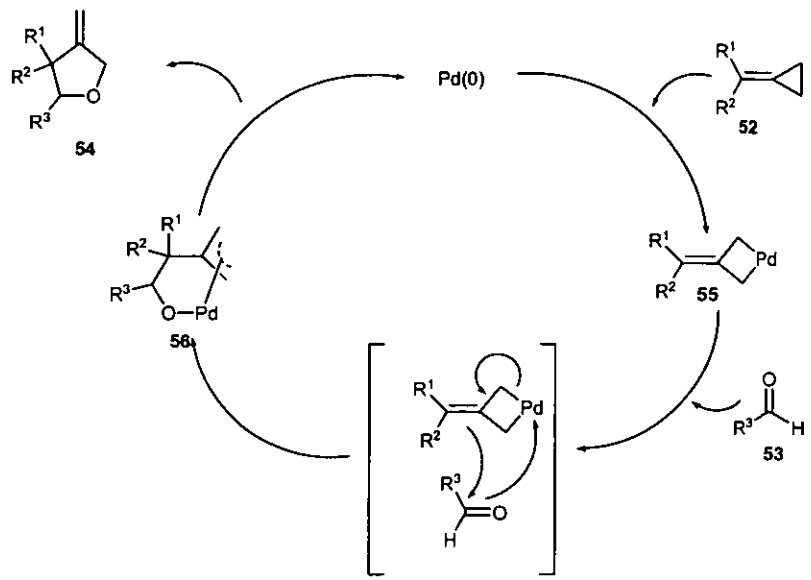
The scope and diversity of this reaction is demonstrated by the large range of alkylidenecyclopropanes and aldehydes successfully cyclized to afford the corresponding [3 + 2] cycloadducts (**Table 1**).

**Table 1**

| Entry | ACP  **52** | Aldehyde  **53** | Time (hours) | Product 54 (% Yield)  |
|---|---|---|---|---|
| **1** | R = R[1]=*n*Bu | Ar = 2-Furyl | 5 | 75 |
| **2** | R = R[1]=*n*Bu | Ar = (5-Me)-2-Furyl | 6 | 65 |
| **3** | R = R[1]=*n*Bu | Ar = 3-Furyl | 12 | 51 |
| **4** | R = R[1]=*n*Bu | Ar = 2-Thienyl | 19 | 64 |
| **5** | R = R[1]=*n*Bu | Ar = (3,4-$OCH_2O$)$C_6H_3$ | 19 | 43 |
| **6** | R = R[1]=*n*Bu | Ar = *p*-$MeOC_6H_4$ | 32 | 38 |
| **7** | R = R[1]=*n*Hex | Ar = 2-Furyl | 11 | 71 |
| **8** | R-R=$(CH_2)_5$ | Ar = (5-Me)-2-Furyl | 20 | 77 |
| **9** | R = $CH_2CH_2Ph$ | Ar = 2-Furyl | | 86 |
| | R[1] = Me | | 16 | (1.1 : 1) |
| **10** | R = $CH_2CH_2Ph$ | Ar = 2-Furyl | | 42 |
| | R[1] = H | | 20 | (1.1 : 1) |

Reagents and conditions: (0.5 mmol) **52** with (1. 5mmol) **53** was carried out in the presence of 2 mol % $Pd(PPh_3)_4$ and 4 mol % tributylphosphane oxide without solvent at 120°C.

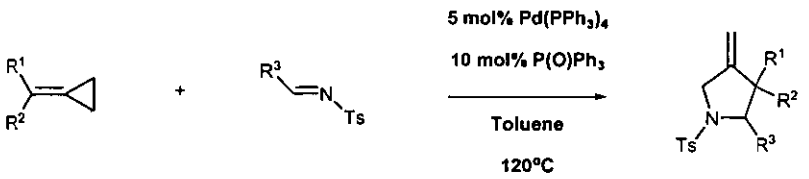
The cyclization reactions were carried out in the presence of 2 mol % $Pd(PPh_3)_4$ and 4 mol % of tributylphosphane oxide at 120°C in the absence of solvent. On addition of the solvent, THF, there was a dramatic decrease in yield observed and the reaction did not occur in the absence of the palladium. The reaction did not boast good diastereoselectivity (1.1 : 1) for unsymmetrically substituted alkylidenecyclopropanes (entries **9** and **10** in **table 1**). They report that substitution on the cyclopropyl ring was detrimental to the successful reaction course and a decrease in yield of the desired cycloadduct was observed on inclusion of an electron-donating group. The reaction mechanism is postulated to follow that described in **scheme 17**.




**Scheme 17**

Initially palladium oxidatively inserts into the distal bond of the alkylidenecyclopropanes **52**, affording the palladacyclobutane complex **55**. The palladacyclobutane in turn undergoes a [3 + 2] pallada-ene type cyclization with the aldehyde, **53**, to form the π-allylpalladium complex, **56**. The desired methylenetetrahydrofuran, **54**, is isolated on reductive elimination of the palladium.

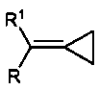
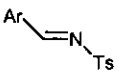
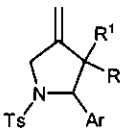
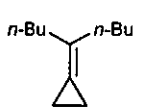
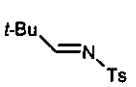
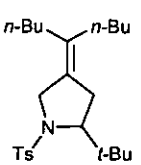
Yamamoto and co-workers went on to publish their studies of palladium catalyzed [3 + 2] cycloadditions between methylenecyclopropanes, **52**, and the carbon-nitrogen double bonds of *N*-tosylimines, **57**, to afford substituted *N*-tosylpyrrolidine cycloadducts, **58 (scheme 18)**. [26, 27]




52 57 58

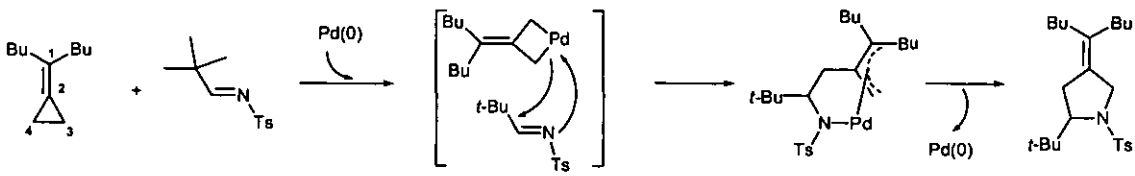
**Scheme 18**

**Table 2**

| Entry | ACP  52 | N-Tosylimine  57 | Time (hours) | Product 58 (% Yield)  |
|---|---|---|---|---|
| 1 | R = R[1]=*n*Bu | Ar = 2-Furyl | 16 | 89 |
| 2 | R = R[1]=*n*Bu | Ar = 2-Thienyl | 17 | 91 |
| 3 | R = R[1]=*n*Bu | Ar = 3-(3,4-$OCH_2O)C_6H_3$ | 16 | 93 |
| 4 | R = R[1]=*n*Bu | Ar = *p*-$MeC_6H_4$ | 12 | 91 |
| 5 | R = R[1]=*n*Bu | Ar = *p*-$MeOC_6H_4$ | 9 | 94 |
| 6 | R = R[1]=*n*Bu | Ar = *p*- $F_3CC_6H_4$ | 24 | 88 |
| 7 | R = R[1]=*n*Hex | Ar = 2-Furyl | 18 | 88 |
| 8 | R-R=$(CH_2)_5$ | Ar = 2-Furyl | 20 | 71 |
| 9 | R = $CH_2CH_2Ph$ R' = Me | Ar = 2-Furyl | 13 | 91 |
| 10 |  |  | 72 |  57 |

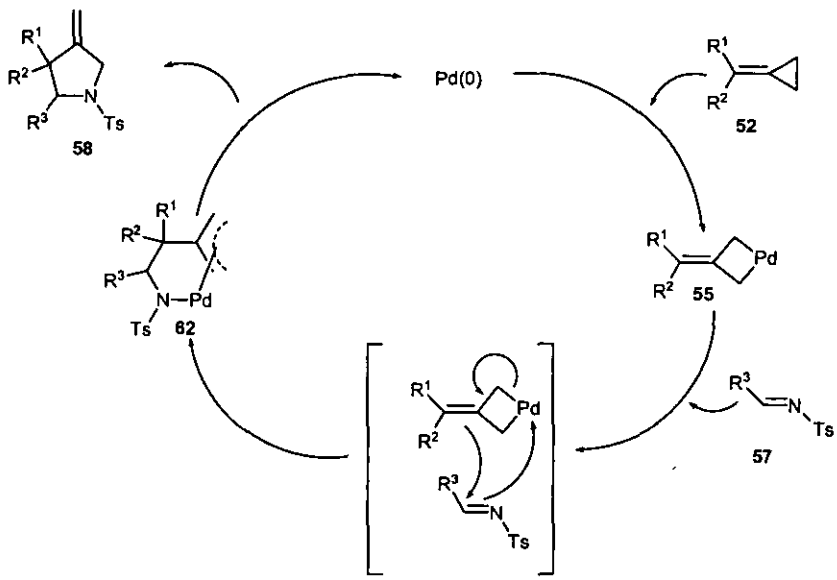
Reagents and conditions: (0.5 mmol) **52** with (0. 5mmol) **57** was carried out in the presence of 5 mol % $Pd(PPh_3)_4$ and 10 mol % triphenylphosphine oxide in toluene at 120°C.

The reactions were carried out in the presence of 5 mol% $Pd(PPh_3)_4$ and 10 mol% triphenylphosphine oxide at 120°C in toluene. The novel methodology boasts excellent yields and excellent regiochemical control. On switching to other solvents such as THF, DMF, dioxane and acetonitrile a reduction in the yield was noted and the reaction did not occur in DCM. The reaction was attempted in the absence of the palladium catalyst, and was found to fail. The cyclization with nonsymmetric substrates (entry 9 in **table 2**) was non-selective. The reaction with *t*-butyl-*N*-tosylimine, **60**, (entry 10 in **table 2**) afforded the [3 + 2] cycloadduct, **61**, showing differing regiochemical preference. In this instance the three carbon component is derived from the C-2,3,4 carbons of the cyclopropyl ring, as opposed to the C-1,2,3 cyclopropyl carbon component for the other cyclizations illustrated (**scheme 19**). A possible rationale could be that the steric demands of the tertiary butyl group force attack from the α- carbon rather than the γ-carbon of the intermediate.



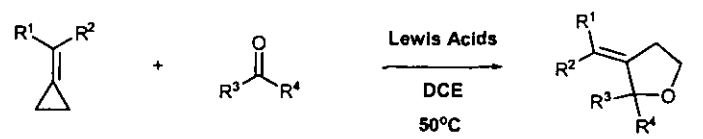

**Scheme 19**

The mechanism for the formation of the cycloadducts is similar to that reported for cycloaddition with aldehydes. Palladium oxidatively inserts into the alkylidene cyclopropyl distal bond. This gives rise to the palladacyclobutane complex **55**, which in turn reacts with the imine **57** to give the π-allylpalladium complex **62**. On reductive elimination of the palladium the desired methylenepyrrolidine is formed **58** (**scheme 20**).




**Scheme 20**

Recently Shi and co-workers have reported a new approach to tetrahydrofuran skeletons using Lewis acid catalysis, starting from methylenecyclopropanes and activated aldehydes and ketones such as diethylketomalonate and ethyl glyoxylate (**scheme 21**). [28]




52 63 64

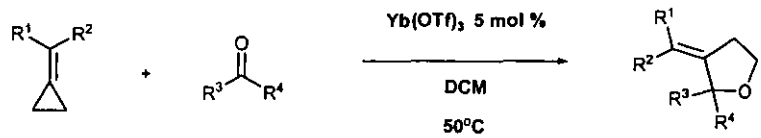
Yields 48 - 86 %

$R^3$ and/ or $R^4$ C(O)OEt

Lewis acids = $Sn(OTf)_2$, $Yb(OTf)_3$, $BF_3.Et_2O$

**Scheme 21**

They reported that the reaction was not successful in the absence of the Lewis acid catalyst. After a screening of Lewis acids available they reported that the optimum Lewis acid was $Yb(OTf)_3$ and chlorinated solvents, DCM and DCE, were the solvents of choice as the reaction did not proceed in polar solvents such as THF, DMF or $CH_3CN$.

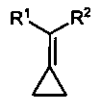
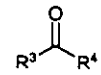
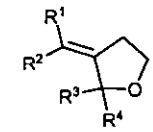



52 63 64

**Scheme 22**

The different methylenecyclopropanes used for cyclization with ethyl glyoxylate and diethyl ketomalonate are listed in **table 3**.

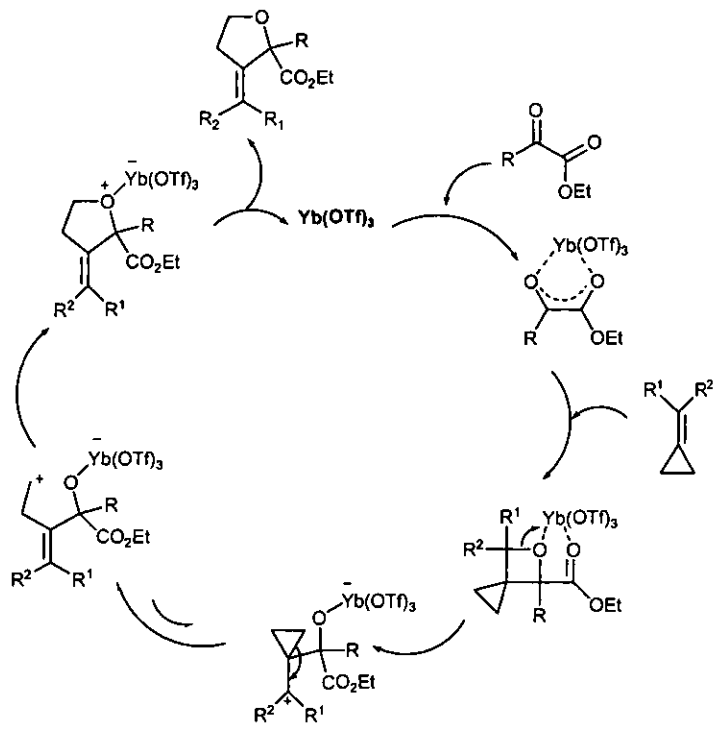
Table 3

| Entry | $R^1$ / $R^2$  52 | $R^3$ / $R^4$  63 | Time (hours) / Temp °C | Yield 64(%) (*E*/*Z*)  |
|---|---|---|---|---|
| 1 | $C_6H_5$ / $C_6H_5$ | $CO_2Et$ / $CO_2Et$ | 24 / 40 | 84 |
| 2 | $C_6H_5$ / *p*-$ClC_6H_4$ | $CO_2Et$ / $CO_2Et$ | 48 / 70 | 51 (1 : 1) |
| 3 | *p*-$MeC_6H_4$ / *p*-$MeC_6H_4$ | $CO_2Et$ / $CO_2Et$ | 18 / 40 | 86 |
| 4 | *p*-$MeOC_6H_4$ / *p*-$MeOC_6H_4$ | $CO_2Et$ / $CO_2Et$ | 2 / RT | 75 |
| 5 | *p*-$MeOC_6H_4$ / H | $CO_2Et$ / $CO_2Et$ | 24 / RT | 48 (11 : 1) |
| 6 | *m*-$C_6H_5OC_6H_4$ / H | $CO_2Et$ / $CO_2Et$ | 24 / RT | 56 (6.1 :1) |
| 7 | *p*-$ClC_6H_4$ / $C_6H_5$ | $CO_2Et$ / $CO_2Et$ | 24 / 70 | 65 (1 : 1) |
| 8 | *p*-$ClC_6H_4$ / *p*-$ClC_6H_4$ | $CO_2Et$ / $CO_2Et$ | 24 / 90 | 54 |
| 9 | $C_6H_5$ / $C_6H_5$ | $CO_2Et$ / H | 48 / RT | 48 |
| 10 | *p*-$MeC_6H_4$ / *p*-$MeC_6H_4$ | $CO_2Et$ / H | 48 / RT | 52 |
| 11 | *p*-$MeOC_6H_4$ / *p*-$MeOC_6H_4$ | $CO_2Et$ / H | 2 / RT | 54 |

Reagents and Conditions : (0.5 mmol) **52** with (0.6 mmol) **63** in the presence of $Yb(OTf)_3$ (5 mol %) using 1,2-dichloroethane (DCE) as solvent

They observe that on introduction of an electron-withdrawing halogen, a decrease in yield is observed and longer reaction times are needed. Conversely, on introduction of an electron-donating substituent, the yields of isolated products were good in a shorter time. It is proposed that electron-withdrawing groups increase the electrophilicity of the substrate and hence increased yields are observed. Conversely electron-donating groups decrease the electrophilicity of the substrate.

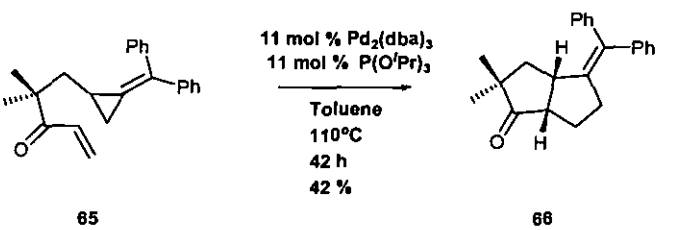
The mechanism that Shi and co-workers proposed for this Lewis acid catalysed [3 + 2] cycloaddition is shown in **scheme 23**.




**Scheme 23**

### 1.2.4 Intramolecular [3 + 2] Cycloadditions[29]

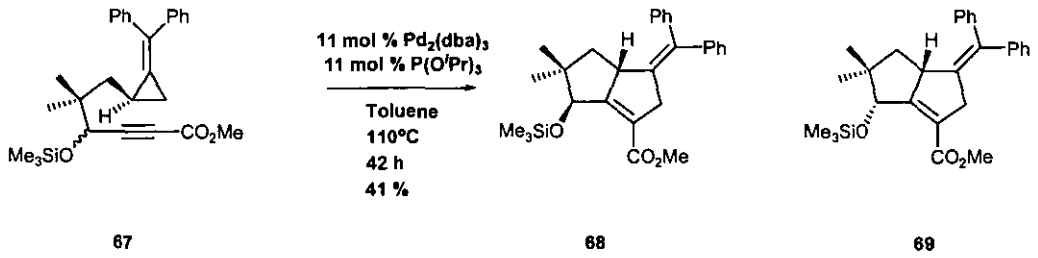
The intramolecular palladium catalyzed cycloaddition reaction was independently established in the late eighties by Motherwell[30,31] and Nakamura.[32] It was thought that the intramolecular variant of the transition metal catalyzed cycloaddition of diphenylmethylene cyclopropanes to electron deficient olefinic and acetylenic acceptors could be used to control the regioselectivity of the reaction and to minimize the problems of competing codimerization, rearrangement and ring opening of cyclopropanes observed in the intermolecular mode.[30] Motherwell went on to describe their studies on the intramolecular [3 + 2] cycloadditions of diphenylmethylenecyclopropane linked by an olefinic and acetylenic, three carbon tether affording bicyclo[3.3.0] octanes (**scheme 24**).




65 66

**Scheme 24**

The enone, **65**, was treated with $Pd_2(dba)_3$ and underwent a kinetically favoured 5-exo-trig cyclization to afford the desired *cis*-fused bicyclic adduct, **66**. Diphenylmethylenecyclopropane was initially chosen to ensure that distal opening of the cyclopropane was exclusively observed.

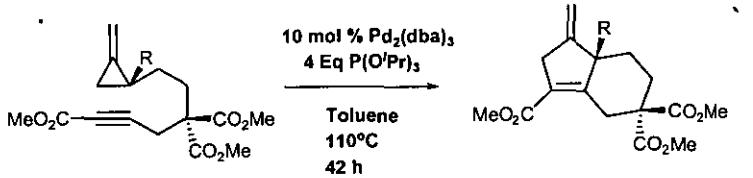



67 68 69

**Scheme 25**

In this paper, Motherwell also went on to describe the cyclization of the acetylenic ester **67** affording the 1 : 1 mixture of diastereoisomers **68** and **69** (**scheme 25**). The isolation of these diastereoisomeric cycloadducts demonstrates the elegance of this methodology as complete regioisomeric control is achieved in this intramolecular reaction.

Motherwell and co-workers then went on to determine the scope of the reaction and its incorporation into the construction of highly functionalised hydrindane skeletons from substituted methylenecyclopropanes (**scheme 26**).[33]




70 71

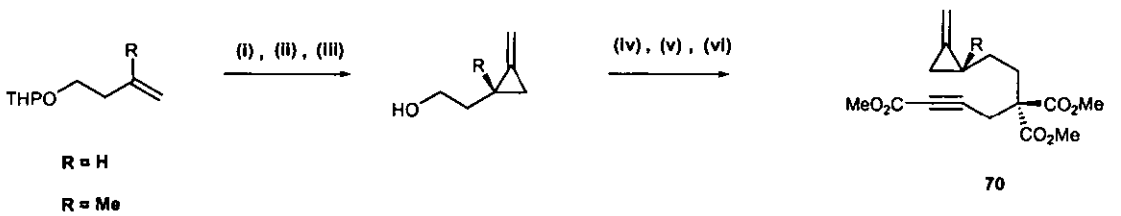
R = H
R = Me

R = H 40 % yield
R = Me 59 % yield

**Scheme 26**

Motherwell reported that the synthesis of the appropriate alkylidene cyclopropane was simply achieved by reaction of the protected but-3-en-1-ol derivatives with methyl chlorocarbene followed by dehydrohalogenation and deprotection. Motherwell then reported that subsequent conversion to the iodide, and alkylation with dimethyl

monopropargyl malonate then methyl chloroformate proceeded well to afford the desired acyclic acetylenes (**scheme 27**).




R = H

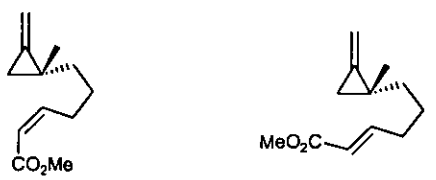
R = Me

**Reagents and Conditions**

(i) *n*-BuLI, $MeCHCl_2$, - 35°C (R = H, 76 % yield, R = Me, 79 % yield)
(ii) $KO^tBu$, DMSO, 70°C
(iii) *p*-TsOH, MeOH (R = H, 76 % yield, R = Me, 68 % yield)
(iv) $PPh_3$, $I_2$, imidazole, $Et_2O$, MeCN
(v) dimethyl monopropargylmalonate, NaH, DMF
(vi) n-BuLI, THF, - 35°C (R = H, 46 % yield, R = Me, 57 % yield)

**Scheme 27**

Motherwell and co-workers then wanted to further establish the factors governing the stereochemical outcome of this type of cycloaddition. They went on to investigate how the geometry of the initial olefin affected the stereochemistry of the reaction.[34]

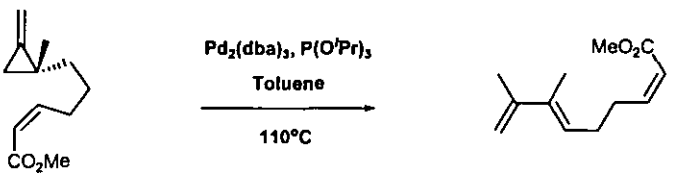



72 73

**Figure 3**

The methylenecyclopropanes **72** and **73** (**figure 3**) were chosen due to their geometrically defined α,β-unsaturated ester acceptors but unfortunately no cycloaddition product was observed with either the *cis*-, **72**, and the *trans*-, **73** ester.

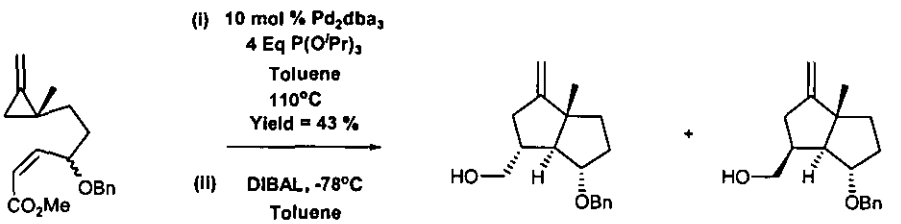
The product isolated from the reaction with the above methylenecyclopropanes **72** and **73** was found to be the triene **74** (**scheme 28**).




**72** **74**

**Scheme 28**

Despite a disappointing result with the α,β-unsaturated esters **72** and **73** shown above, they reported a successful palladium catalyzed cyclization for the *cis* ester containing an ether substituent **75** (**scheme 29**).



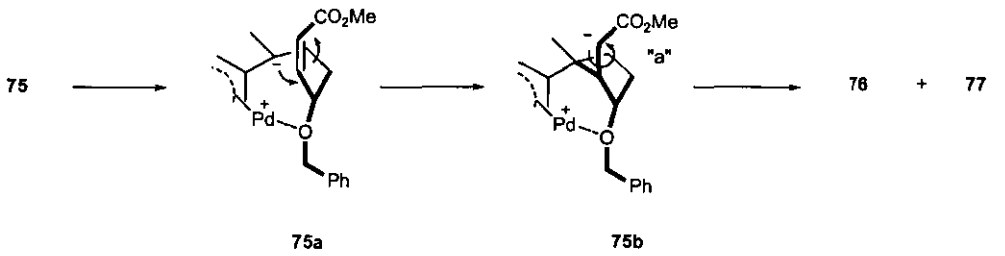

**Yield =** **30 %** **6 %**

**75** **76** **77**

**Scheme 29**

On cyclization of the *cis* ester, **75**, an inseparable mixture of two bicyclic compounds was isolated. The bicyclic alcohols, **76** and **77** were isolated on reduction of the ester moiety of the inseparable mixture with DIBAL in 30 and 6% yield from methylenecyclopropane respectively. It was most interesting to note that the

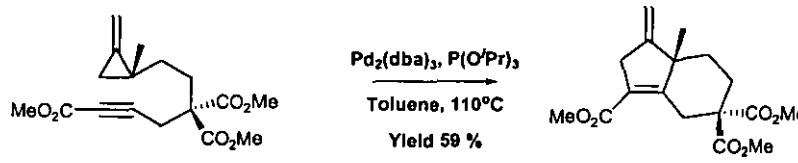
thermodynamically less favourable *trans* fused ring junction was apparent in the bicyclic alcohols and that the stereochemistry between the bridgehead hydrogen and the hydroxymethyl group indicates that the ester underwent an epimerisation prior to the final bond closing step. The *trans* diastereoisomer of **75** did not afford the desired cycloadduct. With both these results in hand, *i.e.* the lack of isolation of the cycloadducts from esters **72** and **73** and the successful isolation of the bicyclic cycloaducts **76** and **77**, Motherwell and co-workers were able to deduce that there was a crucial complexation between the metal atom and the ether oxygen atom (**scheme 30**).




**Scheme 30**

Motherwell suggests that the palladium oxidatively inserts into the distal bond of the methylenecyclopropane followed by ring closure to form the first cyclopentane ring via the intermediates **75a** and **75b**. Here the ether adopts a pseudoaxial orientation in which it is able to stabilize the cationic π-allyl-palladium intermediate. Rotation around bond "a" followed by nucleophilic addition affords the bicyclic cycloadducts **76** and **77**. Conversely the *trans* diastereoisomer is not able to adopt a suitable conformation in which the oxygen is chelated to the palladium and hence no cyclization for this diastereoisomer is observed.

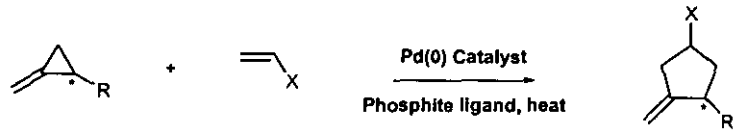
Motherwell and co-workers went on to vary the linking tether length to gain access to bicyclo[3.3.0]octanes and to investigate how the nature of the acetylenic substituent influences the outcome of the reaction (**scheme 31**).[35, 36]




78 79

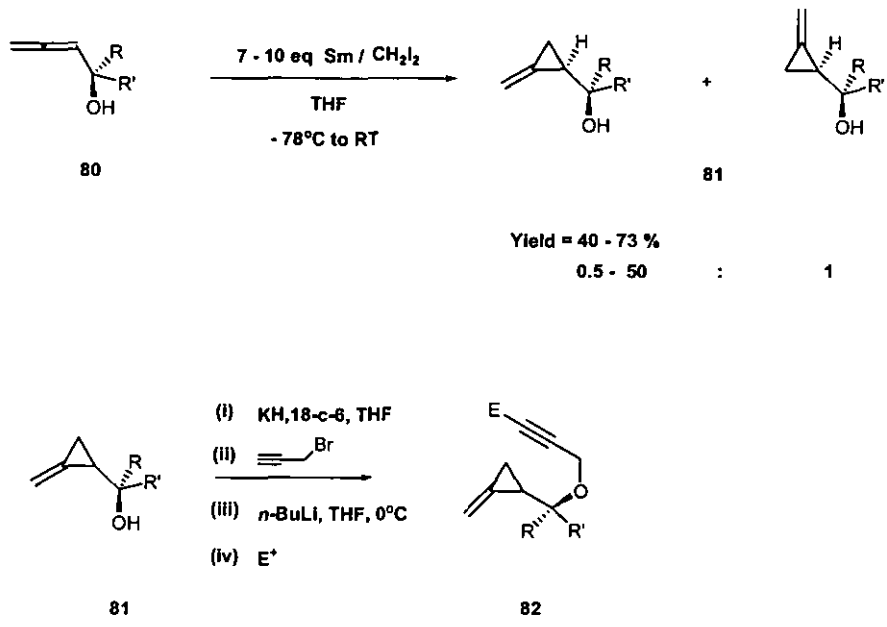
**Scheme 31**

The studies carried out thus far could not tackle the issue of the stereochemical integrity at the cyclopropane stereocentre as denoted by * in **scheme 32** due to the absence of diastereomerically pure starting materials.



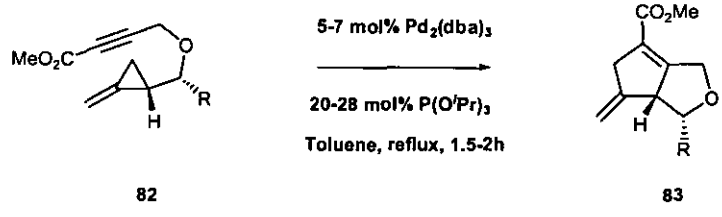

**Scheme 32**

Lautens *et al* addressed this concern by synthesizing diastereomerically pure starting methylenecyclopropanes with a tethered ether alkyne (**scheme 33**). Lautens reported that the synthesis of the starting methylenecyclopropane substituted alcohols **81** were synthesisized by a completely regioselective Sm-directed cyclopropanation of the allenic alcohols **80**. The methylenecyclopropane carbinols **81** were subsequently linked with propargyl and allyl functions via the oxygen atom to afford the tethered methylenecyclopropanes **82**. [37, 38, 39]



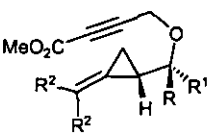
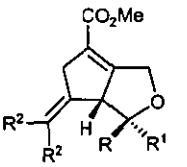
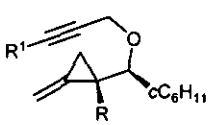
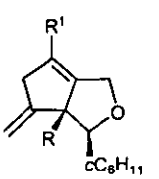
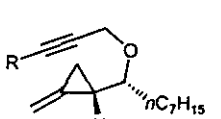
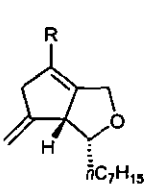

Scheme 33

Now with the diastereomerically enriched starting materials to hand they subsequently treated them with $Pd_2(dba)_3$ and $P(O^iPr)_3$ to afford tetrahydrofuran fused cycloadducts **83** as single diastereoisomers (**scheme 34** and **table 4**).[37, 38, 39]



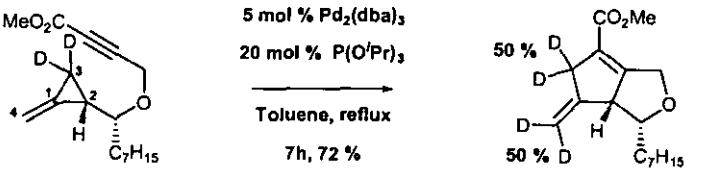

Scheme 34

Table 4

| Entry | ACP | Adduct (% Yield) |
|---|---|---|
| | **82** | **83** |
| |  |  |
| 1 | R = $cC_6H_{11}$, $R^1 = R^2 = H$ | 75 |
| 2 | $R = R^2 = H$, $R^1 = cC_6H_{11}$ | 72 |
| 3 | R = $nC_7H_{15}$, $R^1 = R^2 = H$ | 71 |
| 4 | $R = R^2 = H$, $R^1 = nC_7H_{15}$ | 83 |
| 5 | $R\text{-}R^1 = (CH_2)_5$, $R^2 = H$ | 68 |
| 6 | R = $cC_6H_{11}$, $R^1 = H$, $R^2 = n$Pr | 58 |
| |  |  |
| 7 | R = OMe, $R^1 = CO_2Me$ | 75 |
| 8 | R = Me, $R^1 = CO_2Me$ | 43 |
| 9 | R = H, $R^1 = CH_2OH$ | 85 |
| 10 | R = H, $R^1 = CH_2OTBDMS$ | 100 |
| 11 | R = H, $R^1 = COMe$ | 92 |
| 12 | R = H, $R^1 = TMS$ | 46 |
| |  |  |
| 13 | R = TBDMS | 40 |
| 14 | $R = SiMe_2Ph$ | 40 |

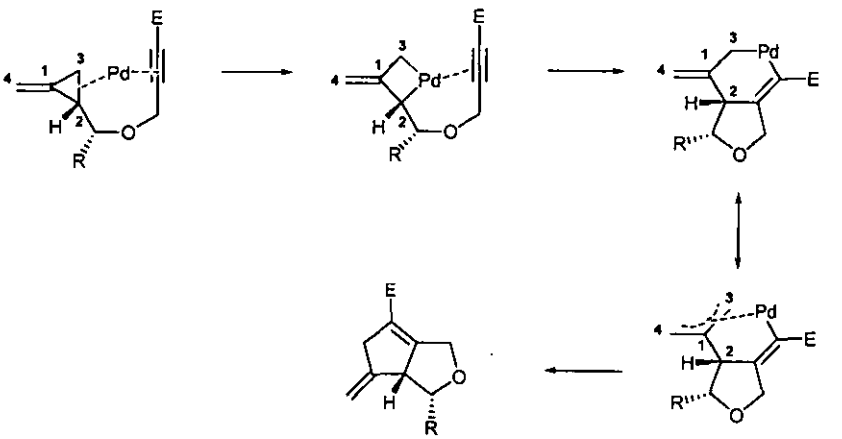
Reagents and Conditions : 2 – 15 mol % $Pd_2(dba)_3$, 2 equivalents $P(O^iPr)_3$, toluene, reflux, 2 hours

The isolation of single diastereoisomers from the reaction indicated that the cyclizations were occurring in a highly stereospecific manner and the relative stereochemistry between the cyclohexyl ring and the bridge hydrogen also indicated that there was a double retention of stereochemistry throughout the reaction. By deuterium-labelling experiments, (**scheme 35**) Lautens *et al* were able to report that not only the insertion of the palladium into the cyclopropane but also the carbometallation step occurs with retention of stereochemistry.




**Scheme 35**

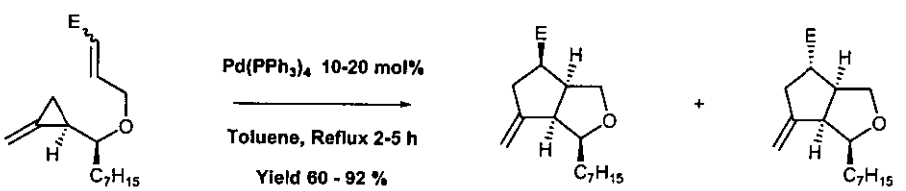
They reported that on reaction of the deuterated methylenecyclopropane with Pd (0) the cycloadduct was isolated with complete scrambling at the vinylic and allylic positions. Recovered starting materials showed no scrambling of the label between C-3 and C-4. They postulated that coordination of the alkyne to the palladium occurred in an edge-on orientation, and subsequent insertion into the cyclopropyl distal bond generates a metallocycle. They reasoned that the insertion step must be the rate determining step due to lack of scrambling in recovered starting material but observed scrambling in the final product. Subsequent σ-allyl interconversion exchanging C-3 and C-4 occurs prior to reductive elimination (**scheme 36**).



**Scheme 36**

In summary, Lautens and co-workers reported that a large range of substitution patterns could be well tolerated by the reaction to afford a diverse range of methylenecyclopentanes. Substitution at the carbinol carbon has little effect on the stereoselectivity or reactivity. Substitution on the exocyclic methylene group was just as well tolerated as the un-substituted methylene group. However, substitution on the cyclopropane $sp^3$ carbon appears to have a clear effect on the reaction. The reaction tolerated a hydrogen and methoxy group on the cyclopropyl carbon, whereas, on introduction of a methyl group at this position, the reaction was not successful. Substitution on the alkyne appeared to have the biggest effect on the success of the reaction. Alkynes bearing an electron withdrawing groups such as an ester or a ketone underwent cyclization in excellent yields. Weaker electron withdrawing groups such as hydroxymethyl also appeared to be well tolerated by the reaction. Conversely an electron donating substituent such as methyl afforded only small amounts of cycloadduct, alongside isolation of un-reacted starting material. On introduction of silicon, the reaction was lethargic and the yield of cycloadducts isolated was moderate, if the reaction was successful at all.

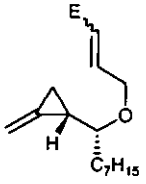
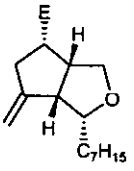
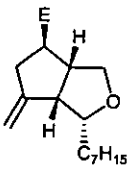
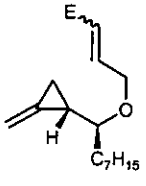
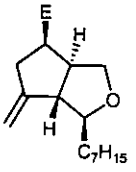
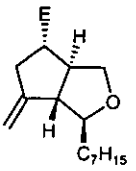
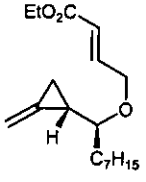
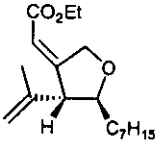
Lautens and co-workers went on to investigate the equivalent stereospecific reaction using tethered alkenes to afford saturated bicyclo[3.3.0] systems.[40] This reaction was of great interest as potentially two new stereocentres could be generated additionally to the pre-existing stereocentre in the cyclopropane (**scheme 37**). Again a high degree of stereocontrol was achieved throughout the reaction and the diastereomeric starting materials react on opposite faces of the electron deficient olefin to afford either the *cis* or *trans* bicyclo[3.3.0] ring systems (**table 5**).




**84** **85a** **85b**

**Scheme 37**

**Table 5**

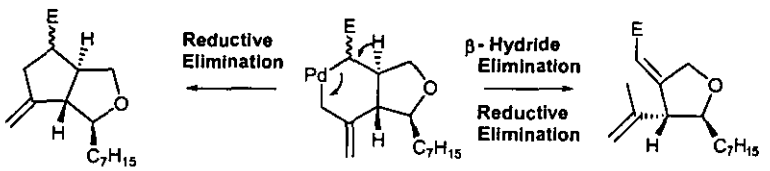
| Entry | MCP (Alkene Configuration) | Catalyst | Product % Yield (ratio) |
|---|---|---|---|
| |  | |   |
| 1 | E = $CO_2Et$ (*E*) | A | 78 (100 : 0) |
| 2 | E = $CO_2Et$ (*E*) | B | 53 (100 : 0) |
| 3 | E = $CO_2Et$ (*Z*) | A | 75 (100 : 0) |
| 4 | E = COMe (*E*) | A | 81 (100 : 0) |
| 5 | E = $SO_2Ph$ (*E*) | A | 60 (0 : 100) |
| 6 | E = CN (*Z* / *E* 1 : 2) | A | 92 (50 : 50) |
| |  | |   |
| 7 | E = $CO_2Et$ (*E*) | A | 87 (50 : 50) |
| 8 | E = $CO_2Et$ (*E*) | B | 95 (65 : 35) |
| 9 | E = $CO_2Et$ (*Z*) | A | 83 (50 : 50) |
| 10 | E = $SO_2Ph$ (*E*) | A | 86 (80 : 20) |
| 11 | E = CN (*Z* / *E* 1 : 4) | A | 91 (40 : 60) |
| 12 |  | C |  40 |

Catalyst A = $Pd(PPh_3)_4$ (10 – 20 mol %), B = $Pd_2(dba)_3$/ $P(O^iPr)_3$ (30%), C = $Pd_2(dba)_3$/ $P(O^iPr)_3$ (37%)

The stereochemical outcome of the bridgehead carbon atom was reported to be dependant on the relative stereochemistry of the pre-existing stereocentres, and the different diastereoisomers display complementary facial selectivities in the addition of

the alkene (**table 5** entries 1-6 *vs* 7-11). Stereochemistry at the double bond was reported not to be significant in the stereochemical outcome (entries 1-3 and 7-9).

Aside from the cyanide example, all the *anti* diastereoisomers afforded one diastereoisomer exclusively whereas the *syn* diastereoisomers afforded a mixture of diastereoisomers with little selectivity. The isolation of the *trans*-fused [3.3.0]bicyclic system **85** has been attributed to the presence of the *trans*-fused methylenepalladacyclohexane intermediate **86 (scheme 38)**.




85 86 87

**Scheme 38**

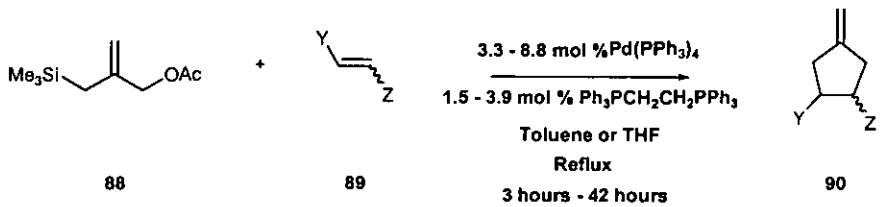
The *trans*-fused transition state was reported to be high in energy and β-elimination was expected to compete with reductive elimination, hence the isolation of the diene **87** for entry 12 when the catalyst $Pd_2(dba)_3$ was employed (**scheme 38**).

# 1.3 Palladium Catalyzed [3 + 2] Cycloaddition Reactions Using Trimethylenemethane (TMM) Derivatives

## 1.3.1 Synthesis of Cyclopentanes from Un-substituted Pd-TMM Complexes

Preliminary studies in this area were reported by Trost and co-workers in the early eighties.[46] There was a great deal of interest in determining an elegant cycloaddition approach to the synthesis of five membered rings to complement the Diels-Alder strategy for the synthesis of six membered rings. The cycloaddition approach to five membered rings seemed like an attractive and obvious place to start due to the simultaneous multiple bond construction nature of the reaction. Trost decided to develop the previously established cycloaddition of trimethylenemethane with olefins[41, 42, 43, 44] and an intramolecular version.[45] These reactions proceeded poorly and there was plenty of room for improvement.

Trost reported a novel palladium catalyzed annulation between 2-acetoxymethyl-3-allyltrimethylsilane **88** and electron deficient olefins **89** affording methylenecyclopentanes **90 (scheme 39)**. [46]

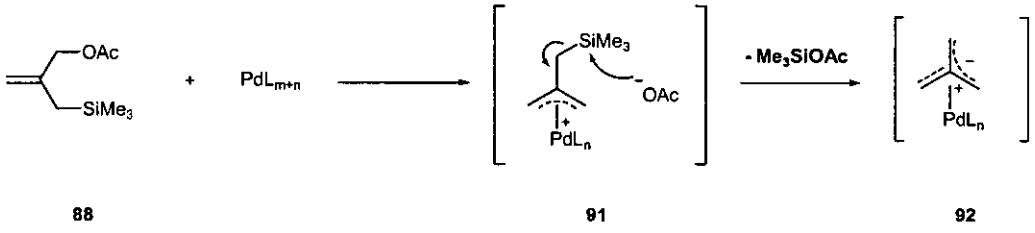



88 89 90

**Scheme 39**

Trost *et al* went on to solve the issues that previously prevented this reaction from being an extremely elegant cycloaddition strategy into cyclopentanes. Trost concluded that the trimethylenemethane synthon needed to posses both an electrophilic and nucleophilic centre, but did not react with itself, and was capable of eliminating substituents in order to produce the active trimethylenemethane zwitterionic active species to participate in the cycloaddition.[47, 48, 49]

Trost went on to deduce that a silyl group would make a good carbanion equivalent and that oxygen anions are good silylophiles and hence would make a good carbocation equivalent. The purpose of the palladium would be to act as an activator. The palladium would promote the ionisation of the acetate. The resulting π-allylpalladium species **91** would have a weakened carbon-silicon bond due to the resulting positive charge. The palladium TMM synthon would lose trimethylsilyl acetate **92** and would carry out the cycloaddition to afford the desired cycloadducts **(scheme 40)**.

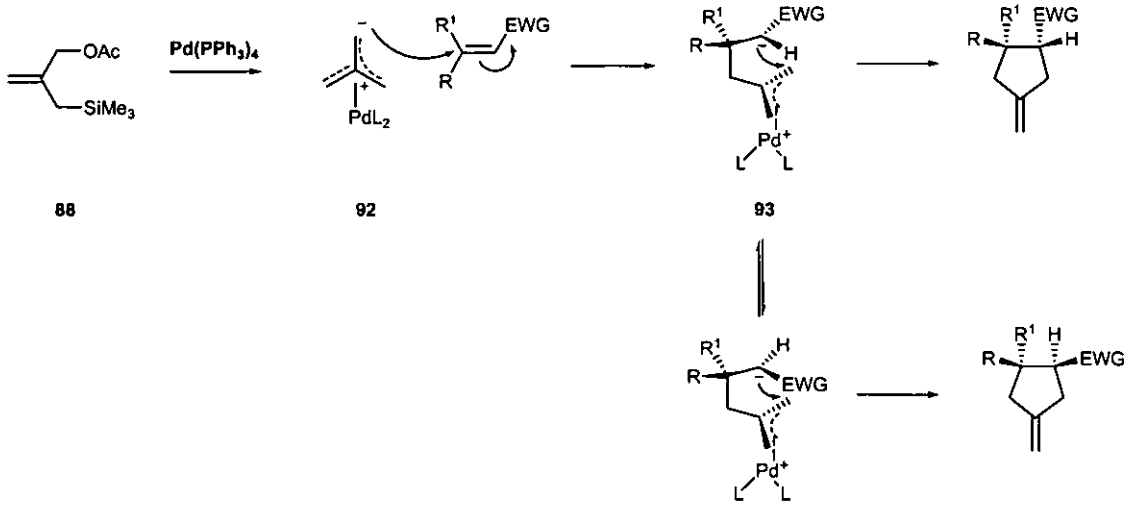



**88** **91** **92**

**Scheme 40**

The scope of the reaction appeared to be large for olefins containing an electron withdrawing substituent including esters,[46] nitriles, ketones and sulfones [46, 47] and the cycloadducts were isolated between 50 - 85%. The choice of reaction solvent had a profound effect on the reaction times and yield observed for the reaction. On switching the solvent from toluene to THF, a shorter reaction time was observed and a

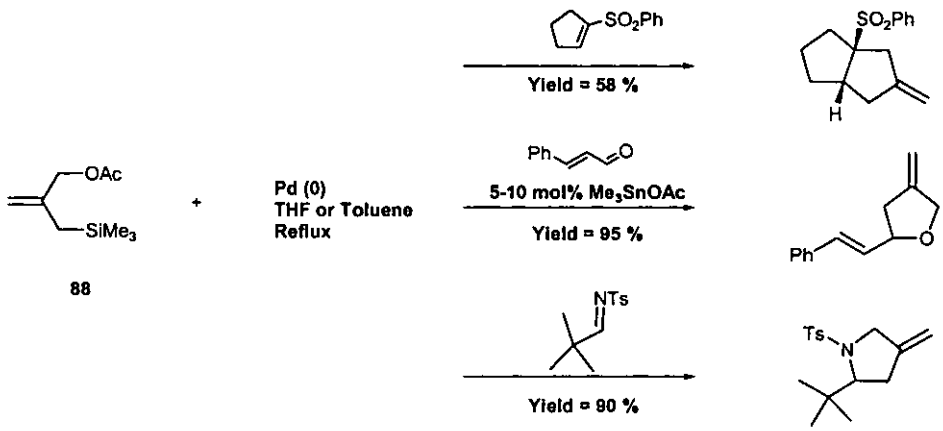
greater yield of cycloadduct was isolated. For *E* olefins, the reaction is extremely stereospecific as the cycloadduct isolated possesses the same geometry, whereas for *Z* olefins, it is believed that isomerization of the starting material occurs, as a mixture of crossover products is isolated.




**Scheme 41**

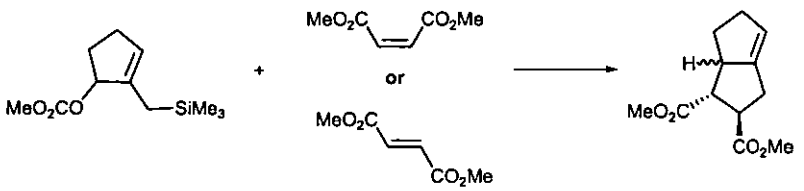
The proposed mechanism for the Michael type conjugate addition of the palladium TMM synthon **88** to the Michael acceptor to generate the stabilized zwitterion **92** is denoted in **scheme 41**. The enolate undergoes a nucleophilic addition step and on reductive elimination of the palladium the zwitterion **93** undergoes a 5-exo-trig ring-closure to afford the desired methylenecyclopentane.

The reaction was not successful for simple alkyl substituted olefins or electron rich olefins. But more recently this methodology has been extended to cyclizations involving carbonyl groups such as aldehydes,[50] ynones,[51] reactive ketones,[52] and *N*-tosylimines.[53]




**Scheme 42**

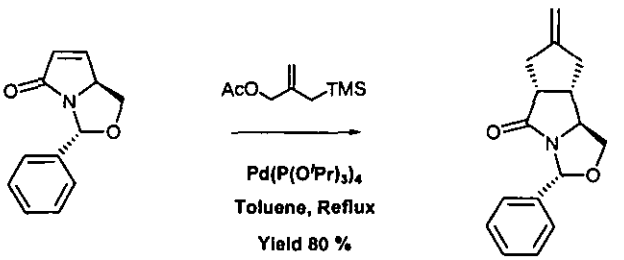
More recently, the cyclization of the TMM, entity when incorporated into a five membered ring has been reported for the efficient synthesis of polyquinane structures.[54]




**Scheme 43**

Unfortunately though it was found that there was competing side reactions such as [4 + 2] cycloadditions and oligomerization, but this has opened up an elegant path into diquinane structures.

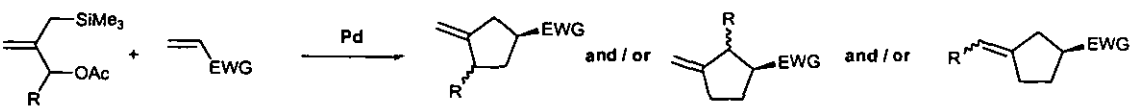
Another example of the incorporation of the Trost's palladium-assisted TMM cycloaddition strategy into a ring construction methodology was reported in 2003 for the synthesis of 5,5-fused proline analogues (**scheme 44**).[55]




**Scheme 44**

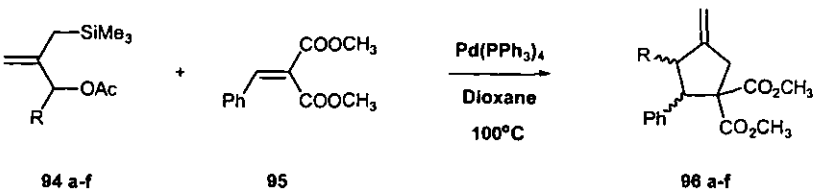
## 1.3.2 Synthesis of Cyclopentanes from Substituted Pd-TMM Complexes

Regiochemistry is an important issue for this class of compounds since the symmetry of the starting material is destroyed. With a possibility of six possible isomers, three possible regioisomers combined with two diastereoisomers for each regioisomer, the mixture isolated could be complex (**scheme 45**).




**Scheme 45**

Initially, Trost used dimethyl dibenzylidenemalonate as an acceptor to test out the regioselectivity of the reaction (**scheme 46**). [56]

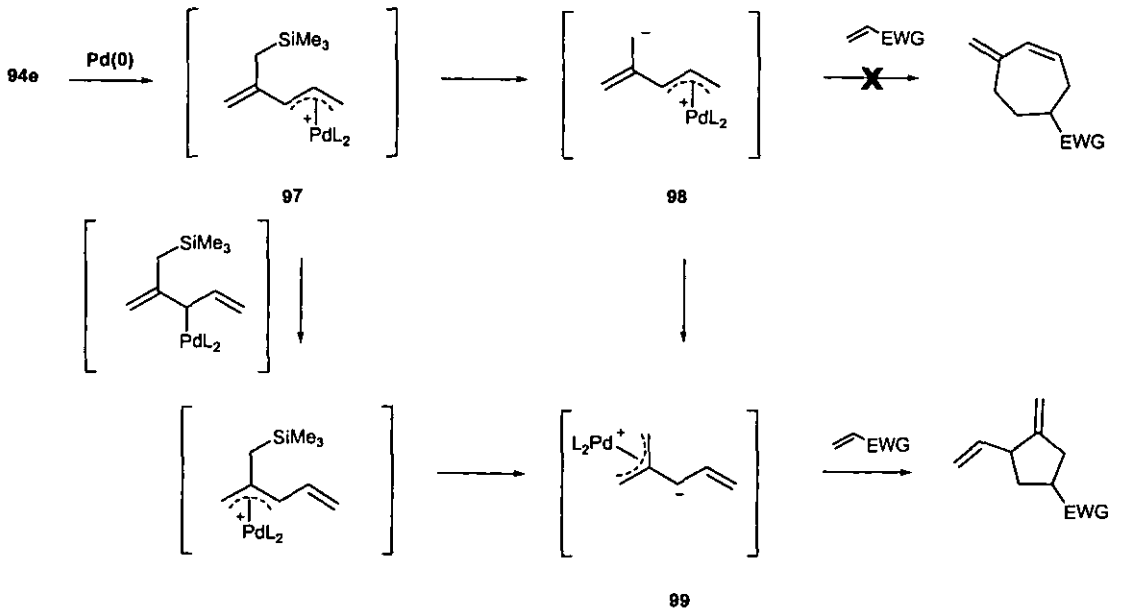



**Scheme 46**

**Table 6**

| Reagent | Product | R | Yield % | Isomer |
|---|---|---|---|---|
| **94 a** | **96 a** | CN | 54 | *trans* |
| **94 b** | **96 b** | COEt | 59 | *trans* |
| **94 c** | **96 c** | Ph | | *cis* + *trans* |
| **94 d** | **96 d** | cyclopropyl | 61 | *cis* + *trans* |
| **94 e** | **96 e** | $CH{=}CH_2$ | 89 | *cis* + *trans* |
| **94 f** | **96 f** | OAc | 86 | *cis* + *trans* |

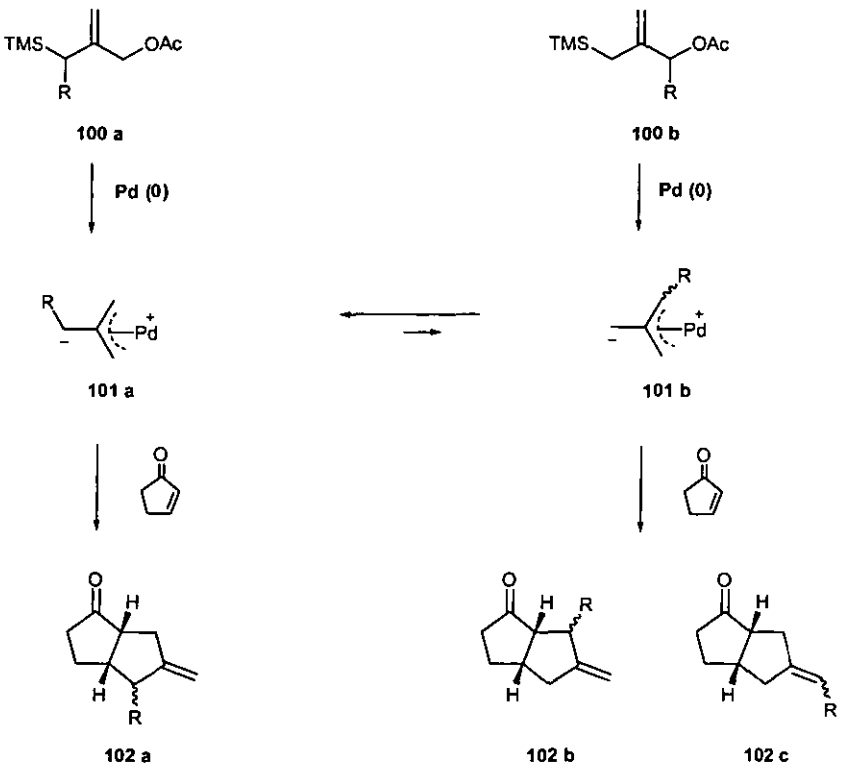
The olefins tested in this reaction are indicated in **table 6**. The surprising result of the isolation of the five membered cycloaduct for the vinyl group **94e** as opposed to the seven membered ring, led Trost to a conclusion about the product-determining intermediate.




**Scheme 47**

The isolation of the five membered ring as opposed to the seven membered ring suggested that the reactive intermediate that must be operating for this reaction follows that described by **98** and not the kinetically favoured π-allylpalladium cation **99**.

Trost was delighted to note that only one regioisomer was obtained and for the olefins bearing an electron withdrawing substituent, only one diastereoisomer was obtained.



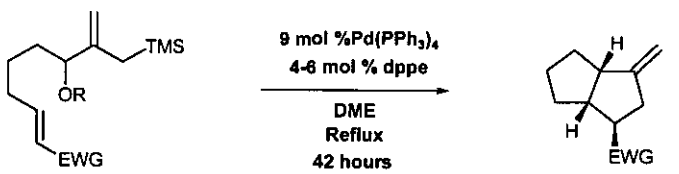

**Scheme 48**

Due to the acquisition of the main regioisomer **102a** for the cyclization with an electrophile such as cyclohexanone, this led Trost on to suspect that the substituted π-allylpalladium TMM complexes **101a** and **101b** undergo equilibration faster than trapping with the electrophile and hence the regioisomer isolated each time resembled that of **102a**.[57]

### 1.3.3 Intramolecular [3 + 2] Cycloaddition Reactions

The issues of regio-, diastereo-, and enantioselectivity for the intermolecular palladium catalyzed [3 + 2] cycloaddition with trimethylenemethane (TMM) could possibly be addressed by extending the intermolecular processes to intramolecular. Preliminary studies of an intramolecular [3 + 2] cycloaddition via TMM-$PdL_2$ intermediates were reported by Trost and co-workers.[58, 59]

On treatment of the substrate **103** with $Pd(PPh_3)_4$ in conjunction with 1,2-bis(diphenylphosphino)ethane (dppe) as the catalyst system in refluxing 1,2 dimethoxyethane (DME) the desired *cis*-fused bicyclo[3.3.0]octane **104** was isolated (**scheme 49**).




**103**

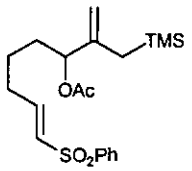
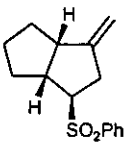
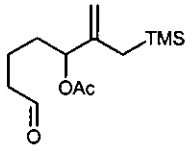
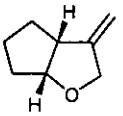
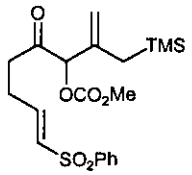
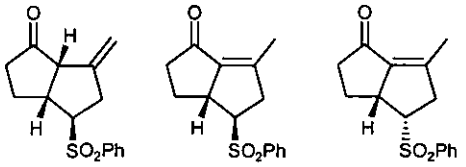
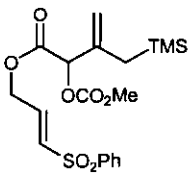
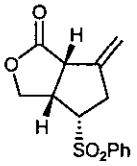
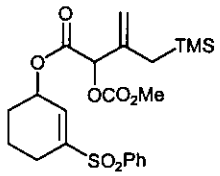
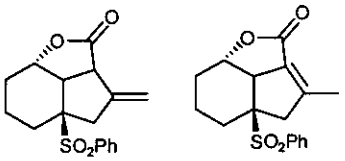
**EWG = $SO_2Ph$**
**R = $OCO_2Me$**

**104**

**Yield 65 %**

**Scheme 49**

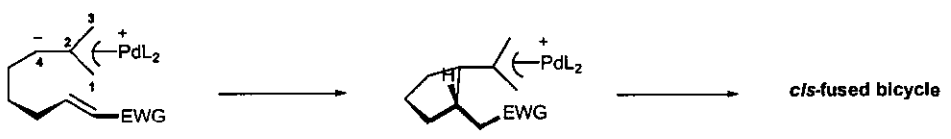
Table 7

| Entry | Precursor | Products | Yield % |
|---|---|---|---|
| 1[a] |  |  | 65 |
| 2[b] |  |  | 31 |
| 3[c] |  |  | 47 (5.4 : 2 : 1) |
| 4[d] |  |  | 16 |
| 5[d] |  |  | 62 (1.7 : 1) |

a : 9 mol % $Pd(PPh_3)_4$ , 4-6 mol % dppe, DME, reflux
b : $Pd_2(dba)_3.CHCl_3$, $P(O^iPr)_3$, $Bu_3SnOAc$, BSA, THF, reflux
c : $Pd(OAc)_2$, $P(O^iPr)_3$, dioxane, 100°C
d : 5 mol% $Pd(OAc)_2$, 30 mol% $P(O^iPr)_3$, dioxane, reflux

When the 1,7-diene (**entry 1, table 7**) was subjected to palladium, the *cis*-fused bicyclo[3.3.0]octane was isolated as a single isomer.[60] High selectivity was also observed in the formation of the *cis*-fused rings from the 1,7-unsaturated aldehyde for **entry 2, table 7**. For entries **3-5**, the cyclization of the carbonyl substituted TMM complexes, high selectivity was achieved but also substantial amounts of products containing exo-cyclic double bonds were obtained. [61]

The regioselectivity of the first ring closure to form a cyclopentane as opposed to a cycloheptane was attributed to the increased stabilization of the negative charge of the TMM complex at the more substituted internal carbon (**scheme 50**).




104

104a

EWG = $SO_2Ph$

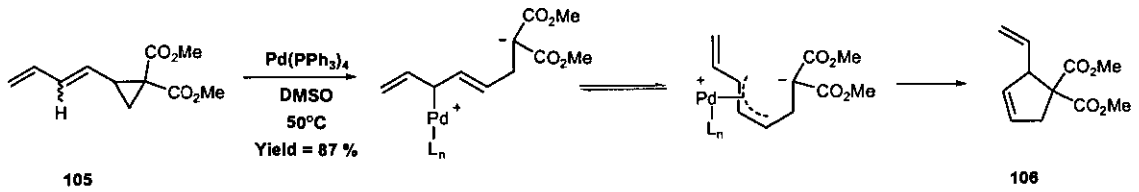
**Scheme 50**

A detailed account of palladium (0) and nickel (0) [3 + 2] catalyzed cycloadditions has been reported to form carbocycles and heterocycles. The research detailed in this thesis will focus on a related palladium catalyzed [3 + 2] cycloaddition strategy to construct heterocycles.

# 2.1 Intermolecular Palladium Catalyzed [3 + 2] Cycloadditions with Vinylcyclopropanes and Carbonyl Moieties

## 2.1.1 The Initial Concept

The foundation of the work reported herein was initially reported in the early eighties. Morizawa *et al* reported that doubly activated vinylcyclopropanes **105** could rearrange under palladium-catalyzed conditions yielding cyclopentenes **106 (scheme 51)**.[62]

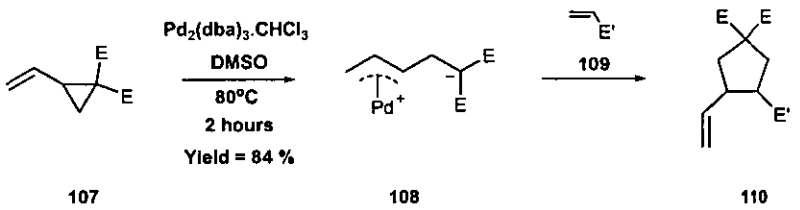



**Scheme 51**

Morizawa proposed that the intramolecular rearrangement proceeded through nucleophilic attack of the Pd(0) to the dienic group to form the zwitterionic π-pentadienylpalladium and stabilized anion moieties under cyclopropane cleavage. He then postulated that the intermediate collapses to form a cyclopentane derivative.

The two electron-withdrawing substituents were crucial to the successful isolation of the correct product due to stabilization of the intermediate $\pi$-allyl zwitterionic species which in turn collapses to form the five membered ring.

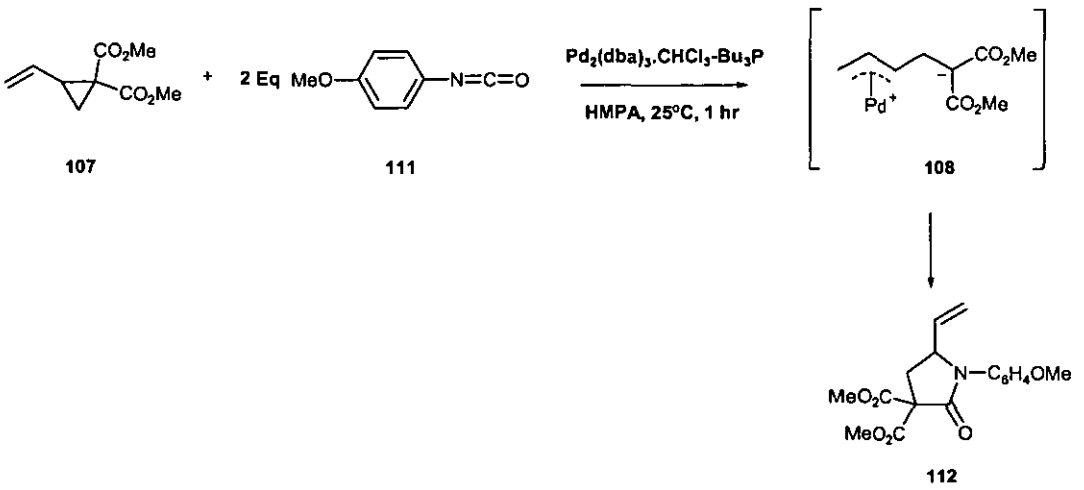
It was of great interest to note that Tsuji *et al* went on to report the synthesis of the five membered carbocycles **110** by the palladium catalyzed [3 + 2] cycloaddition reaction between doubly activated vinylcyclopropane **107** and electron-deficient olefins **109 (scheme 52)**.[63]




**Scheme 52**

Tsuji *et al* postulated that the palladium species oxidatively inserts into the vinyl group and the cyclopropane ring opens to form the palladium π-allylpalladium complex **108**. Tsuji describes this palladium π-allylpalladium species as a 1,3-dipolar equivalent, which acts as an inter-molecular trap with the electron-deficient olefin **109** to form the desired vinylcyclopentanes **110**.

Tsuji *et al* subsequently proceeded to report the synthesis of γ-lactams **112** from activated vinylcyclopropanes **107** and aryl isocyanates **111** using a palladium catalyzed cycloaddition reaction (**Scheme 53**).[64]



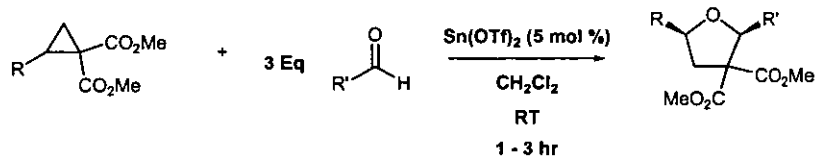

107 111 108 112

**Scheme 53**

Tsuji proposed that the mechanism involved the presence of the intermediate palladium zwitterion **108**, which subsequently undergoes addition to the central carbonyl carbon of the isocyanate **111** to form the five membered ring compounds **112**.

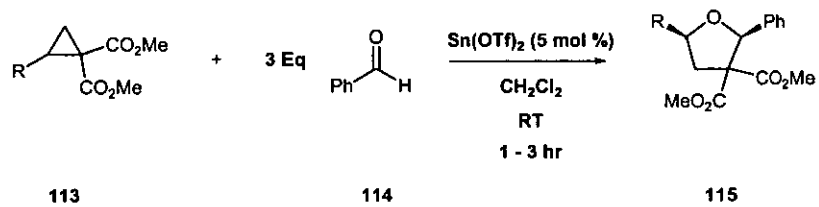
This reported work was a novel and exciting route into five membered heterocycles. However, this methodology does contain a few disadvantages preventing it becoming a very elegant route into five membered heterocycles. First and foremost, the use of the highly toxic solvent, hexamethylphosphoramide (HMPA) and the use of two equivalents of isocycanate are considered the major obstacles. It was suspected that if the reaction could be modified, by utilizing alternative electrophiles and solvents then the methodology could provide a very exciting route into heterocyclic chemistry.

Recently Pohlhaus and Johnson have reported the synthesis of 2,5-disubstituted tetrahydrofurans **115** from donor-acceptor cyclopropanes **113** and aldehydes **114** in the presence of a catalytic amount of $Sn(OTf)_2$ (**scheme 54**).[65]




**Scheme 54**

A range of substituted cyclopropanes has been cyclized with benzaldehyde **114** to afford 2,5-substituted tetrahydrofurans **115** (**scheme 55, table 8**)




**113** **114** **115**

**Scheme 55**

**Table 8**

| Entry | R | Time (h) | Yield (%) | DR |
|---|---|---|---|---|
| **1** | Ph | 2.5 | 100 | ›100 : 1 |
| **2** | 4-ClPh | 4.75 | 96 | ›80 : 1 |
| **3** | 4-OMePh | 3.5 | 98 | ›86 : 1 |
| **4** | 2-furyl | 3.25 | 82 | 23 : 1 |
| **5** | 2-thienyl | 3.25 | 98 | ›83 : 1 |
| **6** | 4-$NO_2$Ph | 15 | 89 | ›19 : 1 |
| **7** | (*E*)-CH=CHPh | 3.5 | 96 | 17 : 1 |
| **8** | C≡CPh | 6 | 92 | 1.6 : 1 |

Cyclopropane (1.0 eq), aldehyde (3.0 eq), $Sn(OTf)_2$ (5 mol %). RT between 23-29°C.

The postulated intermediate is described in **figure 4**.

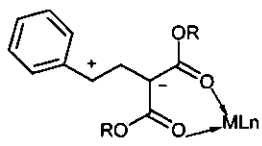
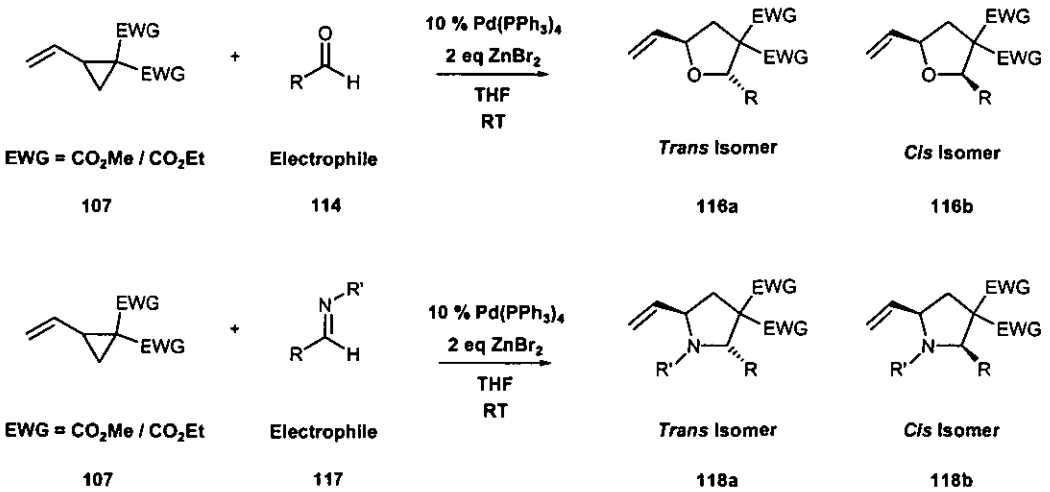



**Figure 4**

### 2.1.2 Previous Work

Working under the supervision of Dr Gareth Pritchard and Professor Sir Jack Baldwin, Oxford University, Lam Tang reported the progress made towards the modification of this methodology.[66] Tang describes the initial results he obtained on developing a palladium catalyzed [3 + 2] cycloaddition strategy.

Tang reported a novel palladium catalyzed [3 + 2] cycloaddition reaction between a doubly activated vinylcyclopropane **107** and the carbon-oxygen double bond of aldehydes **114** and the carbon-nitrogen double bond of imines **117** to afford tetrahydrofurans **116a, 116b** and pyrrolidines **118a, 118b** respectively as a pair of diastereoisomers (**scheme 56**). After optimisation, the reaction was found to boast excellent yields under mild reaction conditions.

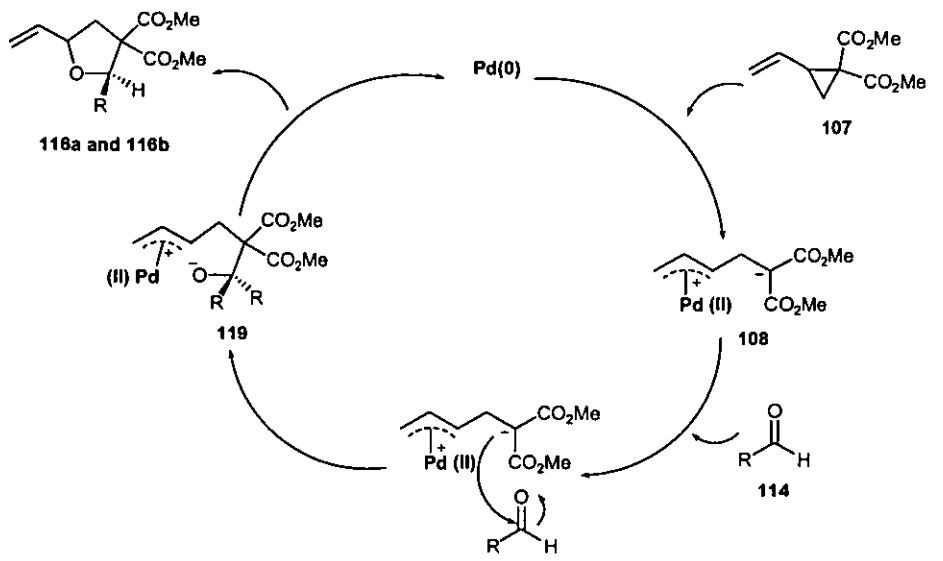



Scheme 56

Tang reported that the Lewis acid, $ZnBr_2$ was an essential variable in the reaction. Isolated yields were considerably increased on its inclusion. The optimum conditions were found to be the employment of stoichiometric amounts of vinylcyclopropane and the electrophile, 10 mol% $Pd(PPh_3)_4$, two equivalents of $ZnBr_2$ in THF at room temperature in most cases. It was detailed that a wide range of functional groups were well tolerated in the reaction indicating that the scope of the reaction could be large. This methodology was already promising to be an extremely powerful tool for the construction of highly functionalised five membered heterocycles. Ambient conditions, high yields, easily accessible stoichiometric equivalents of electrophiles and the employment of relatively mild reagents made this reaction extremely desirable and an improvement on the conditions reported by Tsuji.

### 2.1.3 The Catalytic Palladium Cycle

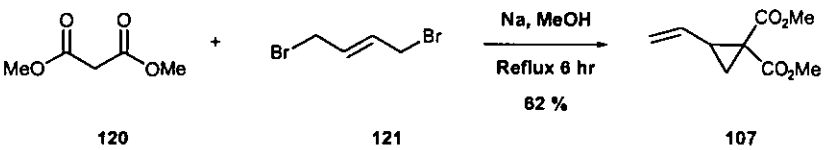
The mechanism in operation for this [3 + 2] cycloaddition is extremely similar to the one reported by Tsuji.[63] It commences with oxidative insertion of palladium (0) into the vinyl group of the cyclopropane **107**. This in turn causes the cyclopropane to ring open and to form the zwitterionic π-allyl palladium(II) complex **108**. The negative charge is stabilized by the presence of the two electron-withdrawing methyl esters. The malonic centre of the π-allyl palladium(II) complex subsequently undergoes a nucleophilic addition to the electrophilic carbonyl to afford a second transient zwitterion **119**. The resultant alkoxide displaces the palladium from the π-allyl with simultaneous reductive elimination of the transition metal, the desired substituted vinyl tetrahydrofuran is formed **116**. As only a catalytic amount of palladium (0) is required, the palladium is assumed to be regenerated on formation of the five membered heterocyclic product (**scheme 57**).




Scheme 57

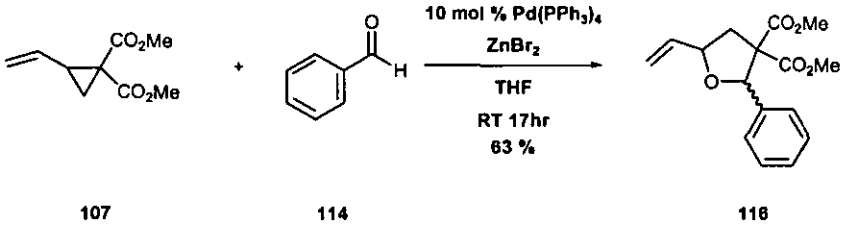
## 2.1.4 Preparation of Vinylcyclopropane 107

In a repeat of the work carried out by Tang, the synthesis of the starting material, the doubly activated vinylcyclopropane **107** was prepared following a literature precedent.[67] The successful synthesis of 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** was achieved following a double displacement of *trans* 1,4-dibromobut-2-ene **121** with the methylene unit of dimethyl malonate **120** in the presence of sodium methoxide. 2-Vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester was isolated in reasonable yield (62 %) (**scheme 58**).




Scheme 58

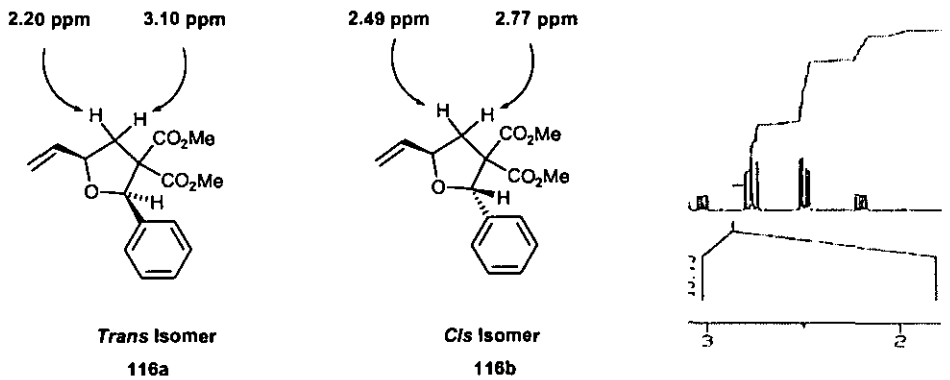
With the vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** now in hand, the palladium catalyzed cycloaddition with the aldehyde moiety of benzaldehyde **114** was attempted (**scheme 59**). This reaction was a repeat of one of the trial reactions carried out by Tang in order to confirm the result he obtained.




107 114 116

**Scheme 59**

Vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** (1 mmol) was treated with benzaldehyde **114** (1 mmol) in the presence of a Lewis acid, $ZnBr_2$ (2 mmol), 10 mol% $Pd(PPh_3)_4$ in THF. The desired 2-phenyl-5-vinyldihydrofuran-3,3-dicarboxylic acid dimethylester **116** was isolated in reasonable yield (63%) as a pair of diastereoisomers (1 : 3 *trans* **116a**: *cis* **116b**). The diastereoisomeric ratio can be determined by the $^1$HNMR spectrum. The diastereoisomeric ratio can be determined from the region between 2-3 ppm of the $^1$HNMR spectrum. This is the region where the hydrogens on 4-C of the tetrahydrofuran ring appear and both diastereoisomers are characteristic in this region.




*Trans* Isomer 116a *Cis* Isomer 116b

**Figure 5**

For the *trans* diastereoisomer, the hydrogen adjacent to the vinyl group appears further up-field than the corresponding hydrogen on the *cis* isomer. For the proton adjacent to the malonic centre, the *trans* diastereoisomer appears further down-field than the corresponding *cis* isomer. Hence in the $^1$HNMR spectrum there is a larger chemical shift difference between the two protons in the *trans* isomer than the *cis* isomer. This evidence is supported by *x*-ray data later on. The $^1$HNMR spectrum detailed in **figure 6** describes how the tetrahydrofuran **116** behaves in the spectrometer.

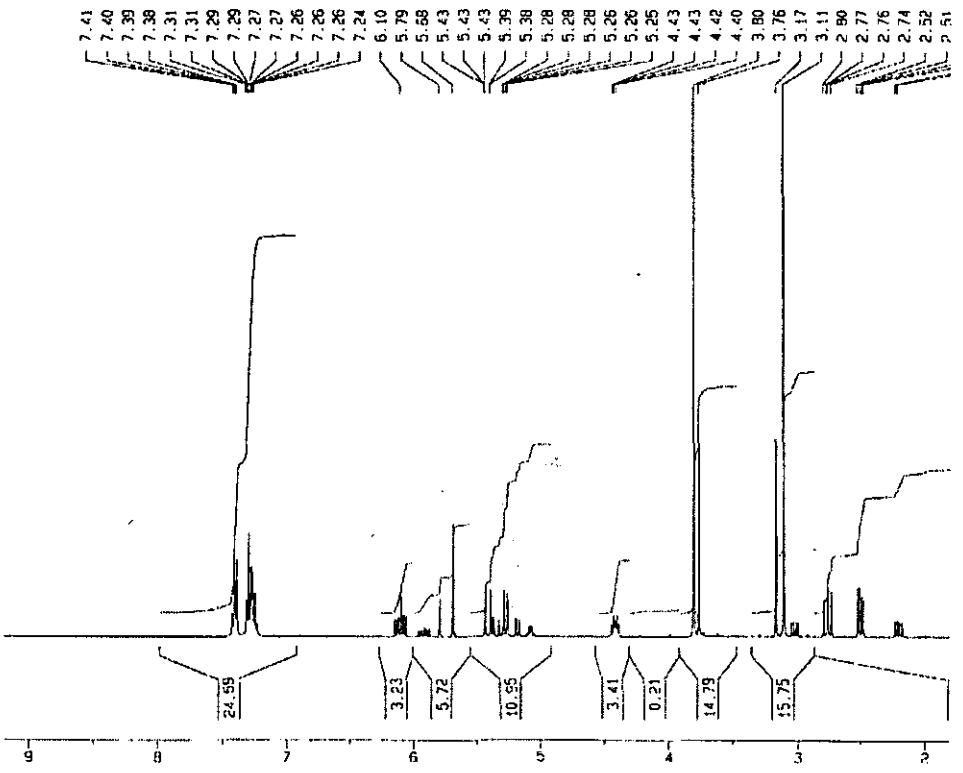



**Figure 6**

It is clear to see both the diastereoisomers in the region of 2-3 ppm and the larger gap between the two protons on the 4-C on the tetrahydrofuran for the *trans* isomer than the *cis*. In this example, the *cis* isomer is the predominant isomer.

The reaction was attempted varying a few parameters to try and improve on the yield and diastereoselectivity of the reaction obtained by Tang (**table 9**).

**Table 9**

| Cyclopropane | Electrophile | Solvent | Lewis Acid $ZnBr_2$ | Yield | Diastereoisomeric Ratio (*trans* : *cis*) |
|---|---|---|---|---|---|
| **107** | **114** | THF | None | - | - |
| **107** | **114** | MeOH | 2 equiv. | 79 % | 1 : 3 |
| **107** | **114** | MeOH | None | 75 % | 1 : 2 |
| **107** | **114** | $H_2O$ / THF | None | 47 % | 1 : 1 |

Reagents and conditions: (1 mmol) **107** with (1 mmol) benzaldehyde **114** was carried out in the presence of 10 mol % $Pd(PPh_3)_4$ and 2 mmol $ZnBr_2$ in solvent at 20°C.

Initially the reaction was carried out in THF in the presence of 2 equivalents of the Lewis acid, $ZnBr_2$. The reaction proceeded in moderate yield and good diastereoselectivity for the *cis* diastereoisomer. It was then attempted to repeat the reaction in the absence of the Lewis acid. The [3 + 2] cycloaddition between the aldehyde **114** and the vinylcyclopropane **107** did not proceed in THF without the Lewis acid, $ZnBr_2$. It is believed that the Lewis acid increases the electrophilicity of the carbon of the carbonyl and hence encourages nucleophilic attack from the malonic centre of the $\pi$-allyl palladium complex (**figure 7**).

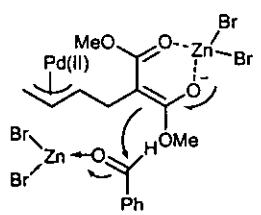



**Figure 7**

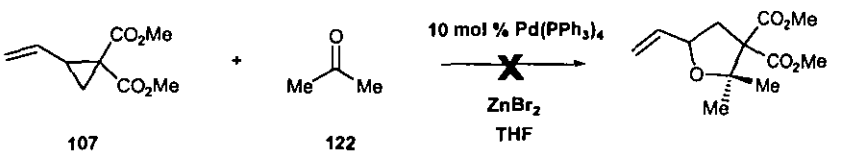
Tang attempted this reaction in various solvents to optimise the scope and limitation of the reaction. It was suspected that polar protic solvents were not compatible with this reaction due to their ability to quench the intermediate $\pi$-allyl palladium zwitterion that is formed in the reaction. It was decided to test out this hypothesis and recovery of the starting materials was expected. It was therefore quite a surprise to note the isolation of the desired tetrahydrofuran in an excellent yield both in the presence and absence of the Lewis acid for the reaction carried out in MeOH. It is not clear at this stage as to why the reaction was successful in this polar protic solvent. The reaction was so successful in the polar protic solvent MeOH, that the reaction was repeated in $H_2O$ and THF. The successful isolation of the desired product demonstrates how robust this reaction was proving to be.

### 2.1.5 Summary and Conclusions

A novel palladium catalyzed [3 + 2] cycloaddition reaction has been reported between 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** and the aldehyde moiety of benzaldehyde **114** to afford highly functionalised tetrahydrofurans **116**. The reaction conditions have been adapted and elaborated slightly to incorporate polar protic solvents. It is not clear at this stage why polar protic solvents should promote the successful isolation of the cycloadducts. This methodology developed is an exciting route into heterocyclic chemistry. The optimised reaction conditions are reported to be mild with the employment of stoichiometric equivalents of substrate and electrophile, 10 mol % $Pd(PPh_3)_4$, two equivalents of Lewis acid, $ZnBr_2$ and the use of non-toxic solvents. In this respect, the reaction conditions have shown to be an improvement on those reported by Tsuji. [63, 64]

## 2.2 Intermolecular Palladium Catalyzed [3 + 2] Cycloadditions with Vinylcyclopropanes and $\alpha$-Keto Esters

As mentioned previously, initial studies carried out by Lam Tang concentrated primarily on novel palladium catalyzed [3 + 2] cycloadditions involving activated vinylcyclopropanes with aldehydes or imines. It was reported that the cyclization attempts on to the simple ketone moiety of acetone **122** failed to afford the desired furan (**scheme 60**).




**Scheme 60**

The suspected rationale behind the failure to isolate the required cycloadduct was thought to be due to the presence of the methyl groups adjacent to the carbonyl moiety. The carbonyl, in this instance, was less electrophilic due to the electron-donating properties of the methyl groups and subsequently not so susceptible to nucleophilic attack from the malonic centre of the $\pi$-allyl palladium species, hence recovery of the starting materials was observed.

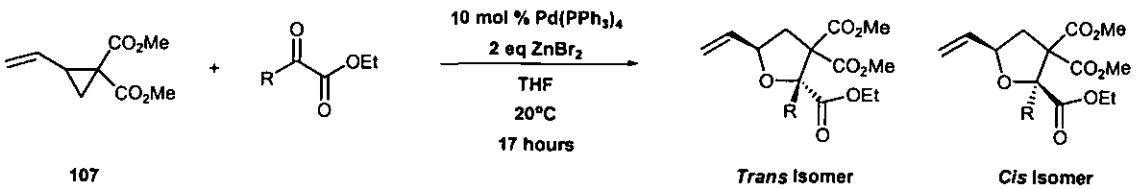
It was thought that ketones may require further activation to successfully participate in a palladium catalyzed [3 + 2] cycloaddition with doubly activated vinylcyclopropane. It was thought that a carbonyl group intended for the [3 + 2] cycloaddition could be activated by an adjacent electron-withdrawing substituent. The electron-withdrawing group would in turn enhance the electrophilicity of the carbonyl

and encourage nucleophilic attack with the malonic centre of the palladium π-allyl species. It was anticipated that α-keto esters could be suitable precursors for the palladium catalyzed cyclization. The presence of the electrophilic ketone moiety, activated by the adjacent electron-withdrawing ester group could make this functional group a suitable electrophile for the [3 + 2] cycloaddition.

### 2.2.1 The Use α-Keto Esters as Electrophiles

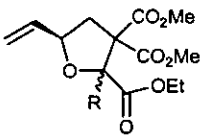
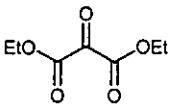
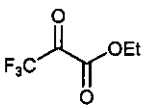
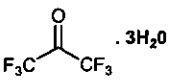
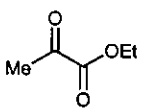
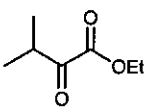
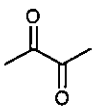
Initially diethylketomalonate **123, table 10** was chosen as a substrate due to the extremely electrophilic nature of the ketone. The presence of the two electron-withdrawing ethyl esters would increase the electrophilicity of the ketone and hence demonstrate whether α-keto esters are, indeed, suitable substrates to participate in this type of palladium catalyzed [3 + 2] cycloaddition. If successful, this example would demonstrate that the original hypothesis was correct and that ketones are a suitable functional group to participate in this [3 + 2] cycloaddition only if activated further by adjacent electron-withdrawing groups.

A range of α-keto esters have been treated with 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** in the presence of 10 mol % $Pd(PPh_3)_4$, 2 equivalents of $ZnBr_2$ in THF for 17 hours at room temperature as described in **scheme 61**.




**Scheme 61**

**Table 10**

| Cyclopropane | Substrate | Yield | Product  | Diastereoisomeric Ratio *Trans* : *Cis* |
|---|---|---|---|---|
| **107** |  **123** | 76 % | **124** | - |
| **107** |  **125** | 68 % | **126** | 7 : 1 |
| **107** |  **127** | **NR** | - | - |
| **107** |  **128** | 42 % | **129** | 1 : 1.5 |
| **107** |  **130** | **NR** | - | - |
| **107** |  **131** | **NR** | - | - |

Reagents and conditions: (1 mmol) **107** with (1 mmol) $\alpha$-keto ester was carried out in the presence of 10 mol % $Pd(PPh_3)_4$ and 2 mmol $ZnBr_2$ in THF at 20°C.

Initially 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** was treated with diethylketomalonate **123** in the presence of $Pd(PPh_3)_4$, 2 equivalents of $ZnBr_2$ and THF at room temperature for 17 hours to afford the desired cycloadduct **124** in good yield (76 %). Due to the symmetry of the starting material, diastereoisomers were not formed in this instance. The good yield of the reaction could be attributed to the extremely electrophilic ketone moiety, with the two adjacent electron withdrawing ester groups present. This reaction was repeated in the absence of the Lewis acid, $ZnBr_2$ in THF. The reaction was successful but a decrease in yield of the product was observed (30 %). This was a surprising result as the Lewis acid has always been a useful variable in this methodology up until this point. It was reasoned that the ketone moiety, in the presence of the two adjacent electron-withdrawing groups, was electrophilic enough to encourage attack from the nucleophilic malonic centre of the zwitterionic $\pi$-allyl palladium (II) intermediate even in the absence of the Lewis acid. The reaction was also repeated in DMF in the absence of the $ZnBr_2$, and again, the yield of the desired cycloadduct isolated was lower (40 %) than the isolated yield for the reaction with the inclusion of $ZnBr_2$. The slight increase in the polarity of the solvent from THF to DMF was suspected to be the rationale for the slight increase in comparative yields between the two reactions carried out in the absence of the Lewis acid. The more polar solvent should stabilize the formation of the zwitterionic $\pi$-allyl palladium complex and hence encourage the nucleophilic attack on the ketone, resulting in an increase in product yield.

With the success of using diethylketomalonate **123** as an electrophile, another substrate possessing a carbonyl adjacent to two electron-withdrawing groups was selected to undergo the palladium catalyzed [3 + 2] cycloaddition. Ethyltrifluoropyruvate **125** was chosen for this purpose. 2-Vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** and ethyl trifluoropyruvate **125** underwent a palladium catalyzed [3 + 2] cycloaddition when subjected to the standard cyclization conditions. The cycloadduct **126** was isolated in good yield (68 %) with the *trans* diastereoisomer predominating. Due to the presence of the strong electron-withdrawing trifluoro and ester groups, it was suspected that the ketone was

electrophilic enough to participate in the [3 + 2] cycloaddition without the $ZnBr_2$. A decrease in yield was observed on repeating the reaction in THF and DMF in the absence of the $ZnBr_2$ (25 % and 36 % respectively). Again, the more polar solvent stabilizes the zwitterionic $\pi$-allyl palladium complex and encouraging nucleophilic attack. The mixture of diastereoisomers was separated by column chromatography. The assignment of diastereoisomers was determined by $^1$HNMR spectroscopy. The hydrogens at the 4-C position on the tetrahydrofuran ring behave differently for the two diastereoisomers in the spectrum and hence are distinguishable by their chemical shift. For the *trans* isomer the hydrogen adjacent to the vinyl group appears at a lower chemical shift than the corresponding hydrogen for the *cis* isomer. Also noteworthy for the *trans* isomer, the hydrogen adjacent to the malonic centre appears at a higher chemical shift than the corresponding hydrogen for the *cis* isomer. There is therefore a greater difference of chemical shifts between the *trans* diastereoisomer hydrogens at C-4 on the tetrahydrofuran ring than that observed for the *cis* diastereoisomer. However for this particular example the prevelant diasteroisomer was assigned as the *trans* isomer even though it behaved as the *cis* isomer in the spectrum due to the high priority of the trifluoro group compared to the ethyl ester with respect to the vinyl group.

As the trifluoromethyl group was well tolerated by the reaction conditions, a progression from the successful isolation of the cycloadduct on utilizing ethyltrifluoropyruvate **125** as an electrophile, led us on to attempt the cyclization using hexafluoroacetone **127**. In this example the carbonyl is adjacent to two electron-withdrawing trifluoro groups and is very electrophilic. The recovery of starting materials could be attributed to the electrophile exisiting in a hydrated form rather than the dehydrated ketone form.

With the success of the cyclcloaddition between 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** and a substrate with two adjacent electron-

withdrawing substituents to the carbonyl, it was decided to attempt the cyclization with an electrophile possessing a ketone moiety activated by only one electron-withdrawing group.

Ethylpyruvate **128** was selected and subjected to 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** in the presence of 10 mol % $Pd(PPh_3)_4$, 2 equivalents of $ZnBr_2$ in THF for 17 hours at room temperature. The product **129** was isolated in average yield (42 %) as a pair of diastereoisomers (*trans* : *cis*; 1 : 1.5). The decrease in observed yield compared to that obtained for the reaction using diethylketomalonate **123** as a substrate, could be attributed to the presence of the electron donating methyl group and hence the ketone moiety was slightly less electrophilic than the ketone moiety in diethylketomalonate **123**. Only starting materials were recovered for the reaction in THF in the absence of Lewis acid. It could be reasoned that the ketone moiety was not electrophilic enough to participate in the nucleophilic addition of the zwitterionic $\pi$-allyl palladium complex without the electron withdrawing properties of the $ZnBr_2$ for this particular example.

A sterically demanding electrophile was chosen to demonstrate the steric constraints of the reaction. Ethyl-3-methyl-2-oxobutyrate **130** was selected due to the presence of the sterically demanding isopropyl group adjacent to the ketone moiety. On recovery of the starting materials for this reaction, it can be presumed that sterically demanding groups adjacent to the ketone are not tolerated in these standard palladium catalyzed cycloaddition conditions. It can be reasoned that a bulky group could hinder the nucleophilic addition of the malonic centre of the palladium $\pi$-allyl species to the electrophlilic ketone moiety and hence starting materials are isolated.

The proposed rationale to the recovery of starting materials when 2,3-dioxobutane **131** was chosen as an electrophile is the presence of the acidic enolizable protons in the substrate (**figure 8**).

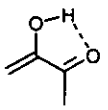
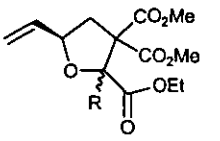
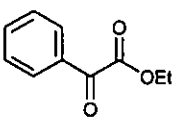
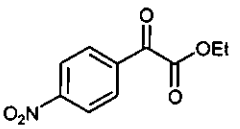
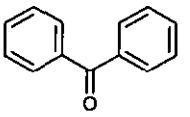
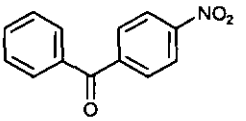
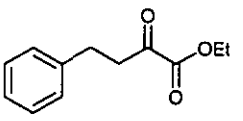
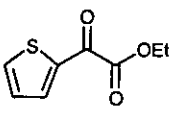


**Figure 8**

With the success of the palladium catalyzed cycloadditions with non-aromatic substrates, the reaction was attempted with a range of aromatic electrophiles. The electrophiles chosen are detailed in **table 11**

Table 11

| Cyclopropane | Substrate | Yield | Product  | Diastereoisomeric Ratio. *Trans* : *Cis* |
|---|---|---|---|---|
| **107** |  **132** | **NR** | - | - |
| **107** |  **133** | 73 % | **134** | 4 : 1 |
| **107** |  **135** | **NR** | - | - |
| **107** |  **136** | **NR** | - | - |
| **107** |  **137** | 62 % | **138** | 1 : 1 |
| **107** |  **139** | **NR** | - | - |

Reagents and conditions: (1 mmol) **107** with (1 mmol) $\alpha$-keto ester was carried out in the presence of 10 mol % $Pd(PPh_3)_4$ and 2 mmol $ZnBr_2$ in THF at 20°C.

Ethylbenzoylformate **132**, was chosen as a substrate primarily due to the successful isolation of the cycloadduct on treatment of ethylpyruvate **128** to the standard palladium [3 + 2] cycloaddition conditions. The recovery of the starting materials indicated that on replacing the methyl group of ethylpyruvate **128**, with an un-activated phenyl ring in ethylbenzoylformate **132** did not appear to be well tolerated by the reaction. We rationalised that the electronic effects of an un-activated ring system adjacent to the ketone moiety and hence in turn, the tetrahydrofuran, appeared to be detrimental to the successful formation of the product.

It was then decided to attempt the cyclization with a phenyl ring activated by an electron-withdrawing substituent. Ethyl 4-nitrophenylglyoxylate **133** was chosen as an electrophile for the reaction so a direct comparison could be made between the activated and un-activated phenyl rings. In this particular example, the phenyl ring is activated by an electron-withdrawing nitro group. The cycloadduct **134** was isolated in good yield (73 %) on treatment of ethyl 4-nitrophenylglyoxylate **133** with 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107**. For this particular example the electron-withdrawing properties of the nitro group increased the electrophilicity of the ketone and hence encouraged nucleophilic attack from the palladium π-allyl species. The conclusion could now be drawn that phenyl rings adjacent to the ketone moiety have to be activated by an electron-withdrawing group for the ketone to participate in the nucleophilic addition with the malonic centre of the palladium π-allyl species.

It was then decided to attempt the [3 + 2] cycloaddition using substrates that did not possess an ethyl ester to confirm that the electron-withdrawing group was essential to the successful isolation of the product. The phenyl analogue of acetone, benzophenone **135** was selected as the substrate as it could re-iterate the previous result obtained by Lam Tang that un-activated ketones are not electrophilic enough to participate in the [3 + 2] cycloadditon. The isolation of starting materials did in fact

indicate that ketones do require further activation by an electron-withdrawing substituent, especially if the group adjacent to the ketone is aromatic.

As previously discussed for ethyl 4-nitrophenylglyoxylate **133**, the introduction of an electron-withdrawing nitro group to the aromatic ring, sufficiently activated the ketone to undergo the cycloaddition. Therefore progression from the unsuccessful cyclization of benzophenone **135**, nitrobenzophenone **136** was then chosen as an electrophile to indicate whether the electron-withdrawing nitro group could encourage the ketone to participate in the [3 + 2] cycloaddition even in the absence of the ethyl ester. Again recovery of starting materials indicated that phenyl rings adjacent to the ketone do require activation by an electron-withdrawing group.

Now it had been established that phenyl rings adjacent to the ketone require an electron-withdrawing group to participate in the cycloaddition, it was interesting to test whether a carbon spacer between the ketone and phenyl ring could make a difference to the outcome of the reaction with an un-activated aromatic group. To test this rationale, 2-oxo-4-phenylbutyrate **137** was chosen as an electrophile. The cycloadduct **138**, was isolated in good yield (62 %) with a 1 : 1 diastereoisomeric ratio. The diastereoisomers were separated by column chromatography and nOe data was able to assist in their identification. The nOe correlation is detailed in **figure 9**.

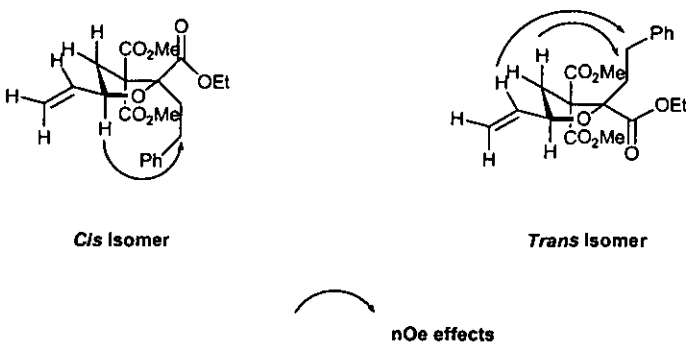



**Figure 9**

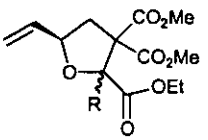
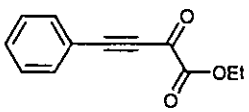
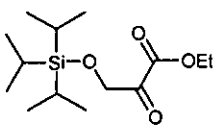
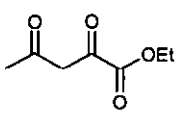
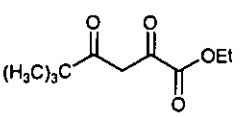
The nOe data for one isomer shows a positive correlation between the hydrogen adjacent to the vinyl group and the hydrogens on the carbon spacer, indicating that they are both on pointing in the same direction *i.e.* the *cis* isomer. The nOe data for the other isomer indicates positive nOes between the hydrogen on the vinyl group and the hydrogens on the carbon spacer and hence indicating that it is the *trans* isomer. This data also confirms the behaviour of the tetrahydofuran C-4 ring protons in the $^{1}$HNMR spectrum. It confirms that the difference in chemical shift between the two ring protons of the *trans* isomer is larger than that observed for the *cis* isomer.

It could therefore be concluded that a carbon spacer is essential between the ketone and the aromatic ring, if the phenyl ring is un-activated.

This also appeared to be the case for the example using ethylthiophene-2-glyoxylate **139** as a substrate. The un-activated aromatic ring next to the ketone moiety could be a plausible explanation as to why this example failed to give the desired cycloadduct.

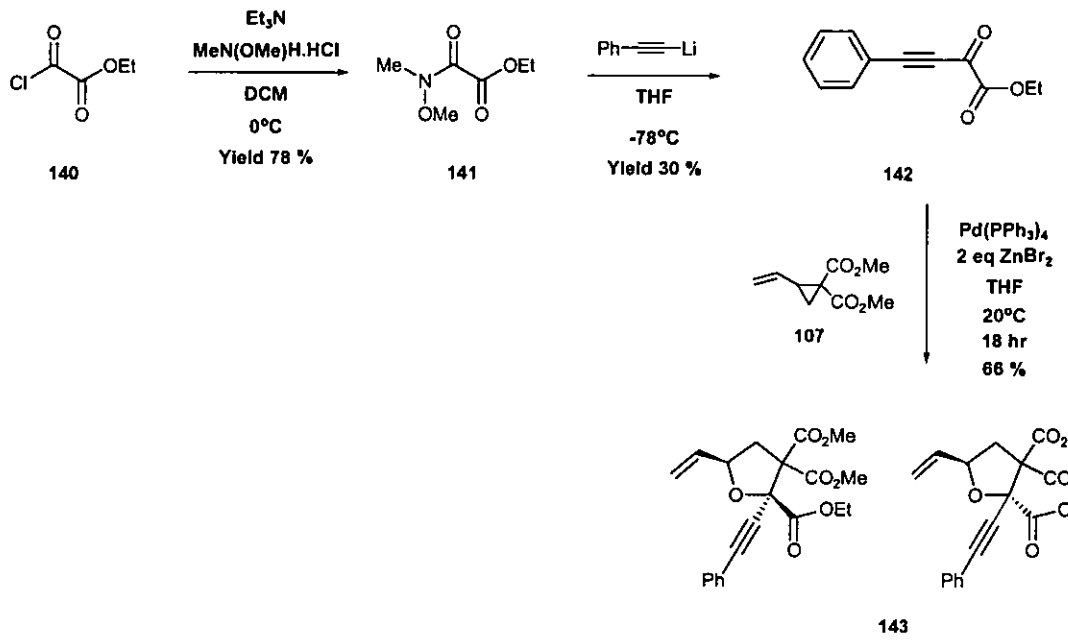
To further explore the scope of the reaction, other electrophiles were chosen to participate in the palladium catalyzed [3 + 2] cycloaddition to indicate the range of functionality tolerated by the reaction conditions. These are listed in **table 12**.

**Table 12**

| Cyclopropane | Substrate | Yield | Product | Diastereoisomeric Ratio. *Trans* : *Cis* |
|---|---|---|---|---|
| | | |  | |
| **107** |  **142** | 66 % | **143** | 1 : 3.3 |
| **107** |  **147** | 56 % | **148** | *cis* exclusively |
| **107** |  **150** | **NR** | - | - |
| **107** |  **151** | **NR** | - | - |

Reagents and conditions: (1 mmol) **107** with (1 mmol) α-keto ester was carried out in the presence of 10 mol % $Pd(PPh_3)_4$ and 2 mmol $ZnBr_2$ in THF at 20°C.

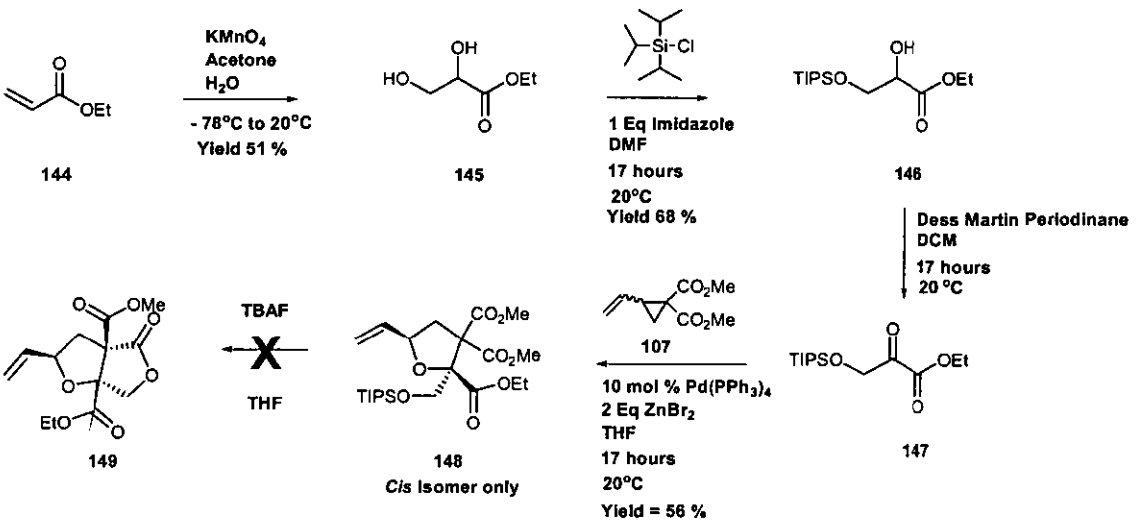
The synthesis of the ethyl 2-oxo-4-phenylbut-3-ynoate **142** was achieved via the intermediate Weinreb amide **141** (**scheme 62**).




**Scheme 62**

*N,O*-Dimethylhydroxlamine hydrochloride was treated with triethylamine and ethyl oxalyl chloride **140** in dry DCM to afford the desired Weinreb amide **141**, monoethyloxalic acid-*N*-methoxy-*N*-methylamide in good yield (78 %).[68] The Weinreb amide **141** was subsequently treated with lithium phenylacetylide to afford the desired $\alpha$-keto ester **142** in poor yield (30 %). Ethyl 2-oxo-4-phenylbut-3-ynoate **142** was then in turn treated with 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107**, $Pd(PPh_3)_4$, Lewis acid and THF to afford the desired furan **143** as a pair of diastereoisomers (3.3 : 1, *cis* : *trans*) in good yield (66 %).

Following a literature precedent, the synthesis of 2-oxo-3-triisopropylsilanyloxy-propionic acid ethyl ester **147** was achieved from the readily available ethylacrylate **144** (**scheme 63**). This was an exciting example to try as the cycloadduct formed could be deprotected and the final step on deprotection of the alcohol, the oxygen anion should subsequently be involved in an intramolcular 5-exo-trig cyclization onto one of the methyl esters with loss of methoxide. This intramolecular cyclization would construct the bicyclic structure **149**.

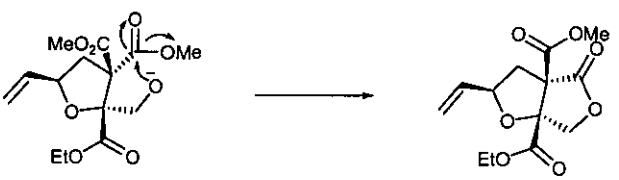



**Scheme 63**

Ethyl acrylate **144** was oxidized with potassium permanganate in acetone and water to afford the diol, 2,3-dihydroxy-propionic acid ethyl ester **145** as a colourless oil in reasonable yield (51%).[69] The primary alcohol was then protected with triiospropylsilyl chloride[70] in good yield (68%), leaving the secondary ready for oxidation using Dess Martin periodinane. The $\alpha$-keto ester formed, 2-oxo-3-triisopropylsilanyloxy-propionic acid ethyl ester **147** was unstable on standing and was taken onto the next step immediately without further purification.

2-Oxo-3-triisopropylsilanyloxy-propionic acid ethyl ester **147** was treated with 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** in the presence of 10 mol% $Pd(PPh_3)_4$, 2 equivalents of Lewis acid, $ZnBr_2$ in THF at room temperature to afford the desired cycloadduct **148** as the *cis* diastereoisomer exclusively in a reasonable yield (56 %). Once again, the $^1$HNMR indicated that the *cis* diastereoisomer had been formed exclusively by the chemical shift of the protons on the 4-C on the ring. It could be postulated that the *cis* isomer was formed exclusively in the reaction due to the steric bulk of the triisopropylsilanyl group lying *cis* with respect to the less sterically hindering hydrogen and *trans* to the bulkier vinyl group.

It was attempted to deprotect the silyl group using TBAF. The oxygen anion should have subsequently participated in a favoured 5-exo-trig cyclization onto the *cis* methyl esters with the loss of methoxide (**scheme 64**). Unfortunately though, there was no conclusive evidence that the desired bicyclic structure **149** had been formed and a complex mixture was observed.

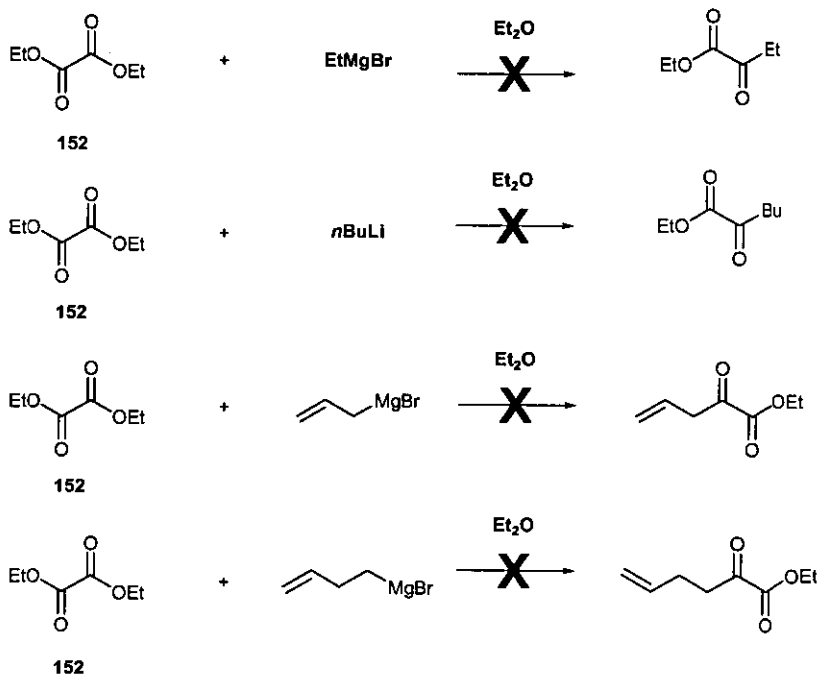



**Scheme 64**

The presence of the acidic enolizable protons in ethylacetopyruvate **150** and ethyltrimethylacetopyruvate **151**, are the suspected cause for the recovery of starting materials when subjected to $Pd(PPh_3)_4$.

### 2.2.2 Synthesis of $\alpha$-keto esters

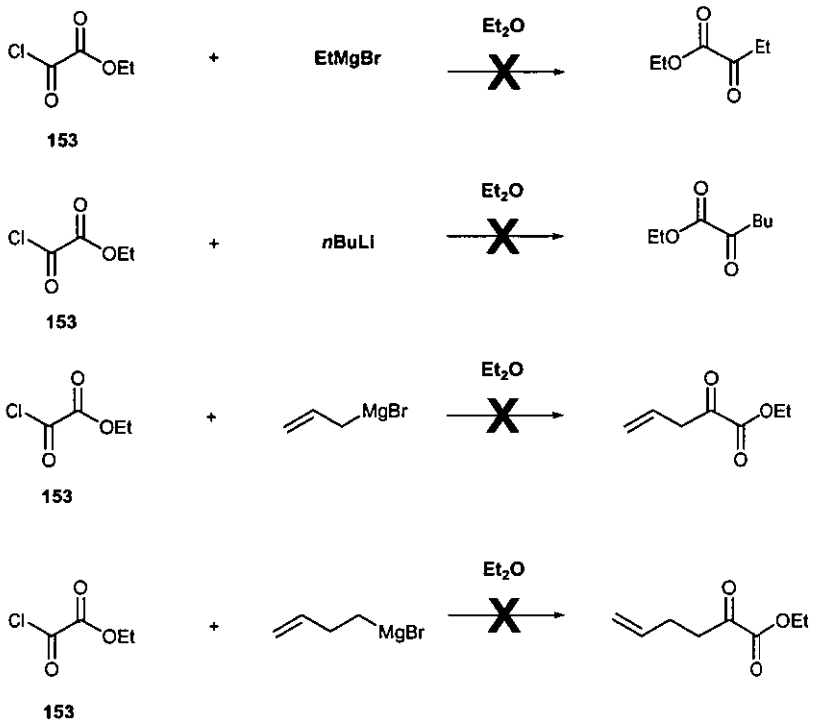
The synthesis of a range of α-keto esters did not prove to be trivial. Initially Grignard addition to diethyloxalate **152** seemed an attractive route into a wide range of ethyl $\alpha$-keto esters (**scheme 65**). [71]




**Scheme 65**

However, the separation of the starting diethyloxalate and over addition products from the intended ketone proved to be extremely difficult due to them having exceptionally similar $R_F$ values and a difference of a few degrees in boiling points. The reactions were repeated varying the equivalents of the Grignard reagent used, the addition times, reaction temperature and solvents used with little success of obtaining the purified desired product.

Unfortunately on switching from diethyloxalate **152** to ethyl chlorooxoacetate **153** the same problems arose and the desired product was totally inseperable from the overaddition products and the unreacted starting materials (**scheme 66**).




**Scheme 66**

### 2.2.3 Summary and Conclusions

A novel palladium catalyzed [3 + 2] cycloaddition has been reported between the zwitterionic π-allyl palladium(II) complex of 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** and the ketone moiety of α-keto esters to afford highly substituted tetrahydrofuran cycloadducts. It appears to be an elegant route into the construction of tetrahydrofurans as in one step a carbon-carbon bond, a carbon-oxygen bond and a quaternary centre have been constructed. The reaction appears to tolerate a large range of functional groups.

However there does appear to be a few limitations to the scope of the reaction.

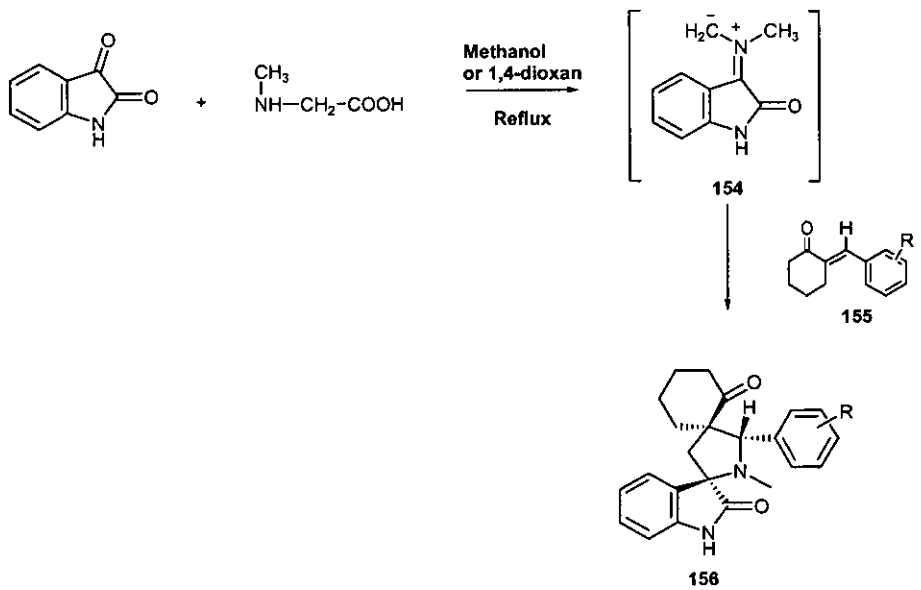
It is apparent that an ester group, or other electron-withdrawing substituents are crucial to the successful isolation of the [3 + 2] cycloadduct to enhance the electrophilicity of the ketone.

Un-activated phenyl or bulky groups adjacent to the ketone do not appear to be tolerated in the successful course of the reaction. However the reaction appears more successful if adjacent phenyl rings are activated by electron-withdrawing groups. Otherwise carbon spacer between the ketone moiety and the un-activated phenyl ring is required.

# 2.3 Intermolecular Palladium Catalyzed [3 + 2] Cycloadditions with Vinylcyclopropane and Isatin

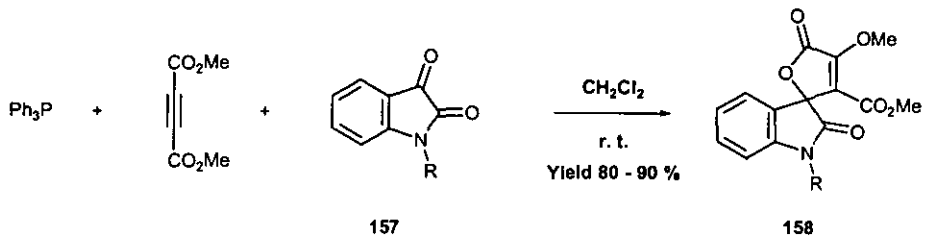
## 2.3.1 Recent Interest in Spiro Fused Heterocycles

Spiro lactones and spiro pyrrolidines have attracted a great deal of interest recently due to the potential pharmaceutical activity they are suspected to possess.[72] Spiro pyrrolidines have been screened for antibacterial and antifungal activity and have been reported to show good to moderate activity against various pathogens and dermatophytic fungi.[72] Raj *et al* have recently reported an efficient route into spiro pyrrolidines **156** by a regioselective 1,3-dipolar cycloaddition of azomethine ylides **154** (1,3-dipoles) with various dipolarophiles **155**.[73, 74]

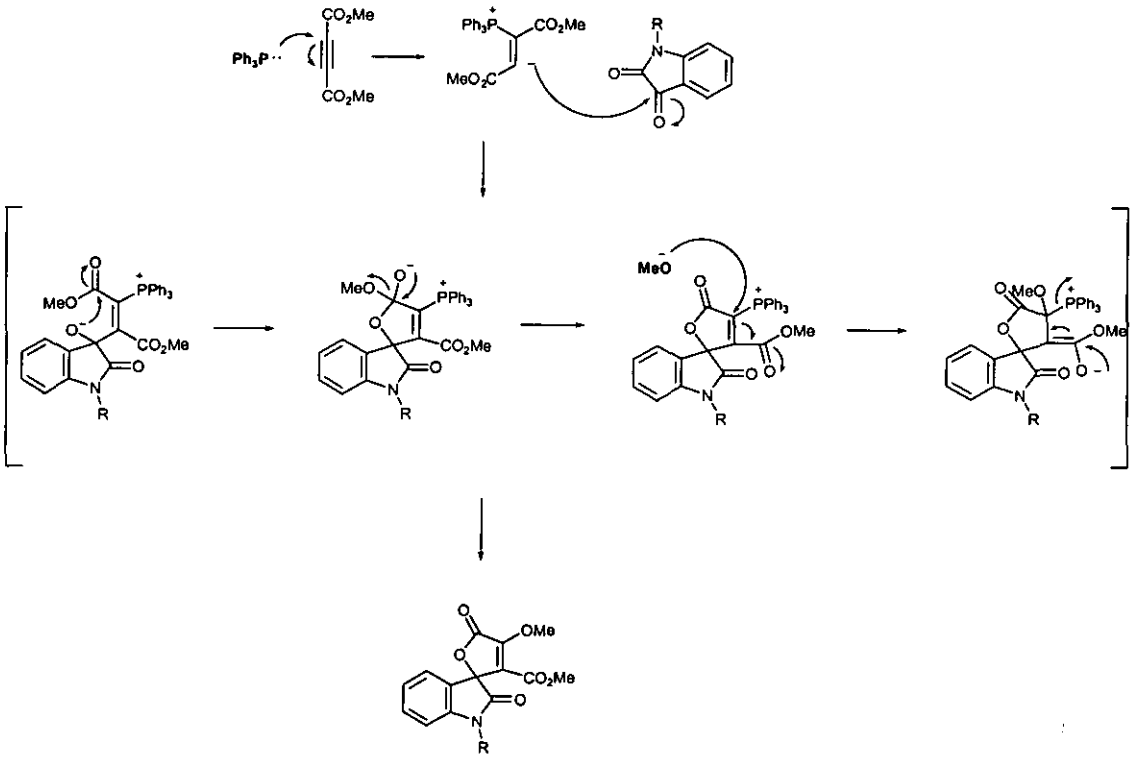



**Scheme 67**

Esmaeili *et al* have recently reported the facile synthesis of highly functionalised γ-spiro iminolactones **158** starting from isatin derivatives **157** and DMAD (dimethyl acetylene dicarboxylate) in the presence of triphenylphosphine affording heterocycles (**scheme 68**).[75]

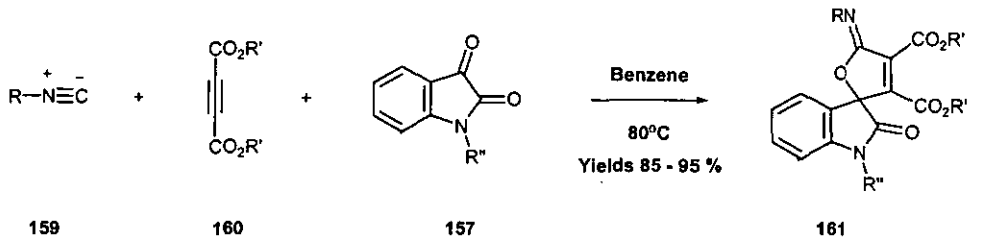



157 158

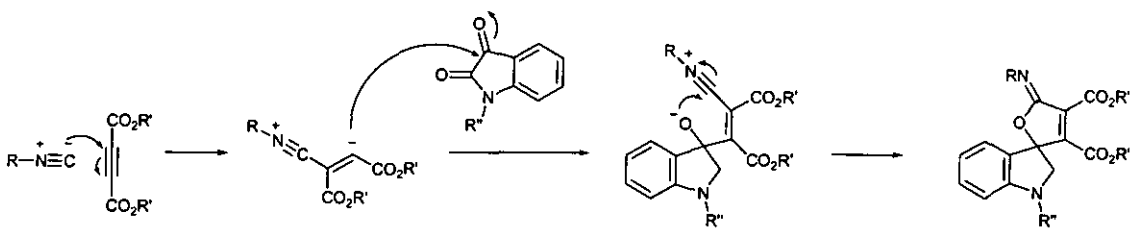



**Scheme 68**

He went on to publish utilizing a cycloaddition approach between alkyl isocyanides **159** and acetylinic esters **160** in the presence of *N*-alkyl isatins **157** in benzene to give **161 (scheme 69)**.[76]



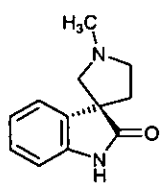

**159** **160** **157** **161**



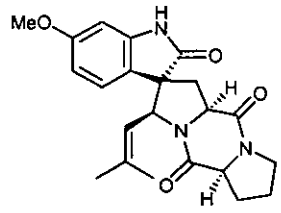
**Scheme 69**

## 2.3.2 Natural Occurrence of Spiro Fused Hetereocycles

Some natural products with this spiro motif are as shown in **figure 10.**



(-) Horsfiline

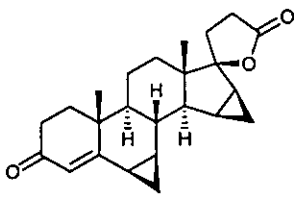


Spirotryprostatin A

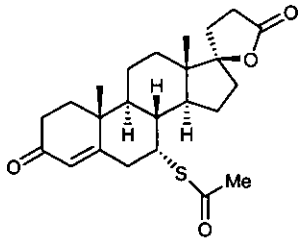
**Figure 10**

(-) Horsfiline[77] and spirotryprostatin A[78] show significant biological activities.

Spiro systems are also present as the key framework of numerous steroids[79] for example drospirenone 1 and spironolactone 2 **figure 11.** [80]



Drospirenone 1



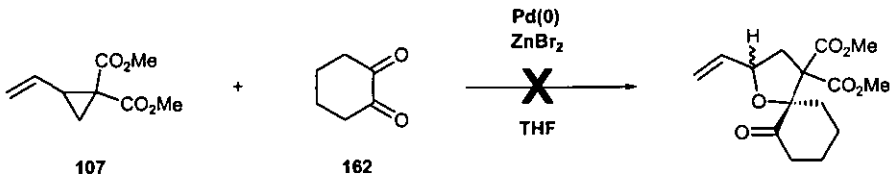
Spironolactone 2

**Figure 11**

### 2.3.3 Application of the Palladium Catalyzed [3 + 2] Cycloaddition to the Synthesis of Spiro Fused Tetrahydrofurans

It was decided to investigate whether the methodology developed within the group would be a feasible route into these spirolactone type of motifs. Based on previous results, successful cyclizations of ketone moieties have been dependent on the presence of an adjacent electron-withdrawing group, hence an electrophilic cyclic ketone would be required.

Initially the commercially available acyclic dicarbonyl cyclohexane-1,2-dione **162** was treated with 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** in the presence of $Pd(PPh_3)_4$ (**scheme 70**). The di-carbonyl was used to indicate whether adjacent carbonyls were sufficiently activated by each other towards nucleophilic attack and hence afford the desired [3 + 2] cycloadduct.



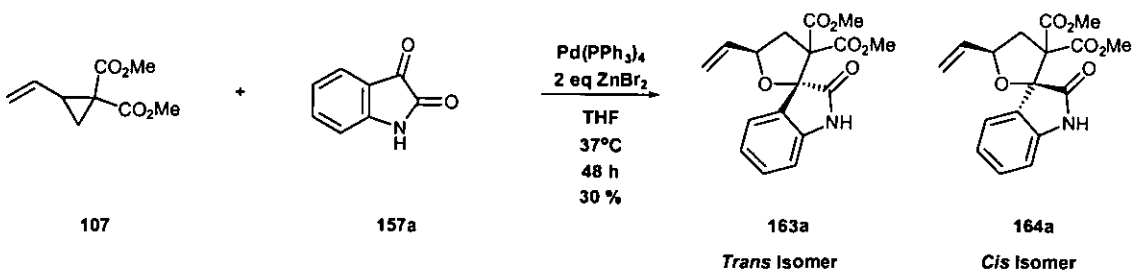

**Scheme 70**

Employing cyclohexane-1,2-dione **162** as the electrophile, the reaction failed to produce the desired spirotetrahydrofuran cycloadduct both in the presence and absence of the Lewis acid, $ZnBr_2$. The failure of the palladium catalyzed [3 + 2] cycloaddition could be attributed to the fact that the ketone moieties were not electrophilic enough to encourage nucleophilic attack. Also the presence of acidic enolizable $\alpha$ protons could also be the underlying cause as to the reaction failure and hence the desired tetrahydrofurans not being isolated. The carbonyls could exist in the hydrated form rather than the dehydrated ketone form.

### 2.3.4 The Use of Isatin as the Electrophile

As the presence of the $\alpha$-acidic protons appeared to be detrimental to the [3 + 2] cycloaddition reaction course, cyclizations with isatin as the electrophile were attempted. Isatin was selected as the presence of the aromatic ring would remove any enolization of the carbonyl moiety and make the [3 +2] cycloaddition reaction course move favourable. Here the adjacent electron-withdrawing group is an amide, hence the ketone moiety should be electrophilic enough to promote nucleophilic attack from the malonic centre of the palladium $\pi$-allyl species.

2-Vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** was treated with isatin **157** in the presence of zinc bromide and palladium(0) in THF to afford the desired spiro tetrahydrofuran in moderate yield (30 %) in roughly 1 : 1 diastereomeric ratio (**scheme 71**). The diastereoisomeric ratio was determined from the crude $^1$HNMR.

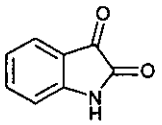
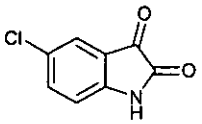
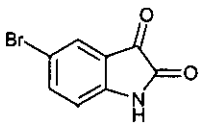
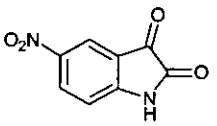
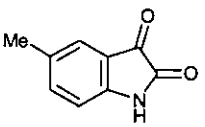
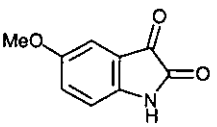



**107** **157a** **163a** *Trans* Isomer **164a** *Cis* Isomer

**Scheme 71**

Due to the successful isolation of the desired isatin spiro fused cycloadduct **163** and **164**, cyclization reactions were attempted on isatins containing various substituents to define the scope of the reaction. **Table 13** describes the electrophiles chosen.

Table 13

| Entry | 107 | Isatin 157 | Yield[a] | Diastereomeric ratio.[b] *Trans* 163 : *Cis* 164 |
|---|---|---|---|---|
| 1 | 107 |  **157a** | 30 % | **163a** : **164a** 1.5 : 1 |
| 2 | 107 |  **157b** | 59 % | **163b** : **164b** 1 : 1 |
| 3 | 107 |  **157c** | 62 % | **163c** : **164c** 1.2 : 1 |
| 4 | 107 |  **157d** | 67 % | **163d** : **164d** 1 : 1.5 |
| 5 | 107 |  **157e** | 53 % | **163e** : **164e** 1: 1 |
| 6 | 107 |  **157f** | 32 % | **163f** : **164f** 1 : 1 |

[a] Isolated yield. [b]Diastereomeric ratio based on $^1$H NMR peak integrations.
Diastereoisomers not separated unless stated. Reagents and conditions: (1 mmol) **107** with (1 mmol) isatin **157** was carried out in the presence of 10 mol % $Pd(PPh_3)_4$ and 2 mmol $ZnBr_2$ in THF at 37°C.

Initially a range of substituents were introduced onto the aromatic ring to explore the range of functional groups tolerated by the reaction conditions and hence discover the scope and limitations of the reaction.

2-Vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** (1 mmol) was treated with isatin **157a** (1 mmol) in THF at 37°C in the presence of a catalytic amount of $Pd(PPh_3)_4$ (10 mol %) and $ZnBr_2$ (2 mmol) to afford the spiro cycloadduct in 30 % yield. When the reaction was attempted in absence of the Lewis acid only a trace of product was observed. The role of the Lewis acid is therefore crucial to the successful formation of the cycloadduct due to activation of the electrophilic carbonyl by electron acceptance. The observed increase in yield for the cyclization of the halogen isatins **157b** and **157c** may be explained by the electon-withdrawing nature of the halogen substituents, which in turn, further activates the carbonyl moiety towards attack from the malonate centre of the palladium π-allyl intermediate.

The diastereoisomers could be differentiated in the $^1$HNMR. For each diastereoisomer the hydrogens on 4-C of the tetrahydrofuran ring have characteristic features in the $^1$HNMR. The $^1$HNMR spectrum of the mixture of diastereoisomers **163b** and **164b** is shown in **figure 12**. The $^1$HNMR spectrum details that the hydrogen closer to the vinyl group for the *trans* isomer appears at 2.58 ppm. For the *cis* isomer the hydrogen closer to the vinyl group appears at 2.78 ppm, *i.e.* further downfield when compared to the corresponding hydrogen in the *trans* isomer. Also for the *trans* diastereoisomer, the hydrogen adjacent to the malonic centre appears further downfield (3.18 ppm) in the $^1$HNMR spectrum in comparison to the corresponding *cis* diastereoisomer (2.98 ppm). There is therefore a greater difference in chemical shift between the *trans* hydrogens on 4-C on the tetrahydrofuran ring than the corresponding *cis* diastereoisomer.

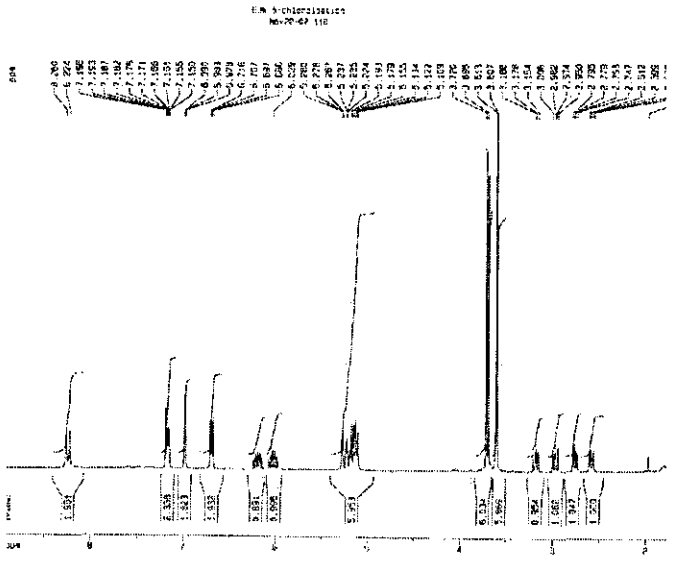


**Figure 12**

The *cis* diastereoisomer **164b** was separated from the mixture by column chromatography (**figure 13**).

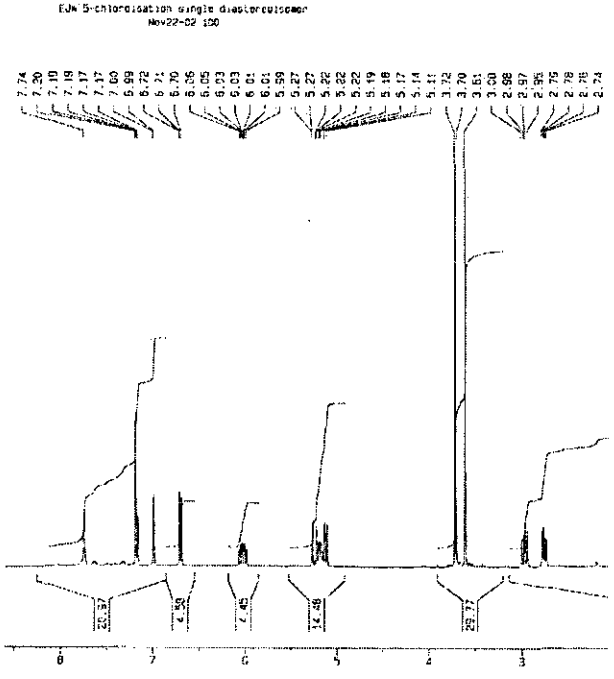


**Figure 13**

The isolation of the single diastereoisomer confirmed that the hydrogens on the tetrahydrofuran ring of the *cis* isomer did appear in the $^1$HNMR spectrum in-between the hydrogens of the *trans* isomer. The structure of the cis diastereoisomer was determined by nOe studies. These detail a positive correlation between the phenyl ring and the hydrogen *ipso* to the vinyl group (**figure 14**). This was good evidence that the hydrogen adjacent to the vinyl group and the phenyl ring were on the same face and hence the amide and the vinyl group were also on the same face and hence this isomer could be characterized as the *cis* diastereoisomer.

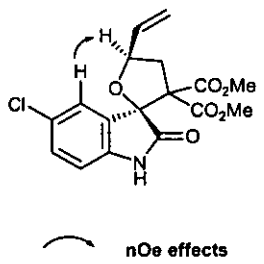



**Figure 14**

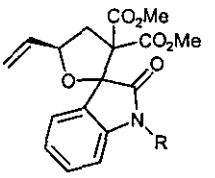
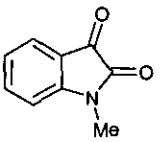
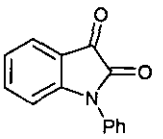
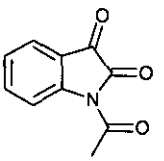
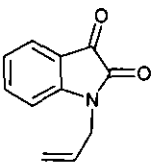
The ratio of diastereoisomers could with confidence now be determined by the crude $^1$HNMR spectra and reported in their respective ratios.

The successful isolation of the diastereoisomers **163d** and **164d** in good yield was again attributed to the strong electron-withdrawing nature of the nitro group and hence enhancing the electrophilicity of the carbonyl, encouraging cycloaddition with the nucleophilic palladium π-allyl intermediate. The cycloaddition between methoxy isatin **157f** and 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** proceeded in decreased yield to afford **163f** and **164f** as expected due to the electron-donating nature of the methoxy group and hence reducing the electrophilicity of the ketone.

As the cycloadditions were so successful for the isatins substituted on the phenyl ring, it was decided to attempt the palladium catalyzed [3 + 2] cycloaddition using isatin

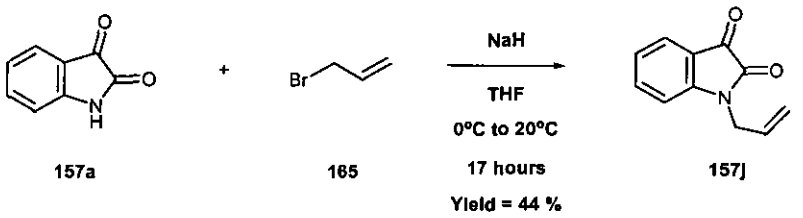
substituted on the nitrogen of the pyrrolidine ring. The substrates chosen are listed in **table 14**.

**Table 14**

| Entry | 107 | Isatin 157 | Yield[a]  | Diastereomeric ratio[b] *Trans* 163 : *Cis* 164 |
|---|---|---|---|---|
| 7 | 107 |  **157g** | 70 % | **163g : 164g** 1 : 1 |
| 8 | 107 |  **157h** | 74 % | **163h : 164h** 1 : 1.5 |
| 9 | 107 |  **157i** | 71 % | **163i : 164i** 1 : 1.5 |
| 10 | 107 |  **157j** | 67 % | **163j : 164j** 1 : 1 |

[a] Isolated yield. [b]Diastereomeric ratio based on $^1$H NMR peak integrations.
Diastereoisomers not separated unless stated. Reagents and conditions: (1 mmol) **107** with (1 mmol) isatin **157** was carried out in the presence of 10 mol % $Pd(PPh_3)_4$ and 2 mmol $ZnBr_2$ in THF at 37°C.

A significant increase in yield of spiro cycloadducts **163 g-j** and **164 g-j** was observed on substituting the nitrogen of the pyrollidine ring. This trend could be reasoned by the absence of the acidic proton or the presence of the electron withdrawing groups on the pyrrolidine ring. Hence the reaction yields are significantly increased on replacing the proton for a phenyl, acetyl and allyl group. Allyl isatin **157j** was synthesized by deprotonating isatin using NaH, the anion in turn participated in an nucleophilic substitution reaction with allyl bromide **165** to afford **157j**.




**Scheme 72**

### 2.3.5 Solvent Effects on the Stereochemical Outcome of the Reaction

Unfortunately, the reaction carried out in the solvent THF gave rather disappointing diastereoselectivities with roughly a ratio of 1 : 1 *trans* : *cis* diastereoisomers being isolated in each case. In order to try and improve the stereochemical outcome of the reaction, different reaction solvents were employed.

The solvent effects on the [3 + 2] cycloaddition between the doubly activated vinylcyclopropane **107** and the isatins **157** have been investigated. 2-Vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** (1 mmol) was treated with 1-phenyl isatin **157h** (1 mmol) in various solvents at 37°C in the presence of a catalytic amount of $Pd(PPh_3)_4$ (10 mol %) and $ZnBr_2$ (2 mmol) to afford the spiro cycloadduct **163h** and **164h**. 1-Phenyl isatin **157h** was chosen due to the high yields obtained previously. The results are summarized in **table 15**.

**Table 15**

| Entry | Solvent | Yield | Diastereomeric ratio[b] *Trans* **163h** : *Cis* **164h** |
|---|---|---|---|
| 1 | Toluene | [a]23 % | 2 : 1 |
| 2 | Acetone | trace | - |
| 3 | DCM | [a]52 % | 6 : 1 |
| 4 | THF | [a]76 % | 2 : 3 |
| 5 | DMF | [a]78 % | 2 : 3 |
| 6 | Acetonitrile | [a]62 % | 1 : 5 |

[a] Isolated yield. [b]Diastereomeric ratio based on $^1$H NMR peak integrations.
Diastereoisomers not separated unless stated. Reagents and conditions: (1 mmol) **107** with (1 mmol) isatin **157h** was carried out in the presence of 10 mol % $Pd(PPh_3)_4$ and 2 mmol $ZnBr_2$ in solvent at 37°C.

The results obtained were encouraging. On decreasing the polarity of the solvent from THF to DCM, a small decrease of yield was observed, but the most important thing to note was that the ratio of diastereoisomers was significantly altered. The major diastereoisomer isolated was *trans* with only a trace of the *cis* isomer being observed. The *trans* diastereoisomer was isolated exclusively by column chromatography and a crystal structure was obtained, **figure 15**. This crystal structure re-enforces the correct structure assignment and diastereoselective outcome of the reaction with **157h** in DCM.

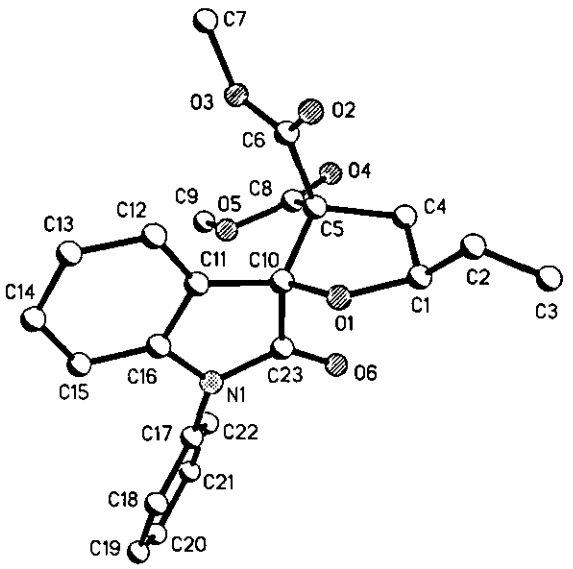



**Figure 15**

The x-ray data of **163h** is indisputable proof that the correct assignment of the diastereoisomers using $^{1}$HNMR spectroscopy had been achieved. The $^{1}$HNMR spectrum for the mixture of diastereoisomers obtained for the reaction carried out in THF is detailed in **figure 16**. Again the characteristics of the hydrogens on the tetrahydrofuran ring between the two diastereoisomers are apparent in the $^{1}$HNMR spectrum. The hydrogen closest to the vinyl group in the *trans* diastereoisomer appears futher upfield (2.63 ppm) compared to the *cis* diastereoisomer (2.80 ppm). It is also apparent that the hydrogen adjacent to the malonic centre for the *trans* diastereoisomer appears further downfield (3.23 ppm) than the corresponding hydrogen of the *cis* diastereoisomer (3.04 ppm).

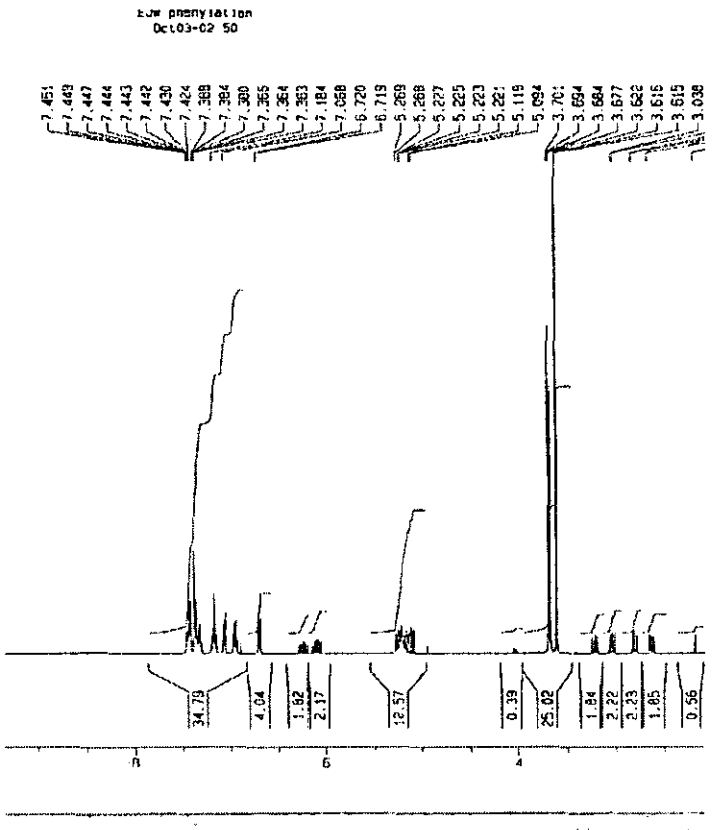



**Figure 16**

The $^{1}$HNMR obtained for the single *trans* diastereoisomer **163h** is shown in **figure 17**. It details that the hydrogens on the tetrahydrofuran ring correspond to the *trans* diastereoisomer **163h**. This is also confirmed by the x-ray data.

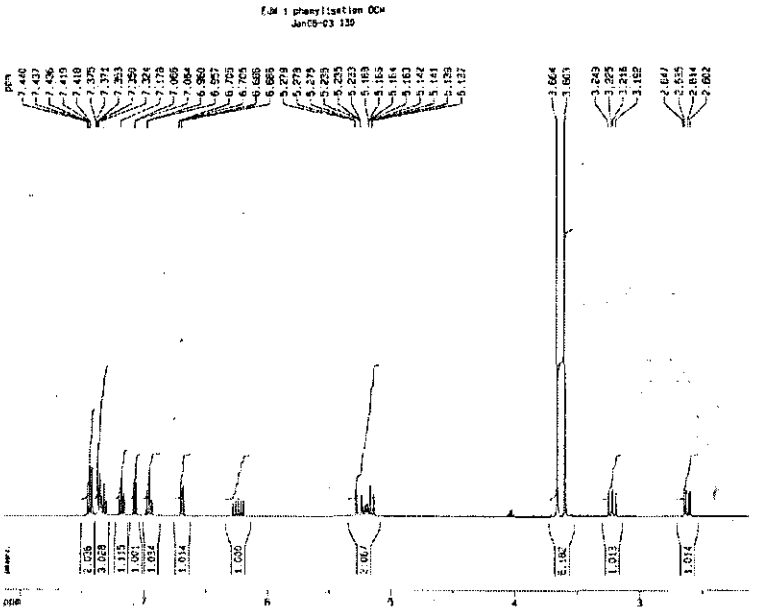


**Figure 17**

On increasing the polarity of the solvent from DCM to acetone, only a trace amount of the desired [3 + 2] spiro cycloadduct **163h** and **164h** was observed, hence the ratio of diastereoisomers was indistinguishable.

The results obtained for the cyclization conducted in DMF, a more polar solvent, are analogous and consistent to those obtained for the cyclization in THF. A good yield of the cycloadduct was isolated and the ratio of *trans* : *cis* diastereoisomers was roughly 1 : 1 with a slight prevalence of the *cis* isomer. On increasing the polarity of the solvent to acetonitrile, the diastereomeric ratio was again altered and opposing to that of DCM. In this instance, the major diastereoisomer afforded was the *cis*.

The polar protic solvent methanol has proven to be a good solvent for this palladium catalyzed [3 + 2] cycloaddition (**table 16**).

**Table 16**

| Entry | Solvent | Yield | Diastereomeric ratio[b] *Trans* **163h** : *Cis* **163h** |
|---|---|---|---|
| **7** | Methanol | [a]70 % | 1 : 2 |
| **8** | Methanol (No lewis acid) | [a]68 % | 1 : 2 |
| **9** | $THF/H_2O$ (No lewis acid) | [a]54 % | 1 : 1.2 |

[a] Isolated yield. [b]Diastereomeric ratio based on $^1H$ NMR peak integrations. Diastereoisomers not separated unless stated. Reagents and conditions: (1 mmol) **107** with (1 mmol) isatin **157h** was carried out in the presence of 10 mol % $Pd(PPh_3)_4$ and 2 mmol $ZnBr_2$ in solvent at 37°C.

The success of the reaction in polar protic solvents was quite surprising due to their potential to quench the intermediate $\pi$-allyl palladium zwitterion that is formed in the reaction. The isolated yields were good and the diastereomeric ratio is consistent with its polarity. It is not clear at this stage why the reaction did occur in this polar protic solvent. It would have been reasoned that this solvent would not have been compatible with the zwitterionic $\pi$-allyl palladium intermediate species due to its ability to quench this reactive intermediate, thus removing the 1,3 dipolar synthon from the reaction mixture and hence bringing the reaction to a halt. The *cis* isomer was prevalent for the reaction both in the presence and absence of Lewis acid. Due to the success of the reaction using methanol as the reaction solvent, it was decided to attempt the reaction in a 1 : 1 mixture of water and THF without the Lewis acid. Again it was most surprising to note that the reaction was successful and the desired

spiro tetrahydrofuran was isolated in reasonable yield (54 %) as a 1 : 1 mixture of diastereoisomers.

### 2.3.6 Summary and Conclusions

A novel and elegant synthetic route into highly functionalised spiro fused tetrahydrofurans has been reported. 2-Vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** has undergone palladium catalyzed [3 + 2] cycloadditions with the ketone moiety of a range of isatins **157** in the presence of a catalytic amount of $Pd(PPh_3)_4$ and two equivalents of $ZnBr_2$. The reaction has shown to be compatible with a number of substituents, both electron-donating and electron-withdrawing ones. The methodology boasts good to excellent yields and the yield of the reaction can be loosely predicted by the electronic nature of the ketone, *i.e* the more electrophilic the ketone, the better the yield of the reaction.

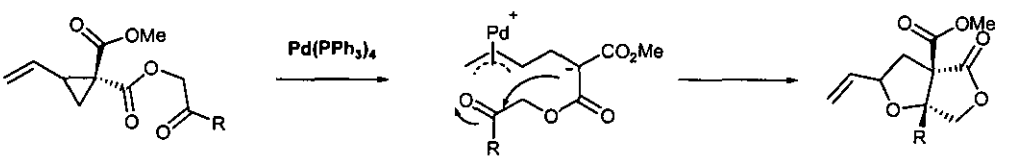
It has been found that the stereochemical preference of the reaction can be manipulated by the choice of the reaction solvent. The choice of a non-polar solvent will afford the [3 + 2] cycloadduct in which the *trans* diastereoisomer predominates. Conversely, the choice of a polar solvent will afford the [3 + 2] cycloadduct in which the *cis* diastereoisomer is prevalent. The [3 + 2] cyclization is also successful in polar protic solvents such as methanol and water demonstrating how versatile and robust this method is proving to be.

The elegance of this reaction is demonstrated, not only by the construction of a carbon-carbon and carbon-oxygen bond, but also, by the establishment of a spiro chiral stereocentre within the one reaction. The pharmaceutical activity of these spiro motifs ensures that this area of chemistry is rapidly expanding and hence the ability to adapt the chemistry established within the group to their synthesis is an exciting prospect.

## 2.4 Intramolecular Palladium Catalyzed [3 + 2] Cycloadditions with Vinylcyclopropanes and Carbonyl Moieties

It was of great interest to investigate whether the palladium catalyzed [3 + 2] cycloaddition could be extended to intramolecular examples. It was interesting to determine whether the intramolecular version of the palladium catalyzed [3 + 2] cycloaddition approach would control the absolute and relative stereochemical outcome of the reaction. In this instance the carbonyl group would have to be built on the arm of the cyclopropane and when treated to palladium catalysis, a fused bicyclic tetrahydrofuran would result.

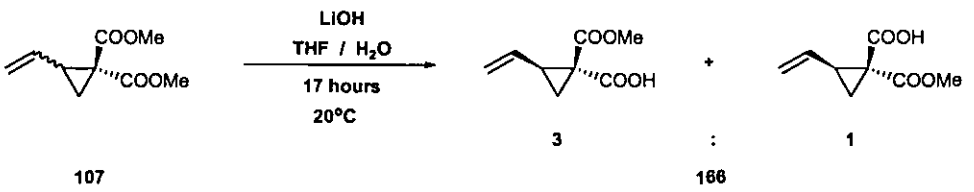
A good synthetic strategy was desired to construct a carbon skeleton on 2-vinylcyclopropane-1,1-dicarboxylic acid methyl ester **107** incorporating a carbonyl functionality (**scheme 73**).




**Scheme 73**

### 2.4.1 Hydrolysis of the Methyl Ester

The first step towards building the carbon skeleton on the cyclopropane was selectively hydrolysing one of the methyl esters (**scheme 74**) to the carboxylic acid in anticipation for alkylation and further functionalization.




**Scheme 74**

2-Vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** was treated with lithium hydroxide in THF and $H_2O$ under a number of conditions as detailed in **table 17** to afford **166.**

**Table 17**

| Equivalents of LiOH used | Temperature °C | Product isolated | Yield of 166 |
|---|---|---|---|
| 1 | RT | SM and desired product | 68 % |
| 1 | 30 °C | SM and desired product | 58 % |
| 2 | RT | Impurities present | - |
| 3 | RT | SM and desired product | 52 % |
| 4 | Reflux | Intractable mixture | - |

Reagents and Conditions: 1 mmol **107**, 20 ml THF, 20 ml $H_2O$, LiOH, 17 hours, RT.

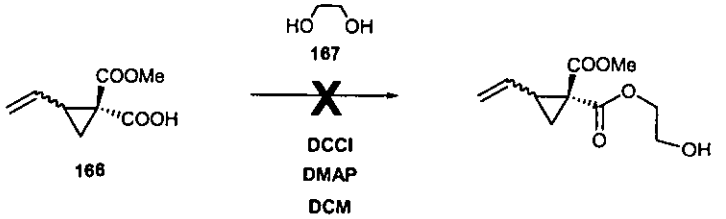
Initially the hydrolysis was achieved in moderate yield (52 %) using 3 equivalents of LiOH in THF / $H_2O$ but this reaction did not prove to be reproducible and repeat reactions resulted in a mixture of the *mono* and *bis* hydrolysed esters.

In order to increase the yield of **166**, the reaction was repeated at a higher temperature. Heating the reaction mixture at reflux temperature caused the cyclopropane moiety to ring-open and on heating the reaction to 30°C, the yield was not improved. The optimum condition for this reaction was found to be 1 equivalent of LiOH as separation of the product from the di-ester cyclopropane starting material can be easily achieved by an acid / base wash, whereas separation of the *mono* and *bis* acid cyclopropane by column chromatography was extremely problematic due to their polar nature.

With one of the methyl esters successfully hydrolysed, a robust alkylating method was desired to incorporate the carbonyl moiety on the vinyl cyclopropane.

### 2.4.2 Alkylating Methods

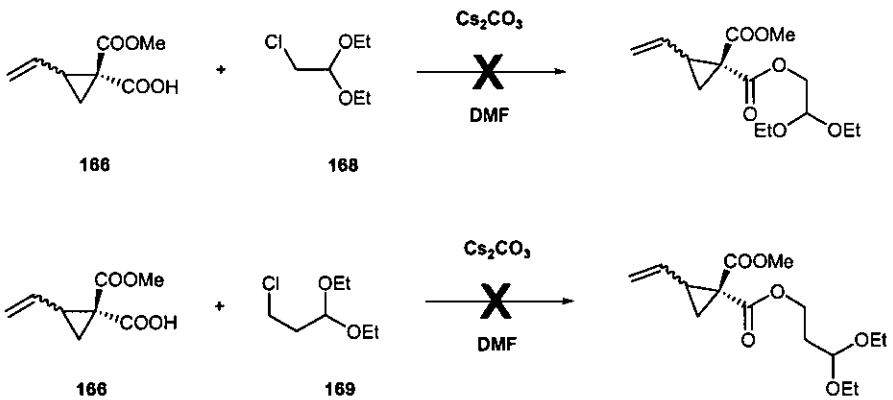
Originally the alkylations were attempted employing coupling reagents and ethane-1,2-diol **167** (**scheme 75**). Ethane-1,2-diol **167** was chosen for a tether initially. If the coupling reaction was successful, the tethered free alcohol could possibly be oxidized up to the aldehyde in anticipation for the intramolecular palladium catalyzed [3 + 2] cycloaddition reaction.




**Scheme 75**

The coupling of ethane-1,2-diol **167** with 2-vinylcyclopropane-1,1-dicarboxylic acid monomethyl ester **166** has proven to be fairly problematic. Initially the coupling agent 1,3 dicyclohexylcarbodiimide was used in the presence of dimethylaminopyridine. Difficult purifiication from the DCCI urea by-product was a contributing factor to this being an unfeasible route to the tethered cyclopropane. The reaction was repeated with a different coupling agent, EDCI, as the urea by-product could be removed during a an aqueous, acidic workup. Again, the reaction mixture was an intractable mixture of products. The reaction was then repeated using THF as the reaction solvent but again the isolation of the desired cyclopropane was not seen.

An alternative synthetic strategy to the coupling step was attempted by introducing a protected carbonyl functionality. It was originally thought that the acetal if successfully tethered could be hydrolysed to the carbonyl and hence treated to the cycloaddition conditions. It was attempted to couple 2-vinylcyclopropane-1,1-dicarboxylic acid monomethyl ester **166** with chloroacetaldehyde diethyl acetal **168** and the analogous 3 chloropropionaldehyde diethyl acetal **169 (scheme 76)**.




**Scheme 76**

The coupling of 2-vinylcyclopropane-1,1-dicarboxylic acid monomethyl ester **166** with chloroacetaldehyde diethyl acetal **168** was attempted in the presence of cesium

carbonate and DMF.[81] $Cs_2CO_3$ was chosen as it is a stronger base for the deprotonation of the acid moiety. Initially, the $Cs_2CO_3$ was introduced into the reaction mixture by titrating 20% $Cs_2CO_3$ solution until a pH of 7 was obtained. DMF was introduced into the reaction mixture and then the reaction mixture was evaporated to dryness to afford the cesium salt of 2-vinylcyclopropane-1,1-dicarboxylic acid monomethyl ester **166** to then be reacted with chloroacetaldehyde diethyl acetal **168**. Unfortunately only the starting 2-vinylcyclopropane-1,1-dicarboxylic acid monomethyl ester **166** was recovered. The reaction was repeated varying the equivalents of $Cs_2CO_3$ but starting materials were isolated each time. This was also the situation for the coupling of 3 chloropropionaldehyde diethyl acetal **169** with 2-vinylcyclopropane-1,1-dicarboxylic acid monomethyl ester **166**.

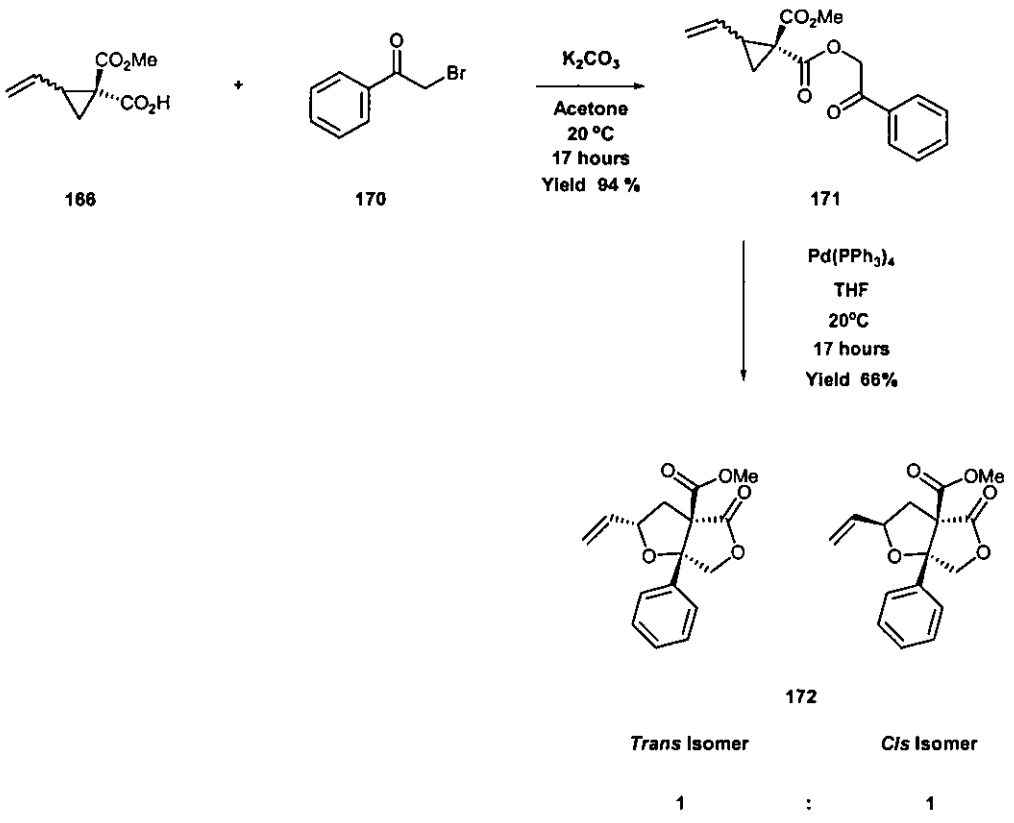
Steric constraints of neopentyl centre were believed to be the cause of the lability of the acid towards an $S_N2$ attack on the alkyl halide.

An alternative method was sought for the coupling step, taking into account steric constraints of the acid.

Moore *et al*[82] reported the preparation of sterically hindered esters using alkylation methods. They described conditions using 4 equivalents of alkylhalides, 2.5 equivalents of $K_2CO_3$ in acetone.

### 2.4.3 Intramolecular Palladium Catalyzed [3 + 2] Cycloaddition

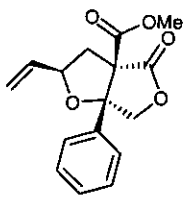
As coupling of the protected carbonyl framework was proving to be problematic, it was decided to try and couple unprotected ketones directly to introduce the carbonyl functionality on to the cyclopropane unit. The conditions reported by Moore were adapted for the coupling of the 2-vinylcyclopropane-1,1-dicarboxylic acid monomethyl ester **166** with 2-bromoacetophenone **170** (**scheme 77**). The acid moiety was deprotonated using the $K_2CO_3$, and subsequent $S_N2$ reaction of the carboxylate anion on the bromoacetophenone afforded the desired alkylated cyclopropane **171**.




**Scheme 77**

The desired tethered cyclopropane **171** was obtained in good yield (94 %). Now that the carbonyl functionality had been introduced on the carbon framework of the cyclopropane unit, cyclization with $Pd(PPh_3)_4$ was the subsequent step. 2-Vinylcyclopropane-1,1-dicarboxylic acid methyl ester 2-oxo-2-phenyl-ethyl ester **171** participated in an intramolecular 5-exo-trig palladium catalyzed [3 + 2] cycloadition to afford the bicyclic 5,5-ring system **172** as a mixture of diastereoisomers in reasonable yield (67 %). The desired bicyclic system **172** was formed in the absence of Lewis acid, $ZnBr_2$. The carbonyl was activated by an ester group and hence was electrophilic enough to experience nucleophilic attack from the malonic π-allyl palladium (II) species.

A small amount of a single diastereoisomer was isolated from the 1 : 1 mixture of the two diastereoisomers. In the $^1$HNMR spectrum, the two diastereoisomers behave differently and can be distinguished by their particular characteristics. The protons on the 4-C on the tetrahydrofuran ring for each diastereoisomer are distinguishable by $^1$HNMR. The hydrogen next to the vinyl group for the *trans* diastereoisomer appears further up-field when compared to the corresponding proton in the *cis* diastereoisomer. Also there is an obvious difference in chemical shift for the proton adjacent to the malonic centre. In the *trans* diastereoisomer this proton appears further down-field than the corresponding proton in the *cis* diastereoisomer. Therfore, for the *trans* diastereoisomer, there is a greater difference in chemical shift than for the corresponding *cis* isomer. From the splitting pattern observed from the hydrogen atoms on the tetrahydrofuran ring it is suspected that the single diastereoisomer is the *cis* isomer (**figure 18**).

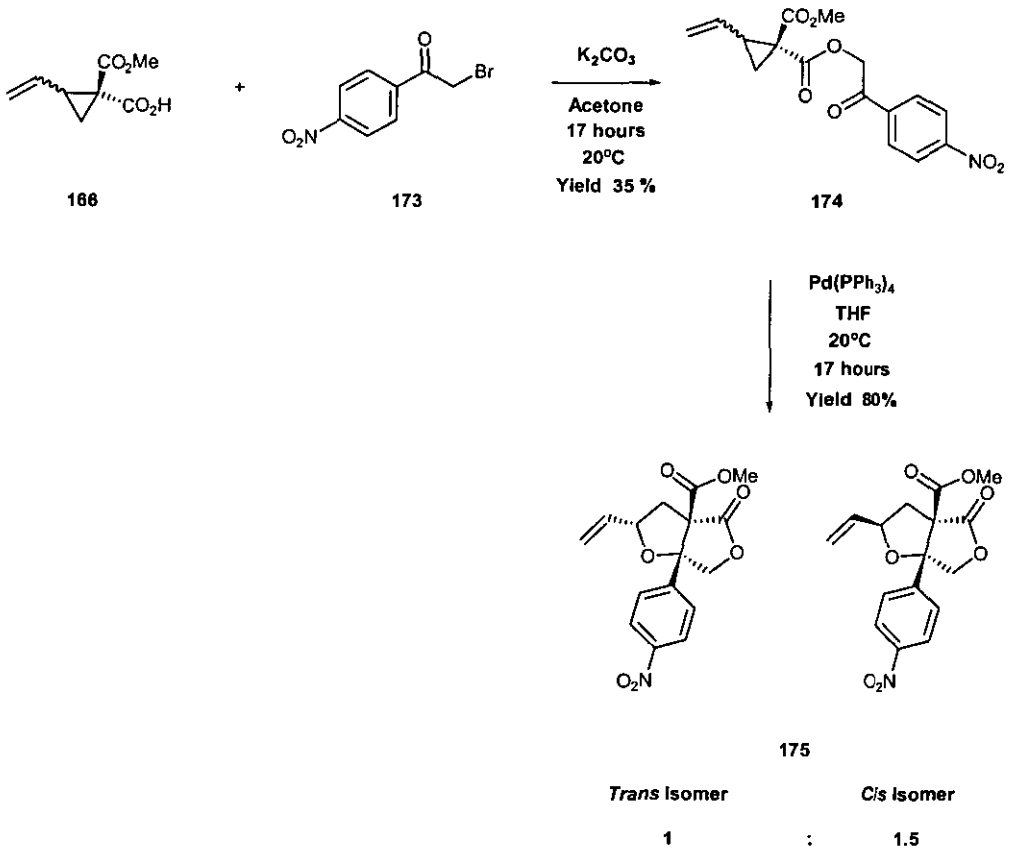



172

**Figure 18**

The palladium catalyzed [3 + 2] cycloaddition methodology reported is a powerful synthetic strategy into the construction of fused bicyclic structures. In one step a complex heterocyclic bicycle has been assembled, in which not only a carbon-carbon bond and a carbon-oxygen have been built, but 2 quaternary centres adjacent to each other have been established.

The reaction sequence was repeated using 2-bromo-4'nitroacetophenone **173** as the alkylating agent (**scheme 78**). It was hoped that the nitro analogue **175** would be crystalline to obtain x-ray data to confirm the *trans* and *cis* assignment.




**Scheme 78**

2-Vinylcyclopropane-1,1-dicarboxylic acid monomethyl ester **166** was treated with 2-bromo-4'-nitroacetophenone **173** in the presence of 2.5 equivalents of $K_2CO_3$ and acetone to afford the alkylated cyclopropane **174** in poor yield (34 %). This in turn underwent a palladium catalysed [3+2] intramolecular cycloaddition, to afford the bicyclic 5,5-ring system **175** in good yield (80 %) as a 1 : 1.5 mixture of diastereoisomers as shown in **scheme 78.**

It was pleasing to note that this example of the fused heterocyclic bicycle was crystalline. After repeated chromatographic separation techniques a small amount of the *cis* isomer was separated from the mixture and the structure and stereochemistry was reinforced by the x-ray crystallography, **figure 19**.

The x-ray structure **figure 19** of the bicyle **175** does detail that the vinyl group, the methyl ester and the phenyl ring are *cis* in relationship to each other.

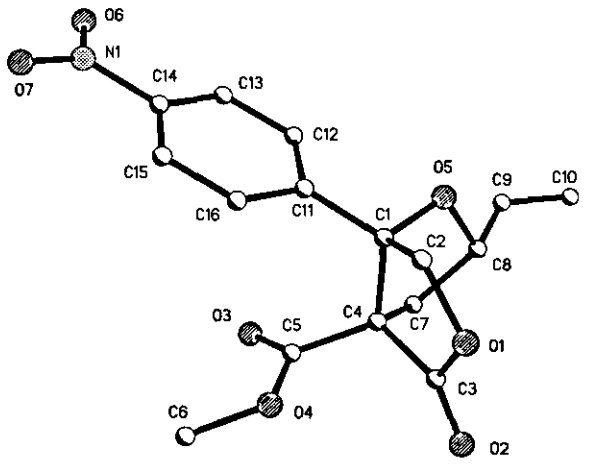



**Figure 19**

This structure was also confirmed by nOe experiments (**figure 20**).

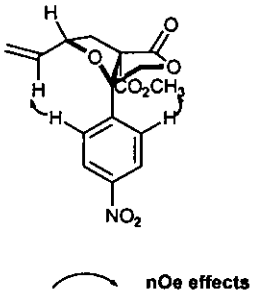



**Figure 20**

The nOe data details a positive correlation between the *ortho* aromatic protons with both the vinyl group and the methyl esters, hence it is suggested that they are on the same face of the molecule.

The $^1$HNMR spectrum of the mixture of diastereoisomers is shown in **figure 21**

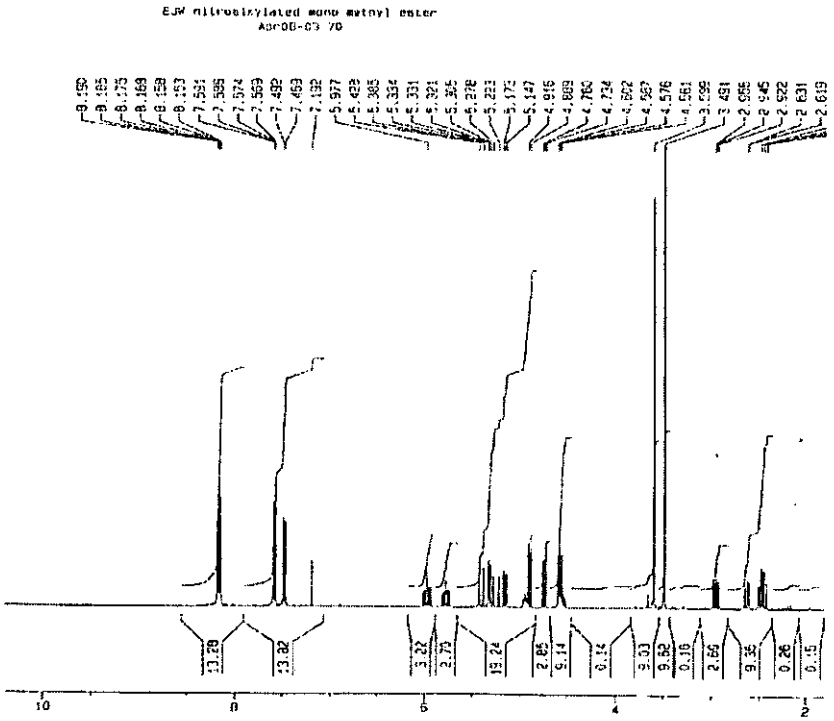


**Figure 21**

Again it is obvious to note on this spectrum that the hydrogens on the tetrahydrofuran ring behave differently for each isomer. For both isomers they appear between 2-3 ppm. The hydrogen for the *trans* diastereoisomer adjacent to the vinyl group appears slightly further up-field in comparison to the corresponding hydrogen of the *cis* isomer. The hydrogen adjacent to the vinyl group for the *trans* diastereoisomer appears significantly further downfield compared to the corresponding hydrogen in the *cis* isomer. Therefore the difference in chemical shift for the two protons on the tetrahydrofuran ring is larger for the *trans* isomer than the *cis*.

The $^{1}$HNMR the *cis* diastereoisomer of **175** is shown in **figure 22**. It indicates that the correct assignment of the diastereoisomers by $^{1}$HNMR has been previously made when used alongside the x-ray data and nOe data.

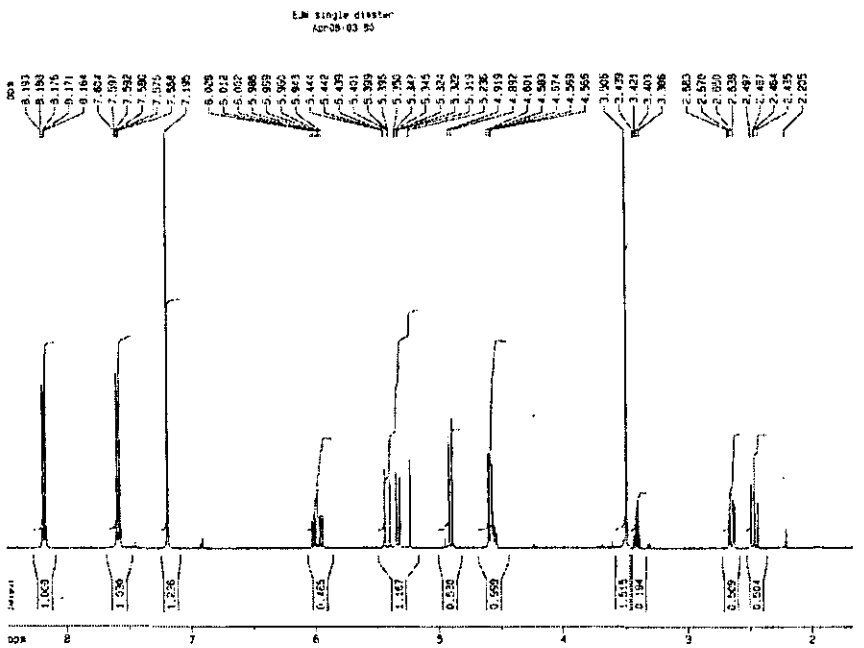
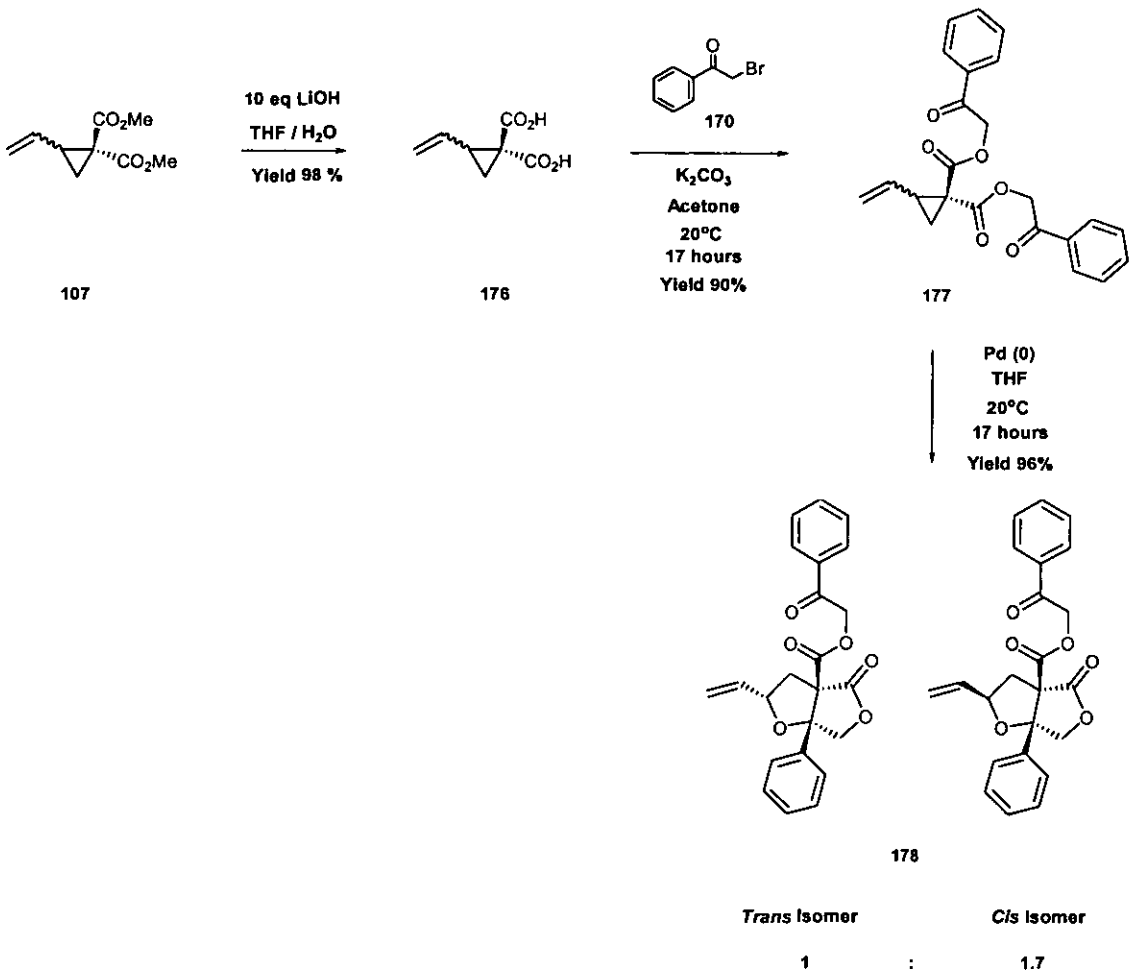


**Figure 22**

### 2.4.4 Hydrolysis of Both Methyl Esters

With both the hydrolysis and alkylation conditions to hand it was decided to attempt to hydrolyse and alkylate both the methyl esters. The alkylation of both acids would simplify the molecule **166** by removing one of the chiral centres.

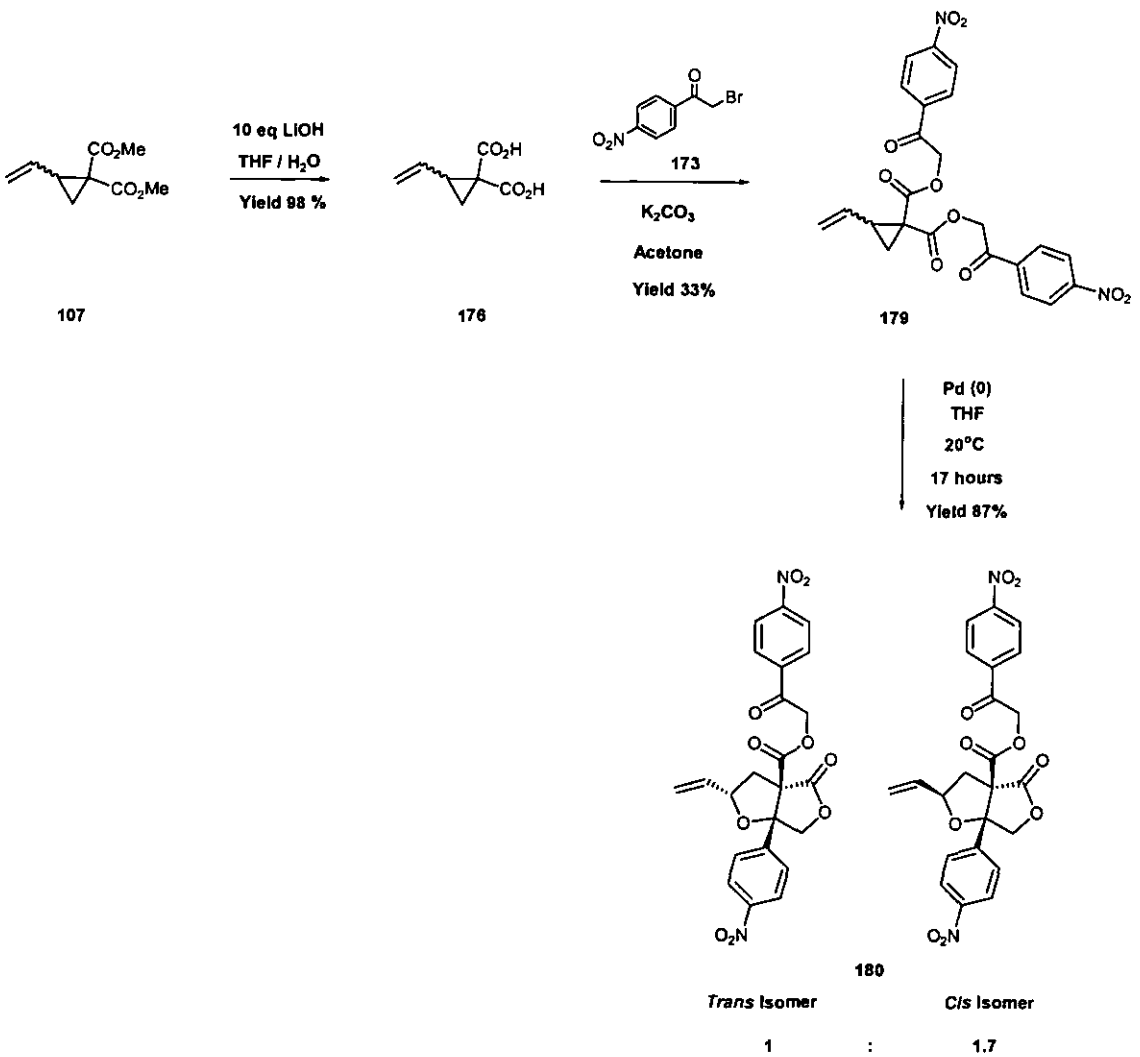



**Scheme 79**

The synthesis of 2-vinylcyclopropane-1,1-dicarboxylic acid **176** was successfully achieved by hydrolysis using 10 mol equivalents of LiOH in THF / $H_2O$, affording an excellent yield (98 %) and purification of the product was not required (**scheme 79**).

The acid moieties were subsequently de-protonated using 2.5 equivalents of $K_2CO_3$ and then in turn alkylated using bromoacetophenone **170** in acetone in good yield (90 %). The desired *bis*-alkylated cyclopropane **177** was then treated with palladium and underwent an intramolecular [3 + 2] cycloaddition to afford 1 : 1 mixture of diastereoisomers in good yield (95 %) to give the bicyclic structure **178**.

The reaction was repeated using 2-bromo-4'-nitroacetophenone **173 (scheme 80)**.

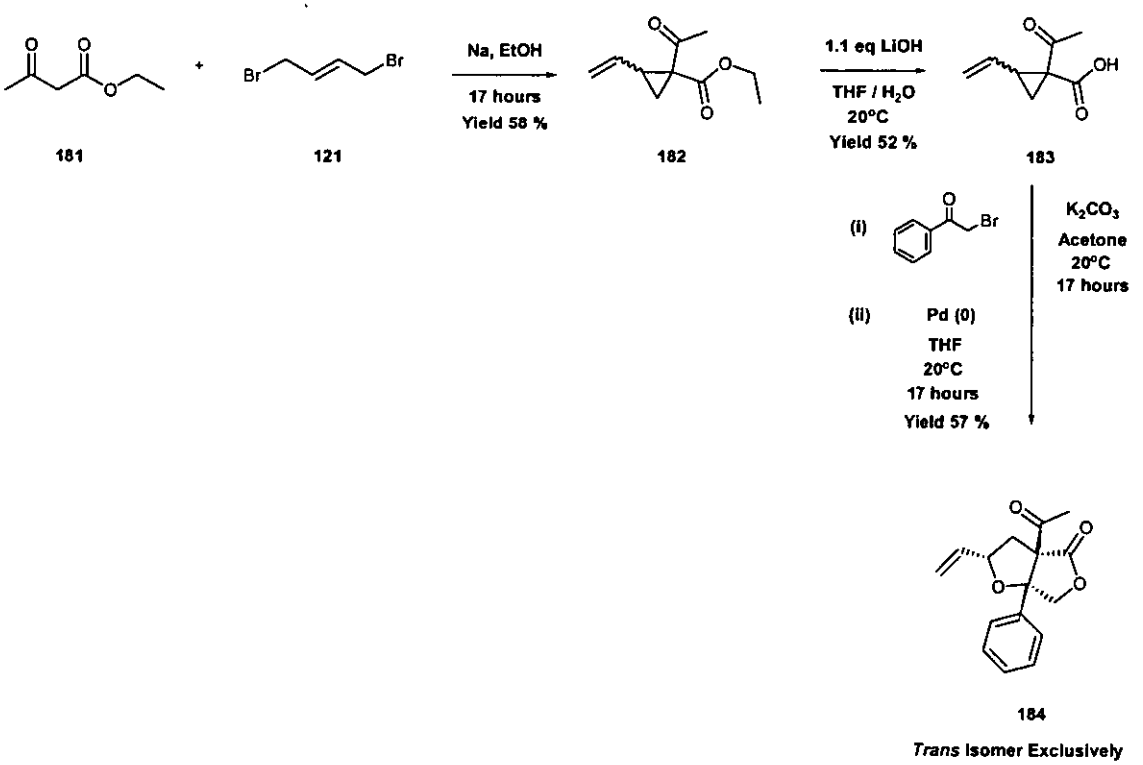



**Scheme 80**

2-Vinyl-cyclopropane-1,1-dicarboxylic acid bis-[2-(4-nitro-phenyl)-2-oxo-ethyl] ester) **179** was obtained in low yield (33 %) as a yellow solid. The main by-products appeared to be related to 2-bromo-4'-nitroacetophenone **173**. The di-alkylated cyclopropane **179** participated in a palladium catalysed [3 + 2] cycloaddition to afford the bicyclic 5,5 system **180** as a pair of diastereoisomers (1 : 1.7; *trans* : *cis*) in good yield (87 %).

The cyclization step follows that of a favoured 5-exo-trig cyclization.

To explore the chemo-selectivity of the reaction it was decided to replace one of the methyl esters with a methyl ketone (**scheme 81**).




**181** **121** **182** **183**

**184**

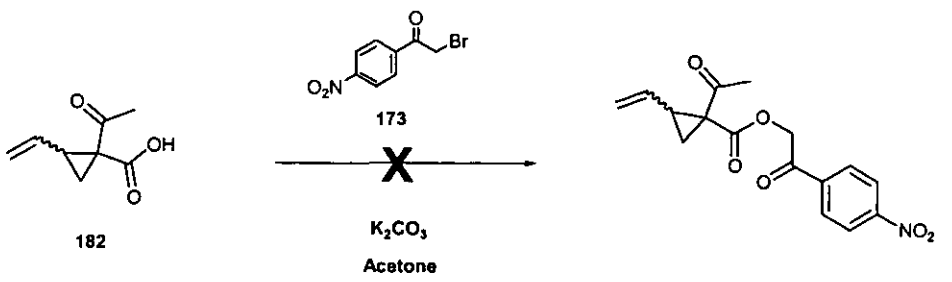
***Trans* Isomer Exclusively**

**Scheme 81**

The synthesis of 1-acetyl-2-vinyl-cyclopropanecarboxylic acid ethyl ester **182** was achieved by following literature precedent by Kierstead *et al.*[83] *Trans* 1,4 dibromobut-2-ene **121** underwent a double displacement with ethyl acetoacetate **181**. The desired cyclopropane **182** was isolated after difficult separation from the starting ethyl acetoacetate **181**. The presence of two chiral centres in the molecule complicated the $^{1}$HNMR and $^{13}$CNMR spectra as both the diastereoisomers were apparent. The ethyl ester moiety of the mixture of diastereoisomers **182** was subsequently hydrolysed to form the cyclopropane monoacid, 1-acetyl-2-vinyl-cyclopropanecarboxylic acid **183**. An acid-base wash was responsible for the clean isolation of the desired product in a reasonable yield (52 %).

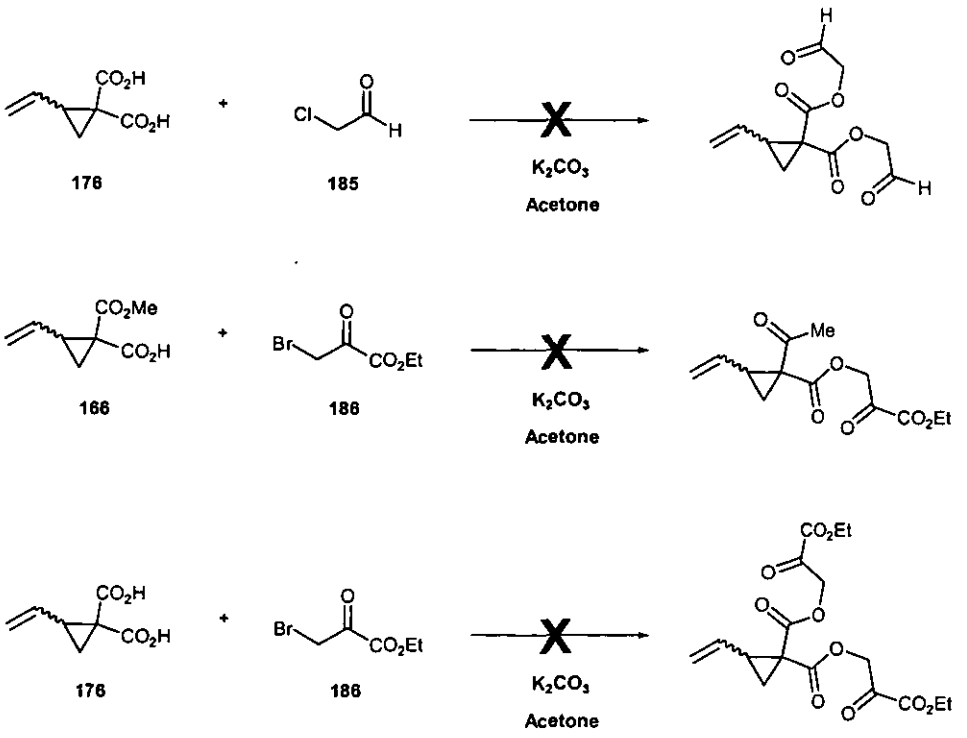
Again a mixture of diastereoisomers was apparent in the $^{1}$HNMR and $^{13}$CNMR due to the two chiral centres. The acid was deprotonated and alkylated with bromoacetophenone. The tethered cyclopropane was formed but it proved very difficult to separate the product from the starting materials. After column chromatography, the isolated oil was still a mixture of starting materials and product and hence the mixture was taken onto the next step without further purification. The subsequent palladium [3 + 2] catalyzed cycloaddition was successful and after purification only the *trans* isomer was isolated. The chemical shift of the protons on the tetrahydrofuran ring indicated that this isomer is the *trans* isomer.

The coupling between 1-acetyl-2-vinyl-cyclopropanecarboxylic acid **182** and 2-bromo-4'-nitroacetophenone **173** was not successful and hence the palladium catalyzed [3 + 2] cycloaddition could not be attempted (**scheme 82**).




**Scheme 82**

Other coupling reagents have been employed in an attempt to vary the tether length to synthesize other ring sizes and introduce different functionality to the bicyclic structure. The cyclopropane diacid **176** was treated with chloroacetaldehyde **185** and starting materials were recovered (**scheme 83**). Both 2-vinylcyclopropane-1,1-dicarboxylic acid monomethyl ester **166** and 2-vinylcyclopropane-1,1-dicarboxylic acid **176** were reacted with ethyl-3-bromopyruvate **186** and neither starting materials or the desired alkylated cyclopropane were isolated. The cyclopropane ring was not detected in the $^1$HNMR data and the product isolated from the reaction could not be determined.




**Scheme 83**

### 2.4.5 Summary and Conclusions

A novel route into a fused heterocyclic bicycle structure has been described. The crux of the chemistry involves an intramolecular palladium catalyzed [3 + 2] cycloaddition. One or both the methyl esters have been hydrolysed and bromoacetophenone has been used as the alkylating agent to deliver a 2 carbon tether, incorporating a carbonyl moiety, to the side arm of the cyclopropane. On treatment of the alkylated cyclopropane to 10 mol% $Pd(PPh_3)_4$ an intramolecular palladium catalyzed [3 + 2] cycloaddition has occurred to afford a bicyclic tetrahydrofuran as a pair of diastereoisomers. The ring closing step can be described as a favoured 5-exo-trig cyclization. The absence of the Lewis acid was noted, but the presence of the ester was sufficient to activate the carbonyl towards nucleophilic attack from the malonic centre of the $\pi$ allyl palladium(II) species.

The methodology described is a powerful tool because in one reaction sequence a carbon-carbon bond and a carbon-oxygen have been constructed and 2 quaternary centres adjacent to each other have been established.

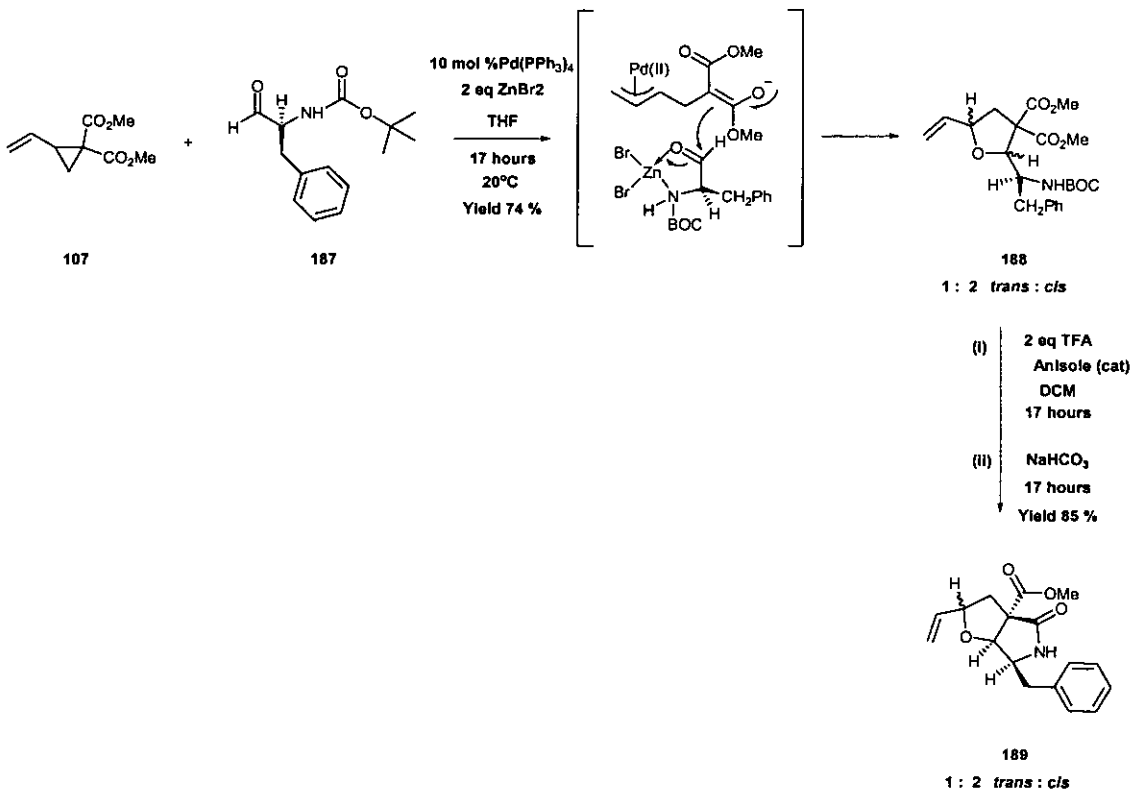
The only constraint to scope of this reaction methodology could be the lack of suitable alkylating agents to tether to the cyclopropane. Other ring sizes could be assembled with a range of functionality if, time permitting, suitable alkylation conditions could be investigated for the range of alkylating agents available.

## 2.5 Palladium Catalyzed [3 + 2] Cycloadditions Involving Chiral Aldehydes

Following on from the work carried out by Tang, the condensation of aldehydes derived from α-amino acids was another point of great interest as the products potentially could open up new routes to glycoproteins and natural products. It was also of great interest to find out whether the stereochemical outcome of the reaction could be controlled by the use of chiral aldehydes.

### 2.5.1 Chiral Aldehydes as Electrophiles

Initially (*S*)(-)-2-(*tert*-butoxycarbonylamino)-3-phenyl propanal **187** was subjected to a palladium catalyzed [3 + 2] cycloaddition in the presence of 10 mol % $Pd(PPh_3)_4$, THF and 2 equivalents of Lewis acid, $ZnBr_2$ to afford the desired cycloadduct in good yield (74 %) as a pair of diastereoisomers with the predominance of the *cis* diastereoisomer (1 : 2; *trans* : *cis*) (**scheme 84**).




**Scheme 84**

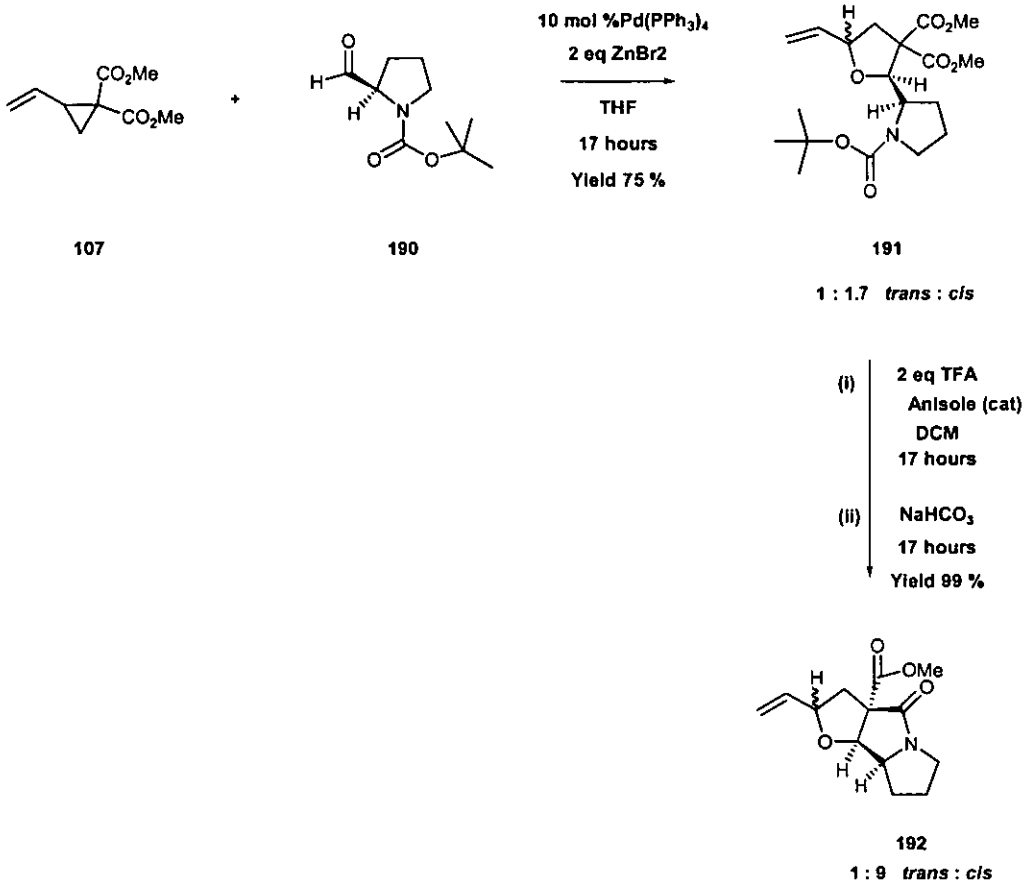
The palladium catalyzed [3 + 2] cycloaddition reaction between (*S*)(-)-2-(*tert*-butoxycarbonylamino)-3-phenyl propanal **187** and 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107**, did not occur in the absence of the $ZnBr_2$ and the starting materials were recovered. The Lewis acid is therefore crucial to the successful formation of the cycloadduct. Unfortunately though, the diastereoisomers were not separated at this stage and the different diastereoisomers can only tentatively be reported based on the $^1$HNMR. It was expected that the oxygen atom and the nitrogen atom coordinate to the zinc, locking the conformation and subsequently the *erythro*-isomer is formed as shown in **scheme 84**.

In order to test this assumption, the tetrahydrofuran **188** formed was subsequently subjected to a *tert*-butyloxycarbonyl deprotection on treatment of trifluoroacetic acid conditions. Thin layer chromatography indicated when the amine had been fully

de-protected. As the de-protected form, the free amine, consequently underwent a 5-*exo*-trig cyclization onto the *cis* methyl ester with the loss of methoxy, on addition of $NaHCO_3$ *in situ*. The cyclization step occurred in excellent yield (85 %) as the same ratio of diastereoisomers as the cycloadduct (1 : 2; *trans* : *cis*) **(scheme 84)**. The diastereoisomers could not be separated at this stage and hence the diastereoisomeric ratio has been determined by $^1$HNMR.

This reaction demonstrates how powerful this methodology is, as a bicylic structure has been created, in which four stereocentres centres have been established, with what we tentatively believe to be absolute stereocontrol of three of the resulting stereocentres.

The palladium catalyzed [3 + 2] cyclization was so successful with (*S*)-(-)-2-(*tert*-butoxycarbonylamino)-3-phenylpropanal **187**, cyclization with commercially available N-(*tert*-butoxycarbonyl)-L-prolinal **190** was attempted **(scheme 85)**. This was an exciting example for us to attempt as on de-protection, potentially a tricyclic structure would result.




**Scheme 85**

*N*-(*tert*-Butoxycarbonyl)-L-prolinal **190** was reacted with 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** in the presence of 10 mol% $Pd(PPh_3)_4$ and 2 equivalents of $ZnBr_2$. The desired functionalised tetrahydrofuran **191** was isolated in excellent yield (75 %) with the stereoselectivity of the reaction favouring that of the *cis* diastereoisomer (1 : 2; *trans* : *cis*). Again unfortunately the diastereoisomers were not separated at this stage so the diastereoisomeric ratio could only be tentatively reported based on $^1$HNMR and the different behaviour of the *trans* and *cis* isomers in the $^1$HNMR.

Subsequent deprotection of the amine under trifluoroacetic acid conditions in the presence of catalytic anisole and DCM afforded the free amine. On addition of

$NaHCO_3$ the free amine underwent a 5-exo-trig cyclization onto the methyl esters to give the heterocyclic tricycle **192**.

This methodology could be an extremely powerful synthetic tool with further work, as in only two steps, starting from simple starting materials a complex tricycle has been constructed with a very prominent natural product core resembling the pyrrolizine alkaloids.

As reported previously for (*S*)-(-)-2-(*tert*-butoxycarbonylamino)-3-phenylpropanal **187**, the palladium catalyzed [3 + 2] cycloaddition reaction between *N*-(*tert*-butoxycarbonyl)-L-prolinal **190** and 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** did not occur in the absence of $ZnBr_2$ and starting materials were isolated. This indicates the importance of the Lewis acid as it indicates that coordination of both the oxygen atom and the nitrogen atom to the zinc, locking the conformation and it is believed that the *erythro*-isomer is formed (**figure 23**).

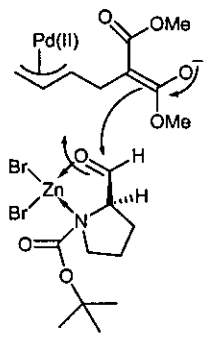
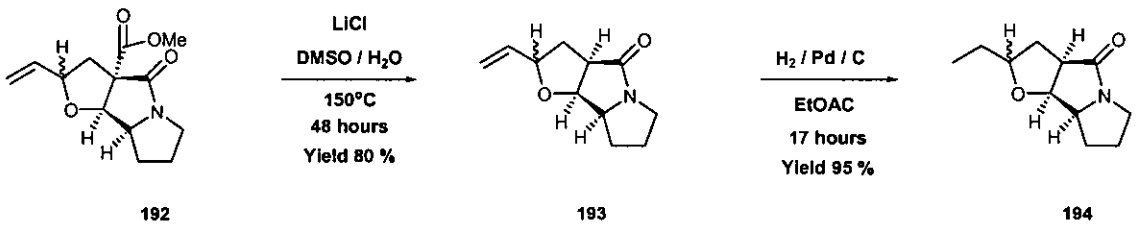



**Figure 23**

With the core of the pyrrolizine having been constructed, the functionality of the tricyclic structure had to be removed. 7-Oxo-2-vinyl-hexahydro-3-oxa-6a-aza-cyclopenta[a]pentalene-7a-carboxylic acid methyl ester **192** was subjected to Krapcho

decarboxylation conditions to remove the methyl ester on the bridging carbon.[84] The tri-cyclic structure was heated to 150°C in DMSO with two equivalents of water in the presence of LiCl to afford the decarboxylated product **193** in good yield (80 %) (**scheme 86**).

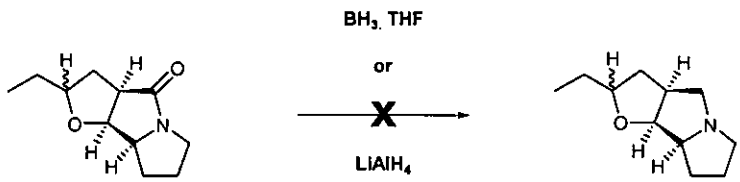



192 193 194

**Scheme 86**

The vinyl group of decarboxylated compound **193** on treatment with palladium, carbon and under an atmosphere of hydrogen, was reduced to afford 2-ethyl-octahydro-3-oxa-6a-aza-cyclopenta[*a*]pentalen-7-one **194**.

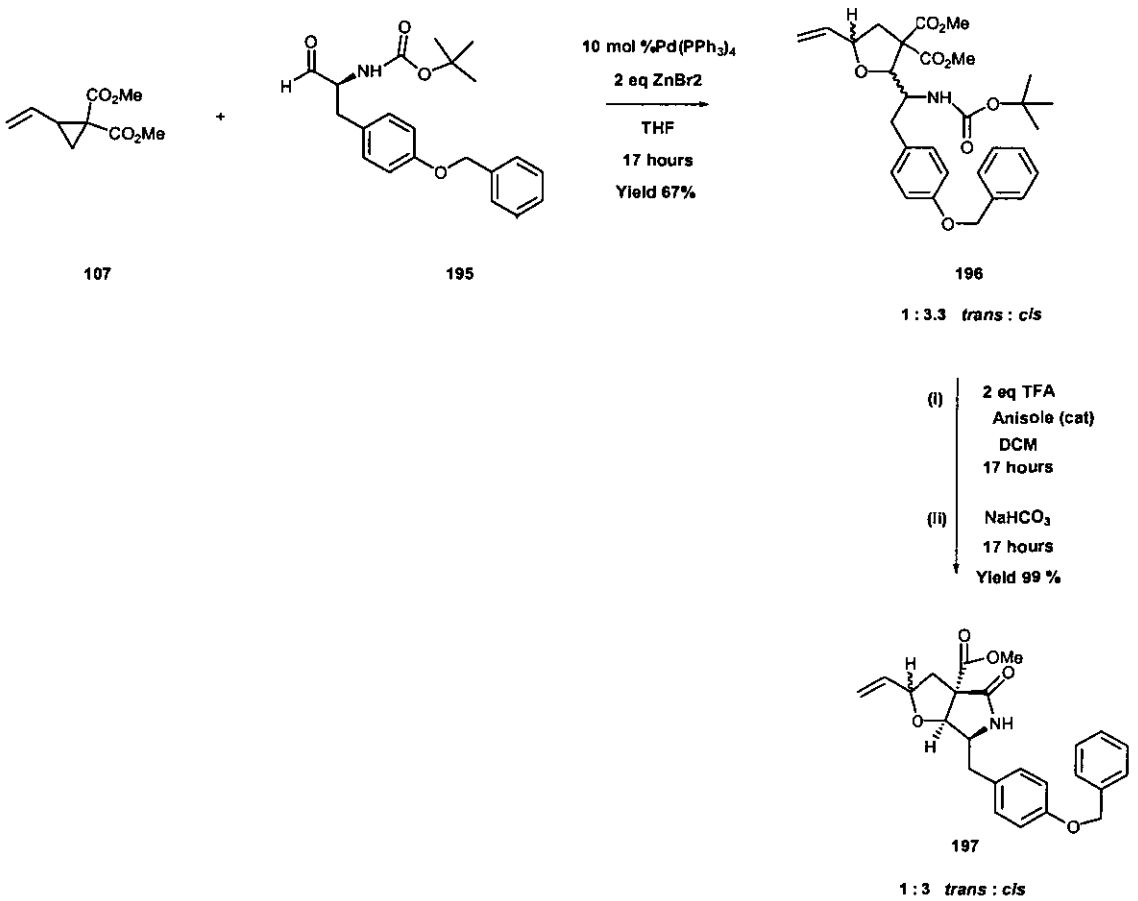
The reduction of the amide proved quite problematic using borane-tetrahydrofuran complex with recovery of starting materials only. The reduction of the amide was also attempted using lithium borohydride (**scheme 87**) but unfortunately there was no evidence of the desired reduced tricycle.




194

**Scheme 87**

Another commercially available BOC protected chiral aldehyde was chosen based on the amino acid tyrosine. This aldehyde was chosen as the benzyl group could potentially be removed under hydrogenation conditions. BOC-TYR(BZL)-aldehyde **195** was treated with $Pd(PPh_3)_4$ and 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** and $ZnBr_2$. The desired cycloadduct **196** was isolated in good yield (67 %) as a 1 : 3 *trans* : *cis* ratio of diastereoisomers (**scheme 88**).




**Scheme 88**

As previously described, the cycloadduct was de-protected in trifluoroacetic acid conditions and the free amine underwent a 5-exo-trig cyclization onto one of the methyl esters on addition of $NaHCO_3$ in excellent yield (99 %) to afford the bicyclic heterocycle **197**.

In only two synthetic steps, a highly functionalised, bicyclic structure has been constructed forming three chiral centres.

In order to try and improve the diastereoselectivity of the reaction, the reaction was repeated in differing solvents. The solvents DCM and acetonitrile were chosen because of their opposing polarities. The reaction in the non-polar solvent DCM did not proceed and the starting materials were recovered. Whereas the reaction carried out in the polar solvent acetonitrile did in fact show an improvement in diastereoselectivity with the *cis* isomer predominating in a 1 : 8 *trans* : *cis* ratio. On cyclization of the free amine, the bicyclic structure was isolated in excellent yield (100 %) in a stereoselective manner as the *cis* isomer was isolated with a trace of the *trans* (1 : 9; *trans* : *cis*).

### 2.5.2 Summary and Conclusions

A novel palladium catalyzed [3 + 2] cycloaddition reaction has been reported between 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** and aldehyde moieties to afford highly functionalised tetrahydrofurans by Tang. This chemistry has been adapted and elaborated to incorporate the aldehyde moieties derived from $\alpha$-amino acids. The BOC protected cycloadducts were deprotected and the free amine underwent a 5-exo-trig cyclization onto one of the methyl esters, with loss of methanol, to afford a highly functionalised heterocyclic bicycle motif.

This methodology is a novel and exciting route into the basic core of pyrrolizine alkaloids. In only two steps a complex bicycle can be constructed in which a carbon-carbon and a carbon-oxygen bond have been constructed. Three chiral centres have

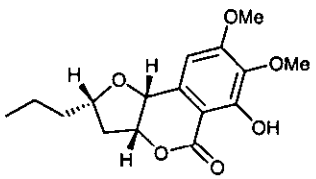
been introduced, two adjacent to each other. This methodology boasts good yields with the use of mild conditions and reagents.

The chemistry was not studied further due to the difficulties in separation of the diastereoisomers. This made obtaining suitable data such as nOes and optical rotations very difficult. It is not clear therefore what is happening during the course of the reaction. It can only be tentatively proposed that the stereochemical integrity of the starting aldehyde is maintained throughout the reaction, and hence stereocontrol of the reaction. It could be that the aldehyde is epimerised during the reaction and the stereochemical integrity of the starting aldehyde is lost. Further work is required for proof of the stereochemical outcome of the reaction.

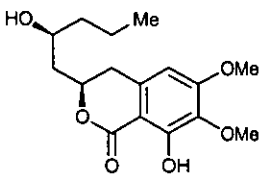
# 2.6 A Palladium Catalyzed [3 + 2] Cycloaddition Route Towards the Synthesis of Monocerin

## 2.6.1 Monocerin Activity

The natural product monocerin **198** was initially isolated as an antifungal metabolite, active against powdery mildew of wheat from the culture filtrates from the fermentations of *Helminthosporium monoceras*.[85] It was consequently isolated from *Fusarium larvarum*.[86] It was isolated alongside the fusarentins **199**, a group of related compounds with known insecticidal activity (**figure 24**).




198



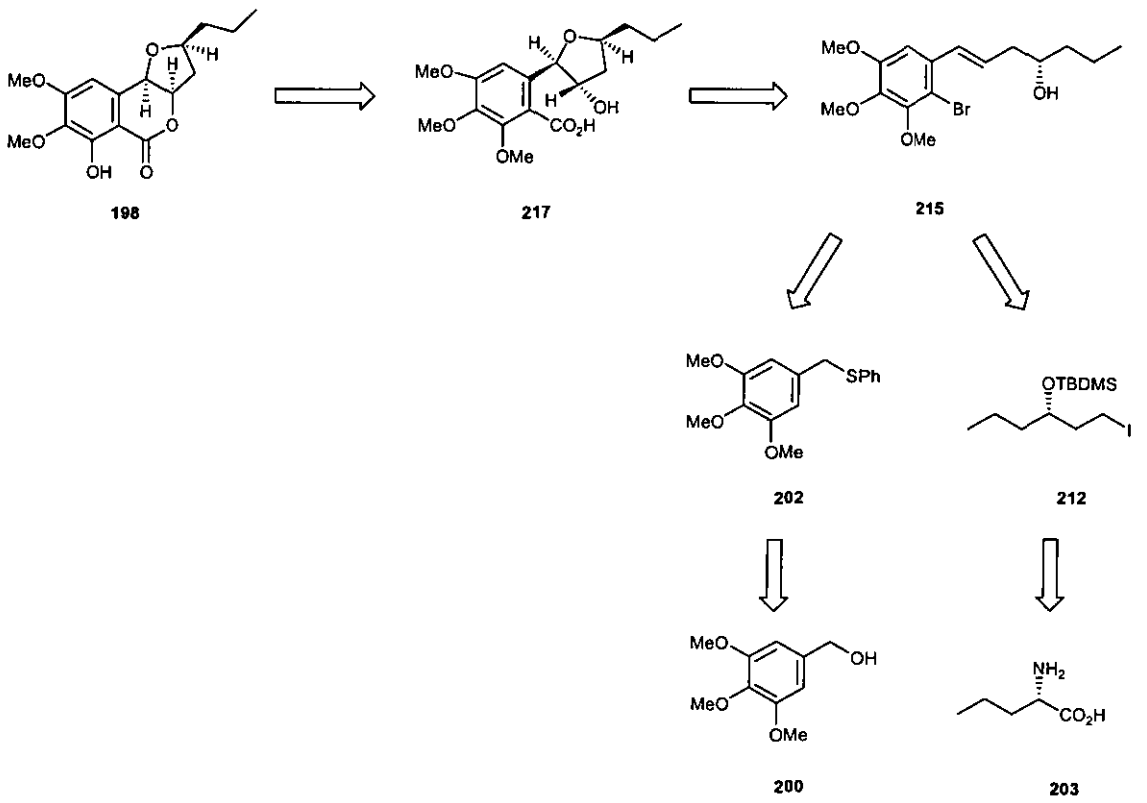

199

**Figure 24**

It has also been isolated from *Readeriella mirabilis*[87] and *Drechslera ravenelii*.[88] Robeston and Strobel went onto report the phytotoxic properties of monocerin, who identified it as a phytotoxin produced by *Exserohilum turcicum*.[89] Hence monocerin has shown to exhibit antifungal, insecticidal and phytotoxic activities. The stereochemistry of monocerin was established [86,90] as 2*S*, 3a*R* and 9b*R* as described in **figure 24**.

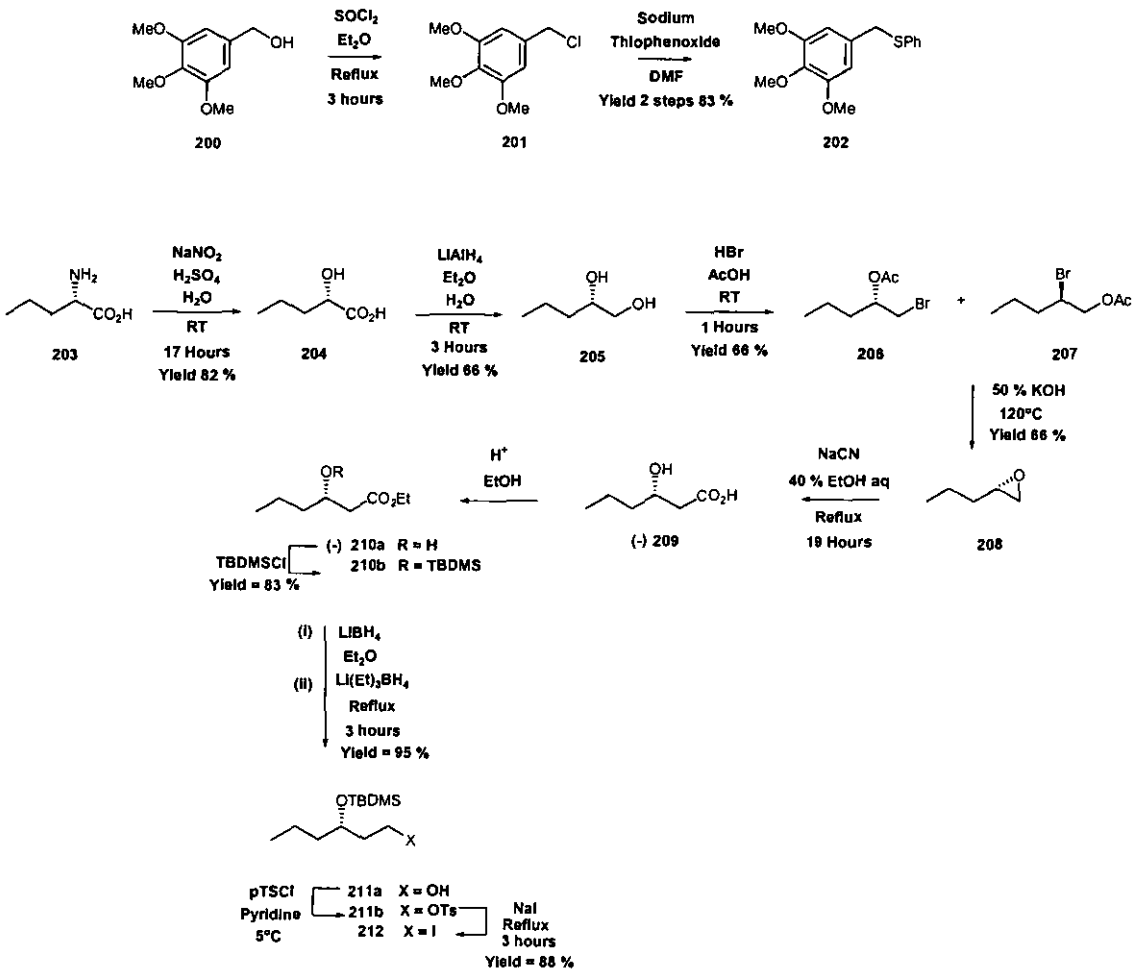
## 2.6.2 Previously Reported Synthetic Routes

The first synthetic route to monocerin **198,** was described by Mori and Takaishi (**Scheme 89**). [91]



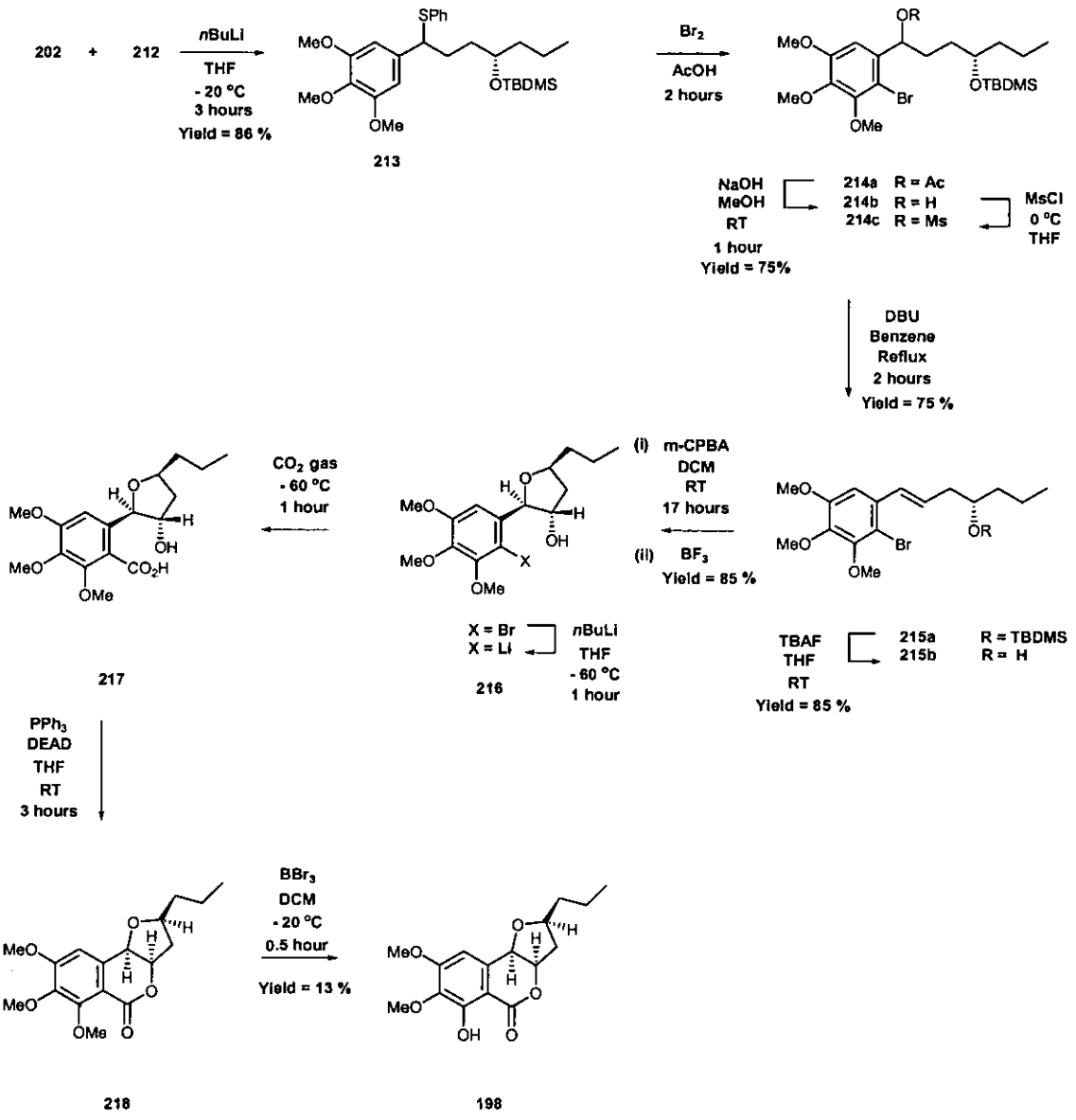

**Scheme 89**

They postulated that the lactone ring of **198** would be constructed by cyclizing **217** under Mitsunobu conditions with an inversion at the stereocentre containing the alcohol. An oxidative cyclization of the side chain and introduction of a carboxyl group to the aromatic ring onto **215** would afford the hydroxy acid **217**. Assembly of the building blocks **202** and **212** would afford **217**. The construction of the aromatic building block **202** could be readily achieved from 3,4,5-trimethoxybenzyl alcohol **200.** The synthesis of **212** could be achieved from the amino acid (*S*)-norvaline **203.**




**Scheme 90**

Initially, 3,4,5 trimethoxybenzyl alcohol **200** was chlorinated with thionyl chloride to yield **201**, which, in turn was treated to sodium thiophenoxide to afford the thiol derivative **202** (**scheme 85**). The other building block was synthesized from (*S*)-norvaline **203**. The amino acid **203** was converted into the epoxide **208** via the hydroxy acid **204**, diol **205** and acetoxy bromides **206** and **207**. The alcohol was protected using TBDMSCl and the ester was reduced using $LiBH_4$ to afford **211a**. The alcohol was tosylated and treated with NaI to afford the other desired building block **212**.




**Scheme 91**

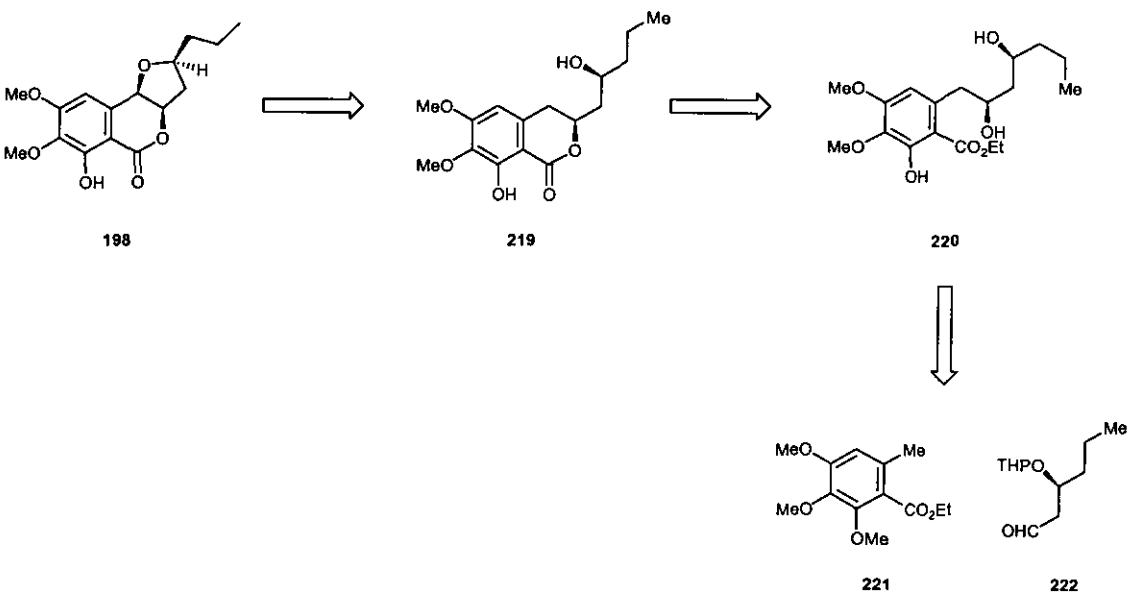
The building blocks **202** and **212** underwent an alkylation reaction to afford **213**. The phenyl ring was brominated to facilitate the introduction of the carboxyl group at a later time. The mixture was subsequently saponified with methanolic NaOH to afford **214b**. The corresponding mesylate **214c** was treated with DBU to give the olefin **215**. The TBDMS alcohol was deprotected and treated with *m*CPBA and $BF_3.OEt_2$ to afford **216**. The introduction of the carboxyl group was achieved following metallation of **216** with *n*-BuLi and reacting the resulting dianion with $CO_2$ gas. The crucial ring-closing step to yield the lactone was achieved under Mitsunobu

conditions. The final partial demethylation of **218** was achieved with boron tribromide to give monocerin **198**.

This synthetic route to monocerin is a powerful route but it is a very involved strategy with a large number of steps, which could be a possible drawback for this methodology.

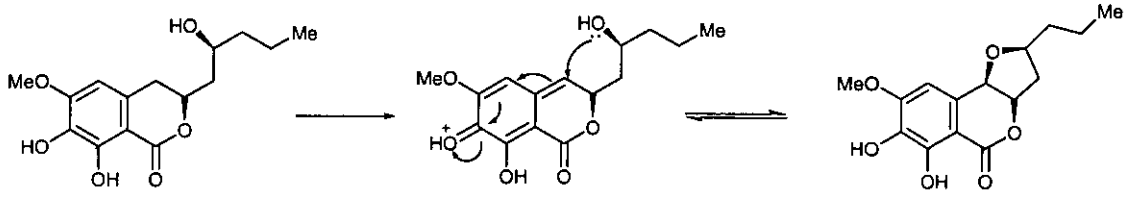
Dillon, Simpson and Sweeney went onto report the second synthetic strategy towards monocerin[92] and the number of synthetic step appeared to be dramatically reduced in comparison to the previously reported route.

The strategy is based on condensation of the benzylic anion derived from ethyl 2,3,4-trimethoxy-6-methylbenzoate **221** and a protected 3-hydroxyhexanal **222**.



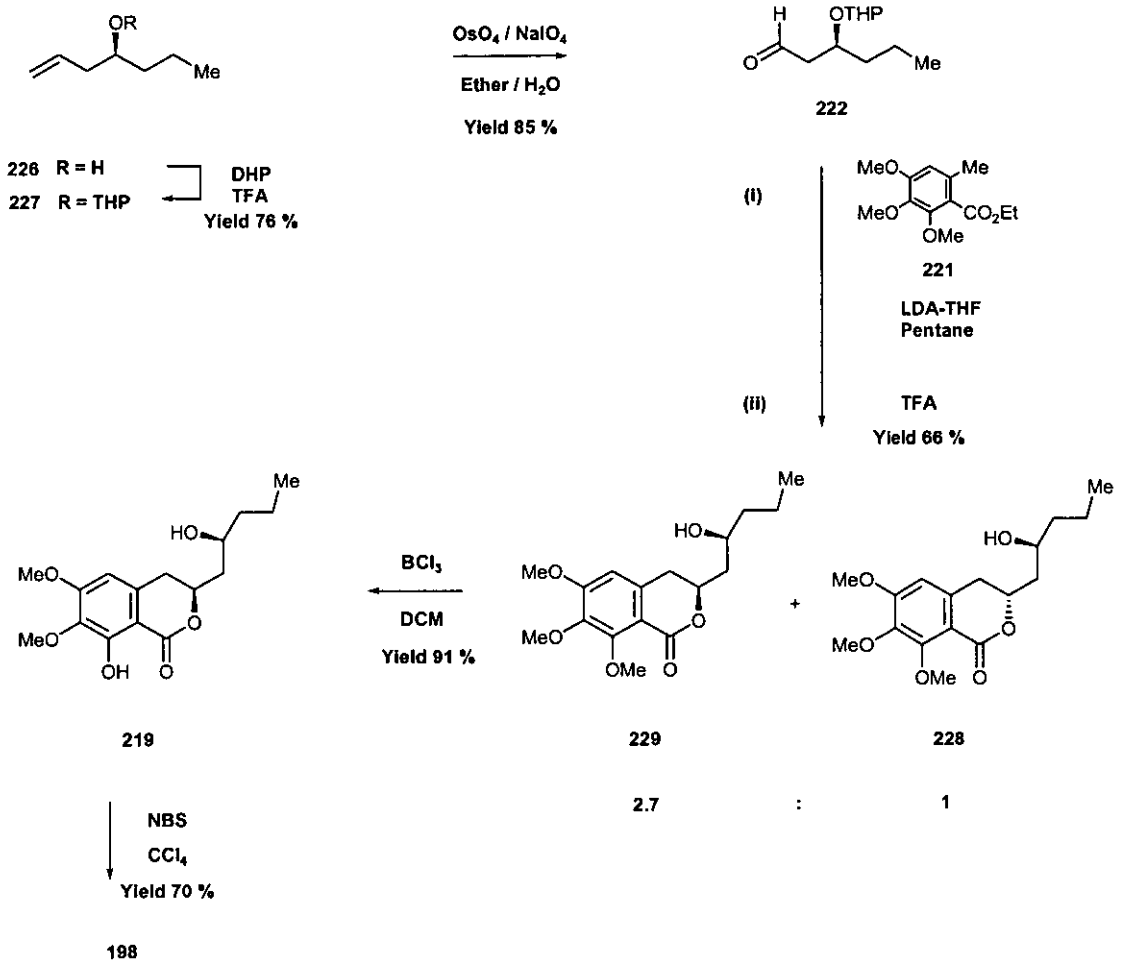

**Scheme 92**

The retrosynthetic analysis of the proposed route to monocerin is detailed in **scheme 92**. They based their anticipated route to monocerin on the biosynthetic studies involving the intermediate fusarentin ether **223** and its oxidation to the quinone methide **224**[87] followed by conjugate addition of the hydoxyl substituent onto the pyran moiety (**scheme 93**). The formation of the quinone methide **224** either by oxidation of **223** or reversible ring opening of **225** has been suggested to be responsible for the observed biological activities of this group of metabolites.[93]




223 224 225

**Scheme 93**




**Scheme 94**

Initially treatment of butyraldehyde with B-allylbis(2-isocaranyl)borane afforded (*S*)-hept-1-en-4-ol **226**. This in turn was converted to the tetrahydropyranyl ether **227** followed by olefin cleavage using catalytic $OsO_4$ and $NaIO_4$ to yield the desired building block **222**. Addition of a pentane solution of ethyl 2,3,4-trimethoxy-6-methylbenzoate **221** at –78°C to LDA resulting in a deep red colour, characteristic of anion formation, which subsequently was condensed with the aldehyde **222**. On deprotection, spontaneous lactonization of the aldol product occurred to afford the desired product as a mixture of diastereoisomers. The major diastereoismer present in the reaction mixture was the required epimer **229**. Partial demethylation of the aromatic ring afforded **219**, which, consequently, was treated to Wohl-Ziegler

bromination conditions. This promoted direct cyclization of the hydroxyl group onto the benzylic position to provide monocerin in good yield.

The analogues of monocerin have recently been synthesized using carbohydrate chemistry but the synthetic route was not suitable for the synthesis of monocerin itself.[94]

### 2.6.3 Palladium Catalyzed [3 + 2] Cycloaddition Strategy

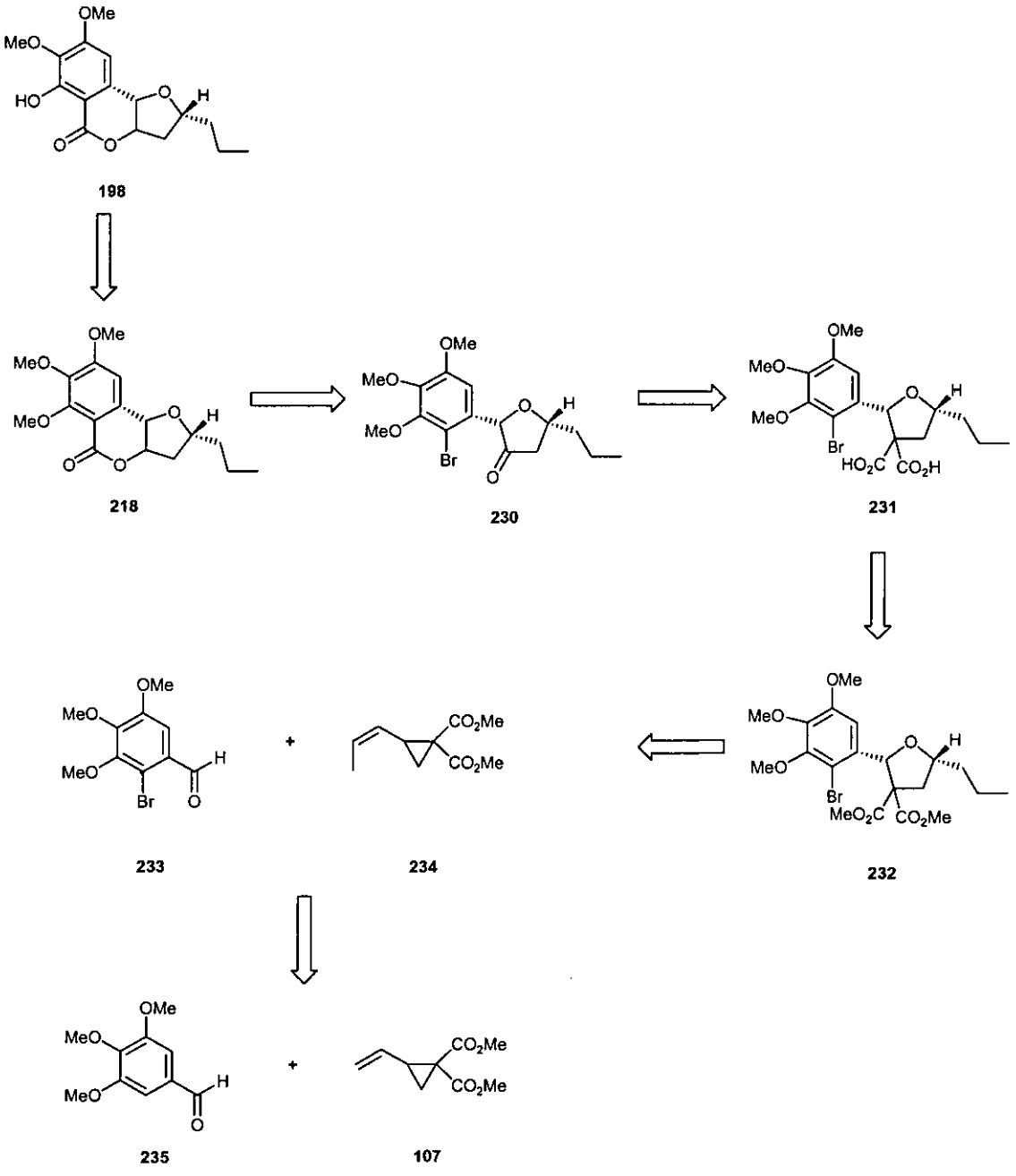
It was decided to attempt to adapt the palladium catalyzed cycloaddition methodology previously described, towards the synthesis monocerin. The crux of the chemistry would involve the palladium catalyzed [3 + 2] cycloaddition to assemble the framework of the natural product, followed by functional group manipulation and ultimately lactonization to afford the pyran ring.

### 2.6.4 Retrosynthetic Analysis

The core of the chemistry will be the construction of the tetrahydrofuran ring *via* the palladium catalyzed [3 + 2] cycloaddition strategy between the brominated 3,4,5 trimethoxybenzaldehyde **233** and the appropriate vinylcyclopropane **234** (**scheme 95**)

The ultimate step will be the partial and selective hydrolysis of one of the aromatic methyl ethers to afford **198**.[91] The lactone ring of **218** will be constructed *via* a crucial palladium catalyzed lactonization with insertion of CO gas incorporating the alcohol of the reduced carbonyl of **230**. The ketone moiety of **230** will be achieved *via* an oxidative decarboxylation of the *gem*-diacid of **231** using $Pb(OAc)_4$.[95] Hydrolysis of the *gem*-diester of **232** will afford the *gem*-diacid moiety of **231**. The building block

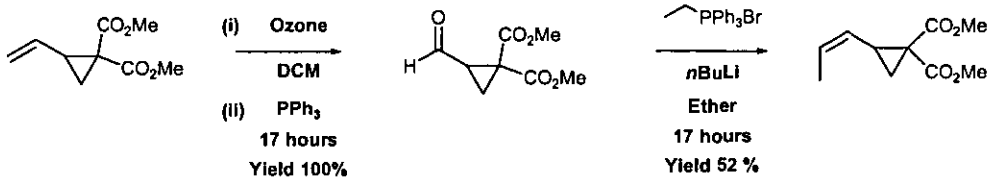
**233** will be synthesized from the bromination of 3,4,5 trimethoxybenzaldehyde **235**. The cyclopropane building block will be assembled by treating 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** to ozonolysis conditions followed by a Wittig olefination. The two building blocks **233** and **234** will undergo a [3 + 2] cycloaddition to construct the tetrahydrofuran ring.




**Scheme 95**

### 2.6.5 Forward Synthesis

Initially, the synthesis of the starting materials was attempted (**scheme 96** and **97**).

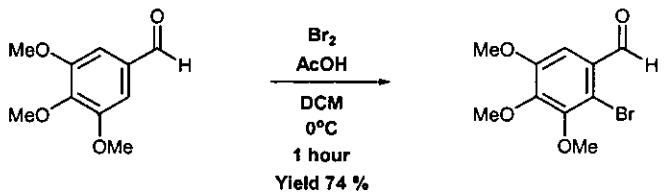



107 236 234

**Scheme 96**

The synthesis of 2-formyl-cyclopropane-1,1-dicarboxylic acid dimethyl ester **236** was successfully achieved by treating 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** with ozone and the reaction quenched with triphenylphosphine to afford the desired cyclopropane aldehyde in excellent yield (100%). A Wittig reaction was subsequently carried out on the aldehyde moiety of the cyclopropane **236** to yield *cis* isomer **234** as the predominant isomer as the ylide is unstabilized, with only a trace of the *trans* isomer detectable in the $^{1}$HNMR, in reasonable yield (52 %).

The synthesis of 2-bromo-3,4,5-trimethoxy-benzaldehyde **233** was achieved following the literature precedent reported by K. Yamada *et al* (**scheme 97**).[96]




235 233

**Scheme 97**

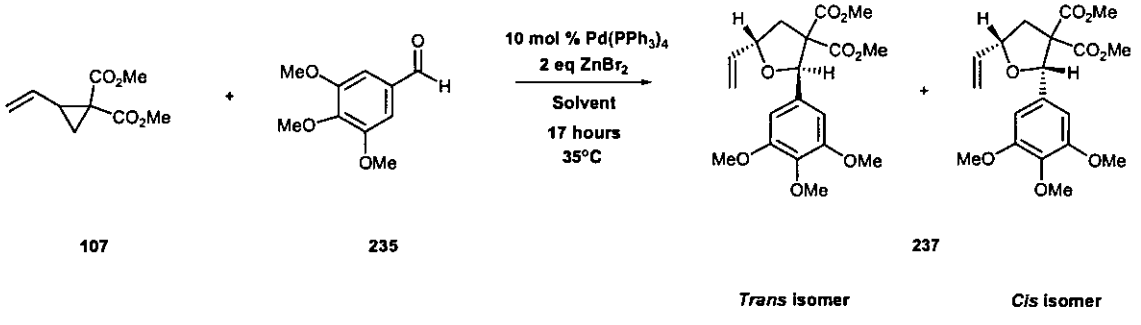
3,4,5-Trimethoxybenzaldehyde **235** underwent an electrophilic aromatic substitution on treatment with bromine and acetic acid. The desired brominated 3,4,5-trimethoxybenzaldehyde **233** was isolated in good yield (74 %).

With the starting materials now in hand, the natural progression appeared to be to attempt the palladium catalyzed [3 + 2] cycloaddition step.

### 2.6.6 [3 + 2] Cycloaddition Studies

Initially it was thought to attempt the synthesis using 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** and 3,4,5-trimethoxybenzaldehyde **235** to practice the functional group manipulations on readily available starting materials.

2-Vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** was subjected to 3,4,5 trimethoxybenzaldehyde **235**, 10 mol % $Pd(PPh_3)_4$ and $ZnBr_2$ **(scheme 98)**. A small study was completed to attempt to find the optimum conditions for the yield and diastereoselectivity for this reaction.




**Scheme 98**

The parameters varied in an attempt to find the optimum conditions are detailed in **table 17**.

**Table 17**

| Solvent | $ZnBr_2$ | Yield of 237 | *Trans* : *Cis* |
|---|---|---|---|
| THF | Yes | 75 | 1 : 3 |
| Methanol | No | 40 | 1 : 2 |
| Methanol | Yes | 73 | *cis* major |
| DCM | Yes | - | - |

Reagents and conditions: (1 mmol) **107** with (1 mmol) **235** was carried out in the presence of 10 mol % $Pd(PPh_3)_4$ and 2 mmol $ZnBr_2$ in solvent at 35°C.

The reaction carried out in THF in the presence of $ZnBr_2$ gave promising results. The yield of the cycloadduct was good and the diastereoselectivity of the reaction was in favour of the *cis* isomer. This was especially pleasing to note as the stereochemistry of the reaction is the same as the natural product, which is a *cis* fused furobenzopyranone skeleton. On replacing the reaction solvent with MeOH, in the absence of $ZnBr_2$, not only a dramatic decrease in yield was observed, but also stereoselectivity of the reaction. Most pleasing to note was that on the inclusion of $ZnBr_2$, a good yield of the cycloadduct was isolated and the stereochemical outcome of the reaction was much improved, with only a trace of the *trans* diastereoisomer being observed in the crude $^1$HNMR. These conditions were considered to be the optimum conditions for the reaction due to the good yield, albeit slightly lower than that obtained for the reaction carried out in THF, but more importantly, the stereoselectivity was the most favourable for the synthesis of the *cis* diastereoisomer. The reaction carried out in DCM did not afford the cyclaodduct and starting materials were recovered.

The *cis* diastereoisomer was isolated exclusively and the structure and stereochemistry for the vinyl group and aromatic ring could be confirmed by x-ray as shown in **figure 24**.

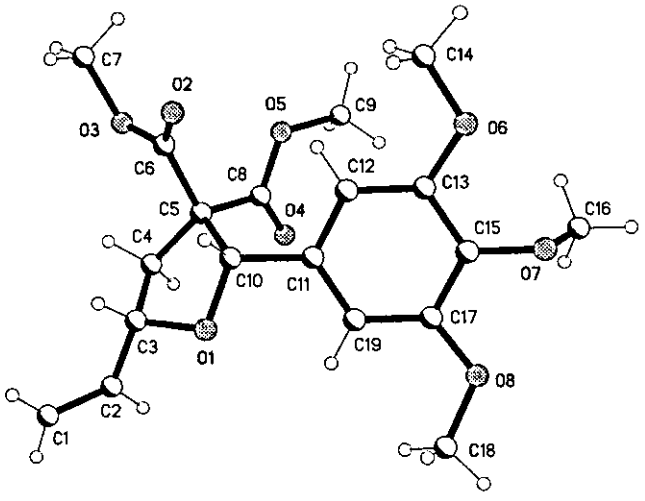



**Figure 24**

It is clear to note from the x-ray that the vinyl group and the aromatic ring are *cis* in relationship to each other. This is also true for the natural product monocerin. The diastereoisomers behave characteristically in the $^1$HNMR spectrum as described previously. The $^1$HNMR of the single diastereoisomer (**figure 25**) does detail that the *cis* isomer has been isolated as the hydrogens on 4-C in the tetrahydrofuran ring appear closer together in chemical shift in comparison to the *trans* isomer.

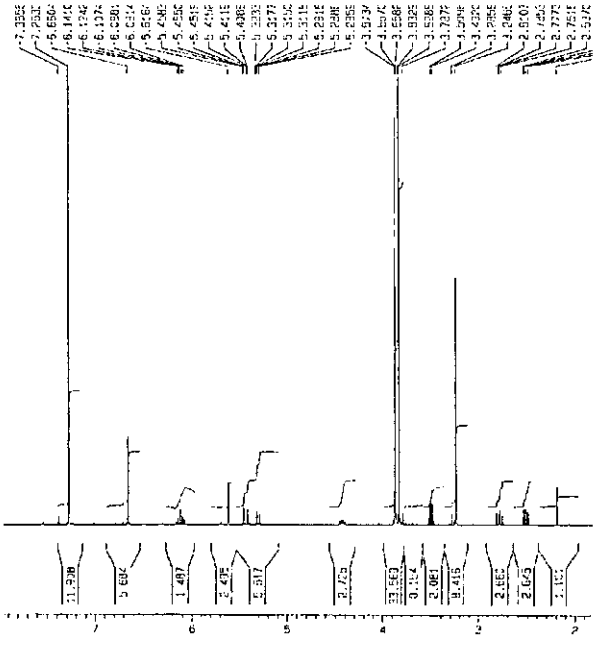
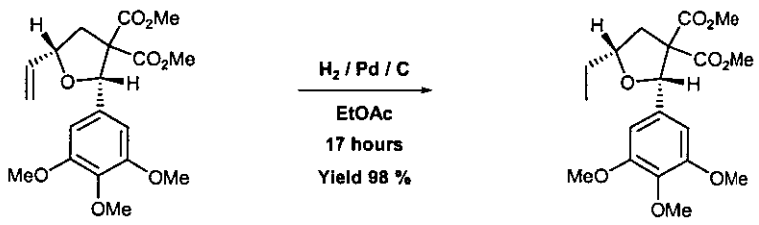


**Figure 25**

Now that a good method had been developed to synthesize the *cis* diastereoisomer as the principal isomer, the synthetic strategy towards moncerin **198** was continued.

Reduction of the vinyl group was easily achieved by treating the cycloadduct **237** to 10 mol % Pd / C in an atmosphere of hydrogen (**scheme 99**).



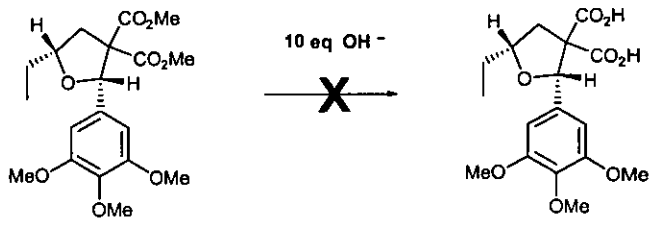

**237** **238**

**Scheme 99**

Now with the cycloaddition and hydrogenation reaction conditions to hand the next step was to tackle the manipulation of the methyl esters.

## 2.6.7 Ester Hydrolysis

The hydrolysis of the methyl esters proved to be far more problematic than originally anticipated (**scheme 100**).




238 239

**Scheme 100**

Initially the conditions previously used to synthesize 2-vinylcyclopropane-1,1-dicarboxylic acid were attempted. The conditions used to try and hydrolyse the methyl esters are shown in **table 18**.

Table 18

| Base | Solvent | Temp °C | Time hours |
|---|---|---|---|
| | MeOH / $H_2O$ | 25 | 48 |
| **LiOH** | MeOH / $H_2O$ | 77 | 17 |
| | THF / $H_2O$ | 25 | 48 |
| | THF / $H_2O$ | 77 | 48 |
| | MeOH / $H_2O$ | 25 | 192 |
| **NaOH** | MeOH / $H_2O$ | 77 | 17 |
| | THF / $H_2O$ | 25 | 48 |
| | THF / $H_2O$ | 77 | 48 |
| | MeOH / $H_2O$ | 25 | 48 |
| **KOH** | MeOH / $H_2O$ | 77 | 17 |
| | THF / $H_2O$ | 25 | 48 |
| | THF / $H_2O$ | 77 | 48 |
| | MeOH / $H_2O$ | 25 | 48 |
| **CsOH** | MeOH / $H_2O$ | 77 | 17 |
| | THF / $H_2O$ | 25 | 48 |
| | THF / $H_2O$ | 77 | 17 |

Reagents and Conditions: 1 mmol **238**, 20 ml solvent, 20 ml $H_2O$, (10 eq) LiOH.

10 equivalents of each base described in **table 18** were employed to attempt to hydrolyse the methyl esters. The same product was isolated each time and was suspected to be the monoalkylated cycloadduct as described in **figure 26**.

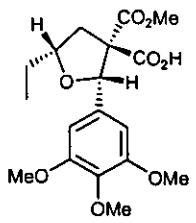
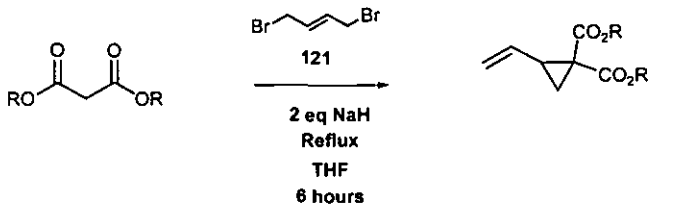



**Figure 26**

The IR spectrum suggested that there was evidence of both an ester an acid due to the presence of the corresponding carbonyl stretches, even after an acid base extraction to separate the product and any potential starting material. The methyl ether region in the $^1$HNMR also over integrated suggesting incomplete ester hydrolysis. The difficulty experienced in the hydrolysis of both esters could be attributed to steric interference of both the vinyl group and the phenyl ring for one of the esters. Also another contributing factor could be the presence of the two carboxylate anions in such close proximity to each other. Acid hydrolysis was also attempted when the cycloadduct was refluxed in 1M HCl for 17 hours. In this instance neither the esters were hydrolysed. The cycloadduct **238** was also treated to LiBr in pyridine, a known method for the hyrdolysis of sterically demanding methyl esters, but both methyl esters were apparent in the product $^1$HNMR and IR spectrums.

## 2.6.8 Ester Variation

Due to the difficulties experienced in hydrolysing the methyl esters, it was thought that the synthesis of cyclopropanes possessing different ester groups could be achieved. The different esters may be more labile to base hydrolysis or could even be manipulated in other ways. The cyclopropane possessing benzyl esters was originally synthesized (**scheme 101**).




R = OBn 240
R = C(CH3)3 241
R = CH2CH3 242

Yield = 73 % 243
Yield = 68 % 244
Yield = 65 % 245

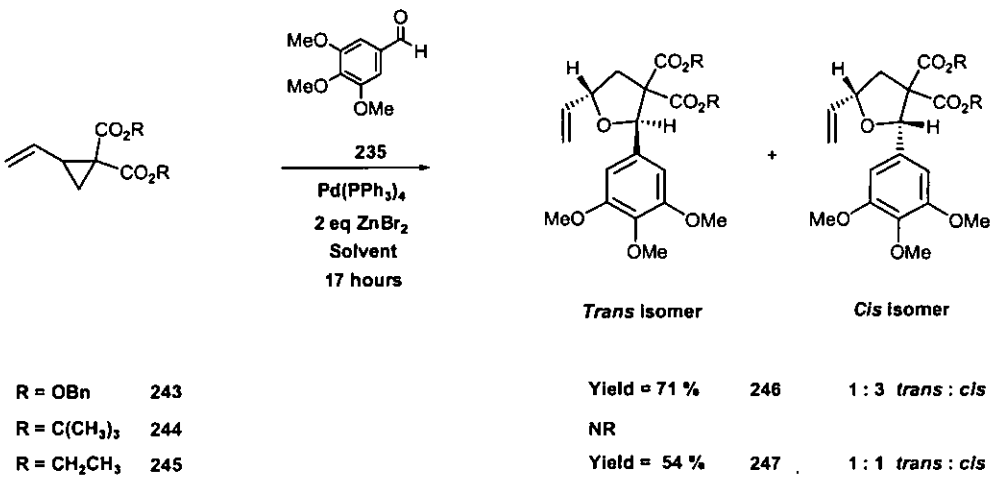
**Scheme 101**

The acidic protons of dibenzylmalonate **240** were deprotonated using NaH and on treatment with 1,4 dibromobut-2-ene **121**, underwent a double displacement reaction to afford the corresponding cyclopropane **243** in good yield. 2-Vinyl-cyclopropane-1,1-dicarboxylic acid dibenzyl ester **243** was synthesized to investigate if the benzyl esters were more labile to base hydrolysis than the methyl esters or more importantly to determine whether the benzyl esters could be removed under hydrogenation conditions as opposed to hydrolysis.

The tertiary butyl ester cyclopropane was synthesized as tertiary butyl esters are more labile to acid hydrolysis than methyl esters and perhaps ester hydrolysis could successfully be achieved by this method. Again 2-vinyl-cyclopropane-1,1-dicarboxylic acid di-*tert*-butyl ester **244** was achieved in good yield (68 %). The ethyl ester analogue **245** was a good example to make for clarity purposes. The ethyl

groups appear in a different region of the $^1$HNMR to the aromatic methyl ethers, hence the extent of the ester hydrolysis achieved will be totally apparent in the $^1$HNMR spectrum.

Now the cyclopropanes were to hand, the progressive step was to test whether they participate in a palladium catalyzed [3 + 2] cycloaddition on treatment with 3,4,5 trimethoxybenzaldehyde **235** and $Pd(PPh_3)_4$ (**scheme 102**).




**Scheme 102**

2-Vinyl-cyclopropane-1,1-dicarboxylic acid dibenzyl ester **243** was treated with 3,4,5 trimethoxybenzaldehyde **235** and $Pd(PPh_3)_4$ and 2 equivalents of $ZnBr_2$. **Table 19** details the solvents chosen for the reaction.

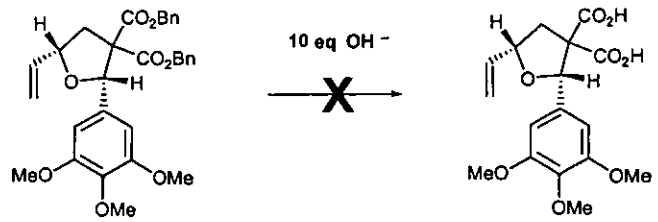
**Table 19**

| Solvent | Yield % of 246 | *Trans* : *Cis* |
|---|---|---|
| MeOH | Ester Exchange | |
| THF | NR | |
| DMF | 25 | 1 : 1 |
| DMSO | 50 | 1 : 2 |
| MeCN | 36 | 1 : 1 |
| DCM | 71 | 1 : 3 |

Reagents and conditions: (1 mmol) **243** with (1 mmol) **235** was carried out in the presence of 10 mol % $Pd(PPh_3)_4$ and 2 mmol $ZnBr_2$ in solvent at 35°C.

Initially the reaction conditions were adopted from the methyl ester cycloaddition, *i.e.* the reaction solvent chosen was methanol and $ZnBr_2$ was included. The product isolated indicated that the benzyl esters had exchanged in the methanol for methyl esters. The reaction was repeated in THF but surprisingly only starting materials were recovered. It was decided to attempt the reaction in a more polar solvent to stabilize the zwitterionic palladium $\pi$-allyl intermediate species and hence encourage nucleophilic attack on the aldehyde moiety. This appeared to be a fundamental factor as the reactions performed in the more polar solvents did in fact afford the desired tetrahydrofuran **246** albeit with disappointing reaction yields and diastereoselectivities. Surprisingly the reaction carried out in the solvent DCM appeared to be the optimium conditions for this reaction, boasting the greatest reaction yield with the better reaction stereoselectivity.

With the desired cycloadduct now in hand, manipulation of the benzyl esters was the next step. The cycloadduct **246** was treated to the hydrolysis conditions reported previously for the methyl esters (**scheme 103**).




246

**Scheme 103**

The conditions used for the attempted hydrolysis are listed in **table 20.**

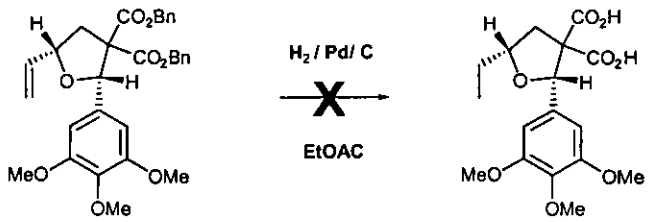
**Table 20**

| Base | Solvent | Temp °C | Time Hours |
|---|---|---|---|
| **LiOH** | THF / $H_2O$ | 25<br>77 | 48 |
| **NaOH** | THF / $H_2O$ | 25 | 48 |
| **KOH** | THF / $H_2O$ | 25 | 48 |
| **CsOH** | THF / $H_2O$ | 25 | 48 |

Reagents and Conditions: 1 mmol **246**, 20 ml solvent, 20 ml $H_2O$, (10 eq) LiOH.

Unfortunately the same problems reported for the methyl esters arose for the benzyl esters. The apparent stretches for both the acid and ester moieties in the IR spectrum and the over-integration of the aromatic region in the $^1$HNMR spectrum indicated that hydrolysis of the esters was not complete. Again it is believed that steric impositions of the vinyl and the aromatic group on the same face as one of the benzyl esters could be the cause of the incomplete hydrolysis.

It was also attempted to reduce benzyl esters under hydrogenation conditions (**scheme 104**).




**246**

**Scheme 104**

The benzyl cycloadduct **246** was treated to an atmosphere of hydrogen and palladium on carbon. The reduction of the vinyl group was successful but again only one of the benzyl esters was reduced. This was also the case when the cycloadduct in EtOH, was treated with high pressures of hydrogen using the hydrogenator.

The palladium catalyzed [3 + 2] cycloaddition of 2-vinyl-cyclopropane-1,1-dicarboxylic acid di-*tert*-butyl ester **244** with 3,4,5 trimethoxybenzaldehyde **235** was not successful to afford the corresponding cycloadduct (**table 21**).

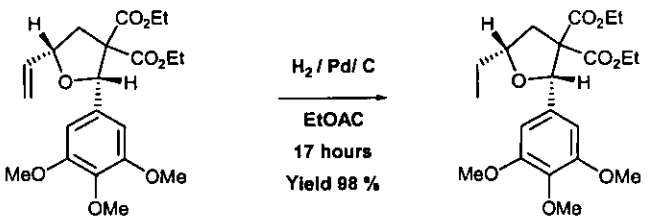
**Table 21**

| Cyclopropane | Solvent | Outcome |
|---|---|---|
| **244** | THF | NR |
| **244** | DCM | NR |
| **244** | DMSO | NR |

Reagents and conditions: (1 mmol) **244** with (1 mmol) **235** was carried out in the presence of 10 mol % $Pd(PPh_3)_4$ and 2 mmol $ZnBr_2$ in solvent at 35°C.

A small range of solvents was employed to attempt to drive the reaction to completion. Unfortunately starting materials were recovered each time. It is postulated that the bulky tertiary butyl groups prevented the zwitterionic palladium $\pi$-allyl intermediate from participating in the nucleophilic addition to the aldehyde of 3,4,5 trimethoxy benzaldehyde.

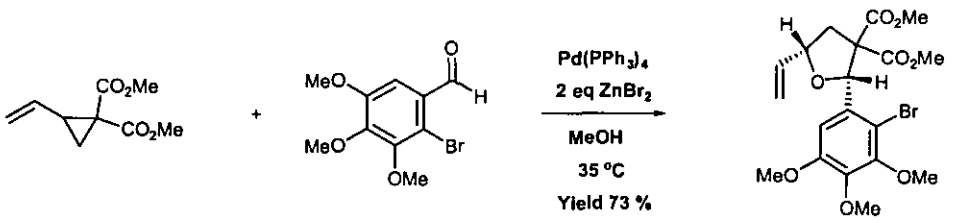
The cycloadduct 2-(3,4,5-trimethoxy-phenyl)-5-vinyl-dihydro-furan-3,3-dicarboxylic acid diethyl ester **247** was successfully isolated on treatment of 2-vinylcyclopropane-1,1-dicarboxylic acid diethyl ester **245** in DCM with 3,4,5 trimethoxybenzaldehyde **235**, $Pd(PPh_3)_4$ and $ZnBr_2$. The yield of the reaction was moderate 54 % and the stereoselectivity of the reaction was slightly disappointing with 1 : 1 diastereoisomers being isolated. The vinyl group was reduced under hydrogentation conditions (**scheme 105**).




**Scheme 105**

The hydrolysis of the ethyl esters did indicate that only one of the ethyl esters was hydrolysed.

It was decided to attempt the synthesis with the bromo-3,4,5-trimethoxybenzaldehyde **233** to practice the functional group manipulation with the bromide substituted on the aromatic ring (**scheme 106**).

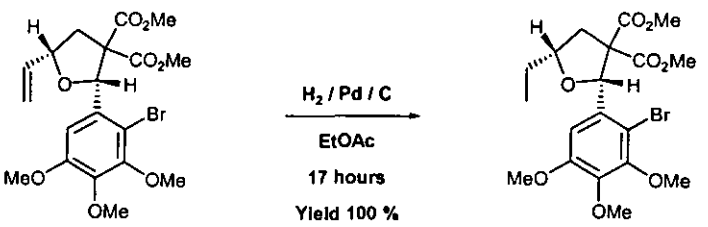



**107** **233** **249**

| *Trans* | : | *Cis* |
|---|---|---|
| 1 | : | 10 |

**Scheme 106**

The palladium catalyzed [3 + 2] cycloaddition between 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** and 2-bromo-3,4,5-trimethoxy-benzaldehyde **233** proceeded successfully in good yield (73 %) and good diastereoselectivity (*trans* : *cis* ratio 1 : 10). The cyclopropane substituted with the methyl esters was chosen as the reaction carried out in MeOH with $ZnBr_2$ was much more stereoselective for the *cis* isomer than other reaction solvents. The vinyl group was again reduced under hydrogenation conditions (**scheme 107**).




**249** **250**

**Scheme 107**

Unfortunately due to time restriction, the synthesis towards the natural product monocerin was left at this stage.

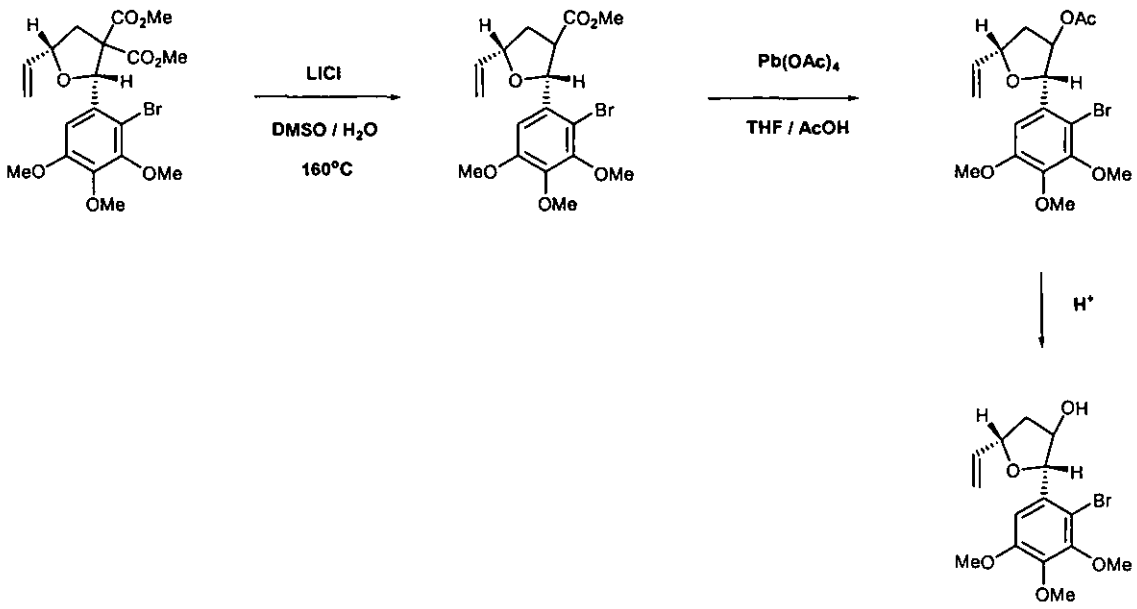
### 2.6.9 Summary and Conclusions

The [3 + 2] cycloaddition strategy developed and reported herein was adapted towards the synthesis of monocerin. The palladium catalyzed [3 + 2] methodology has shown to work in good yields and the stereoselectively of the reaction for the correct diastereoisomer, the *cis* diastereoisomer, has shown to be excellent, given the correct variables are employed.

The methodology has been shown to be a very powerful tool as in the one step, the [3 + 2] cycloaddition step, all the carbons that are present in the natural product, except one have been assembled. Problems have been encountered during the functional group manipulation of the cycloadduct from the [3 + 2] cyclization steps and due to the unforeseen difficulties encountered in the hydrolysis step, the synthesis of monocerin by this route has not yet been completed. The hydrolysis and subsequent removal of the *bis*-diester has proven not to be trivial. A number of cyclopropanes containing different esters have been synthesized to provide more facile methods for the manipulation of this group, but unfortunately this proved not to be the case.

### 2.6.10 Future synthetic strategy

The future studies on this work could concentrate on the manipulation of the methyl esters of the cycloadduct. Krapcho decarboxylation conditions could be employed to remove one of the methyl esters (**scheme 108**).




**Scheme 108**

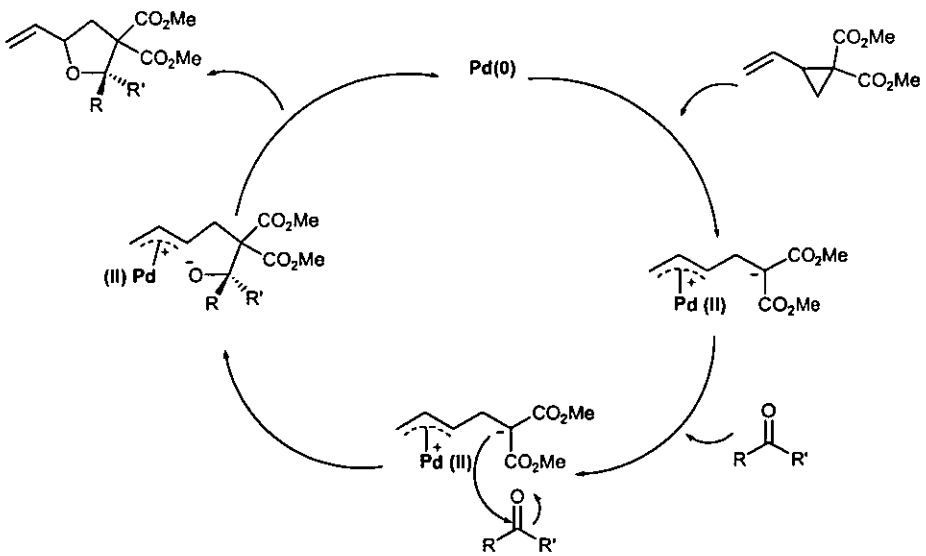
$Pb(OAc)_4$ in THF / AcOH could be employed for the conversion of the carboxylic acid moiety in to the acetate.[97] Hydrolysis of the acetate should be achieved using mild acidic conditions to afford the alcohol.

The alcohol would then be in place for the lactonization step with the insertion of CO gas to afford the final lactone ring. The final step, the partial demethylation should be achieved following the literature precedent previously reported.

## 3.0 Summary and Conclusions

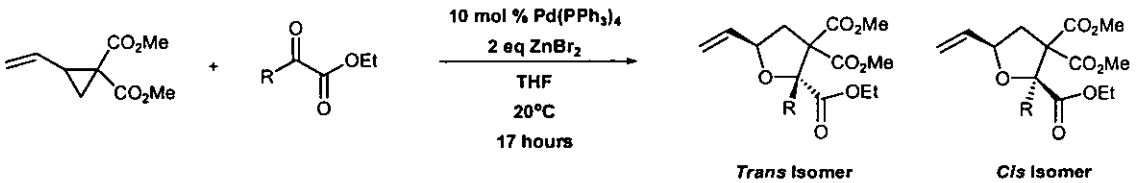
A novel palladium catalyzed [3 + 2] cycloaddition approach to tetrahydrofuran rings has been reported. 2-Vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** has been employed as the 1,3,dipole synthon to participate in the cycloaddition. A wide range of activated carbonyl moieties have been employed successfully as the 2-unit synthon in the reaction.

The mechanism in operation for this [3 + 2] cycloaddition is thought to commence with oxidative insertion of palladium(0) into the vinyl group of the cyclopropane (**scheme 109**). This in turn causes the cyclopropane to ring open and to form the zwitterionic π-allyl palladium(II) complex. The negative charge is stabilized by the presence of the two electron-withdrawing methyl esters. The malonic centre of the π-allyl palladium(II) complex subsequently undergoes a nucleophilic addition to the carbonyl to afford a second transient zwitterion. The resultant alkoxide displaces the palladium and on reductive elimination of the palladium (0) the desired substituted vinyl tetrahydrofuran is formed. As only a catalytic amount of palladium (0) is required, the palladium is assumed to be regenerated on formation of the five membered heterocyclic product.




**Scheme 109**

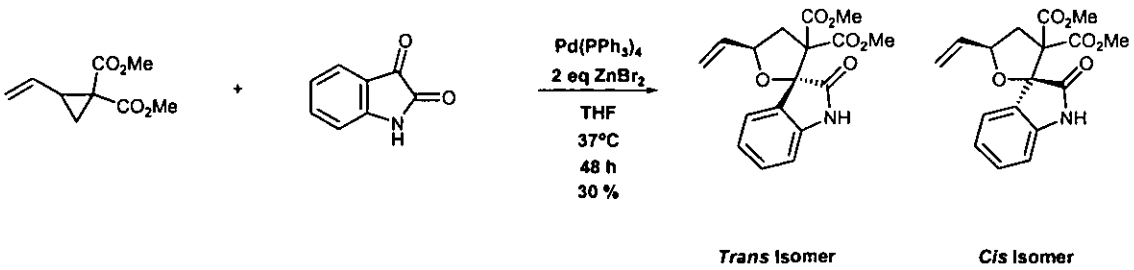
A range of α-keto esters have been employed as electrophiles to undergo a palladium catalyzed [3 + 2] cycloaddition with 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** to afford substituted tetrahydrofurans as *cis* and *trans* diastereoisomers (**scheme 110**). The ketone moiety in this instance was activated by adjacent ethyl ester groups and has shown to be a successful substrate for the cycloaddition. The presence of the adjacent electron-withdrawing group was essential for the successful [3 + 2] cycloaddition as it enhances the electrophilicity of the ketone and makes it more susceptible to nucleophilic attack from the malonic centre of the palladium π-allyl species. The reaction is not successful in the absence of the electron-withdrawing group.




**Scheme 110**

The scope of the reaction was shown to be large, but also there appeared to be a few limitations to the reaction. Bulky groups adjacent to the ketone are not tolerated in the reaction and phenyl rings adjacent to the ketone have to be activated further by an electron-withdrawing substituent.

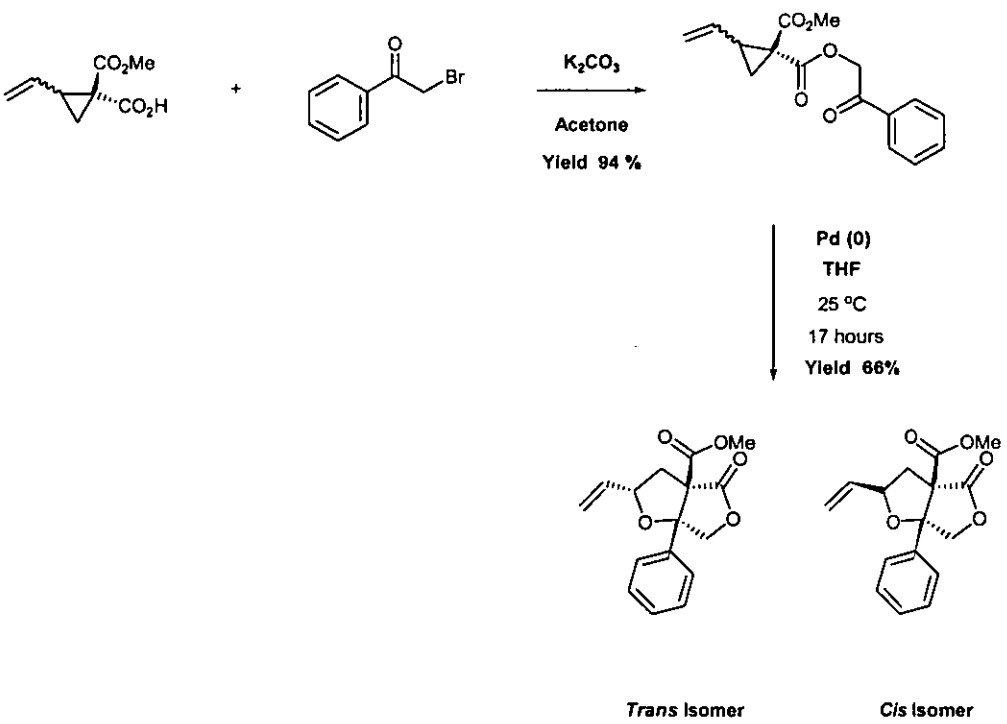
The reaction also appears to be very successful when the ketone moiety is activated by the presence of an adjacent electron-withdrawing amide. A range of isatins was employed as substrates and the [3 + 2] cycloaddition reaction afforded a range of spiro tetrahydrofurans (**scheme 111**).




**Scheme 111**

The diastereoselectivity of the reaction can be manipulated by the choice of the reaction solvent. If the solvent employed for the reaction is non-polar, the major diastereoisomer observed is the *trans* isomer. Conversely, if the reaction solvent is polar, the predominant diastereoisomer isolated from the reaction mixture is the *cis*.

The palladium catalyzed [3 + 2] cycloaddition strategy to five membered heterocycles has also been applied to an intramolecular approach. The ketone moiety in this situation was tethered onto the cyclopropane. On treatment of the tethered cyclopropane with $Pd(PPh_3)_4$, the ketone participated in a [3 + 2] cycloaddition and a subsequent 5-exo-trig- ring closing step afforded a bicyclic fused heterocycle (**scheme 112**).




**Scheme 112**

The methodology described is a powerful tool because in one reaction sequence a carbon-carbon bond and a carbon-oxygen have been constructed and 2 adjacent quaternary centres have been established. A range of alkylating agents have been employed to compile a small library of bicyclic structures synthesized, but unfortunately the range of alkylating agents available has limited this study to the synthesis of fused 5,5 bicyclic structures.

This [3 + 2] cycloaddition approach has also been very successful when employed towards the synthetic route of the natural product monocerin. The cyclization step between 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester and 3,4,5-trimethyoxybenzaldehyde has worked well, boasting good yields and excellent diastereoselectivity towards the isomer of the natural product, but unfortunately, the functional group manipulation proved problematic and due to time constraints, the synthesis towards the natural product has not yet been completed.

# 4.0 General Information

## 4.0.1 Solvents and Reagents

All solvents and reagents were purified by standard techniques as reported in Perrin, D.D.; Armarego, W. L. F., Purification of Laboratory Chemicals, 3rd edition, Pergamon Press, Oxford, 1988 or as used as supplied from commercial sources as appropriate.

Reagent chemicals were purchased from Aldrich Chemical Company Ltd., Lancaster Chemical Synthesis Ltd., Acros (Fischer) Chemicals Ltd., Avocado and Strem Chemicals UK

Solvents, where necessary, were dried and stored over 4A molecular sieves prior to use. 40-60 petroleum ether (P.E. 40-60) refers to the fraction of light petroleum ether which boils between 40-60°C. DCM, $Et_2O$, MeOH and THF refer to dichloromethane, diethyl ether, methanol and tetrahydrofuran respectively.

## 4.0.2 Chromatographic Procedures

Analytical thin layer chromatography (TLC) was conducted using aluminium-backed plates coated with 0.2 mm silica. Plates were visualised by quenching of UV light (254 nm) fluorescence as well as through staining with 1 % vw/v potassium permanganate in aqueous alkaline solution followed by heat as appropriate. Flash chromatography was conducted using Merck Kiesgel (70-230 Mesh ASTM) as the

stationary phase. Samples were applied as saturated solutions in the appropriate solvent. Pressure was applied to the column by the use of hand bellows.

### 4.0.3 Spectra

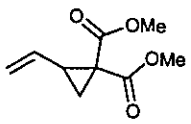
Infra-red spectroscopy (IR) was conducted in the range of 4000-600 $cm^{-1}$, using a Perkin-Elmer Fourier Transform Paragon 1000 Spectrophotometer (with internal calibration). Samples were dissolved in an appropriate solvent and applied as a thin film to the IR plates. Liquid samples were applied neat to the plate and run as thin films. Only the major absorbances have been quoted. The following abbreviations have been quoted: w, weak; m, medium; s, strong; br, broad. $^1H$ nuclear magnetic resonance (NMR) spectra were recorded using either a Bruker AC-250 or DPX-400 spectrometer. For $^1H$ spectra recorded in $CDCl_3$, $CD_3OD$, $C_6D_6$, $d_6$-DMSO or $D_2O$, chemical shifts were quoted as parts per million (ppm) and are referenced to the residual solvent peak and tetramethylsilane (TMS) as the internal standard. The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br). Assignment of individual proton signals was assisted by analysis of $^1H$ COSY spectra. Coupling constants ($J$ values) are reported in Hertz (Hz). Diastereoisomer ratios were calculated from the integration of suitable peaks in the $^1H$ NMR spectra. $^{13}C$ NMR spectra were recorded using a DPX-400 spectrometer with DEPT editing to assist assignment. Chemical shifts are quoted in ppm relative to tetramethylsilane (TMS).

Mass spectra (high/low resolution) were recorded using a Fisons VG Quattro II SQ instrument, with modes of ionisation being indicated as EI and FAB and with only the molecular ion, molecular ion fragments and major peaks being reported. Accurate masses were recorded using a Kratos MS-80 instrument.

### 4.0.4 Other Data

Melting points were determined using an electrical 9100 Thermal Melting Point instrument and are uncorrected. A Bruker SMART 1000 CCD diffractometer ω rotation with narrow frames was used to collect X-ray data. Yields (unless otherwise stated) are quoted for isolated pure products.

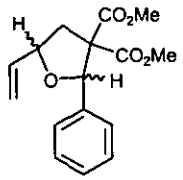
**2-Vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester[67] (107)**




To a stirred solution of sodium methoxide, prepared from sodium (1.150 g, 50.00 mmol) methanol (20 ml), was added dimethylmalonate **120** (5.89 ml, 51.50 mmol) followed by a solution of *trans*-1,4-dibromobut-2-ene **121** (5.350 g, 25.00 mmol) in methanol (20 ml). The mixture was refluxed for 2.5 hours and then cooled to room temperature. The white precipitate was filtered off and the filtrate was concentrated *in vacuo* to give an oily residue. The residue was partitioned between $Et_2O$ (30 ml) and distilled water (30 ml). The layers were separated and the organics were washed with distilled water (2 x 30 ml), dried ($MgSO_4$) and concentrated *in vacuo* to afford a pale yellow oil (5.350 g). The product was purified by flash chromatography ($SiO_2$, $Et_2O$ : P.E. 40-60; 1 : 4) to afford the desired cyclopropane **107** as a colourless oil (4.600 g, 15.50 mmol, 62%); $\nu_{max}$ (thin film)/$cm^{-1}$ 2955w (C-H str), 1730s (C=O str), 1438s, 1331s, 1274s, 1211s, 1131s; $\delta_H$ (400 MHz; $CDCl_3$) 1.58 (1H, dd, *J* 5.0 and 9.0 Hz, 3-C(H)H), 1.73 (1H, dd, *J* 5.0 and 7.5 Hz, 3-C(H)H), 2.59 (1H, m, 2-CH), 3.74 (6H, s, 2 x $OCH_3$), 5.15 (1H, d, *J* 8.0 Hz, $CH_2$=CH), 5.28 (1H, d, *J* 15.0 Hz, $CH_2$=CH), 5.40 (1H, m, $CH_2$=CH); $\delta_C$ (100 MHz; $CDCl_3$) 20.91 (3-$CH_2$), 31.78 (2-CH), 36.08 (1-C), 52.90, 53.04 (2 x $OCH_3$), 119.01 ($CH_2$=CH), 133.32 ($CH_2$=CH), 168.10, 170.33 (2 x C=O); *m/z* (EI) 184 ($M^+$, 25 %), 152, 124, 113, 96, 93, 79, 71, 65, 59, (Found 184.0733, $C_9H_{12}O_4$ requires 184.0736).

**2-Phenyl-5-vinyldihydrofuran-3,3-dicarboxylic acid dimethylester (116)**

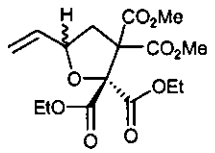
(1 : 3; *trans* : *cis* in THF), (1 : 3; *trans* : *cis* in methanol), (1 : 2; *trans* : *cis* in methanol without $ZnBr_2$), (1 : 1; *trans* : *cis* in 50% $H_2O$ : THF without $ZnBr_2$)




To a stirred solution of 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** (0.184 g, 1.00 mmol) in anhydrous THF (5 ml) was added benzaldehyde **114** (0.106 g, 1.00 mmol) and zinc bromide (0.450 g, 2.00 mmol) at room temperature. This mixture was left to stir for 10 minutes under nitrogen before a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.115 g, 0.10 mmol) was added. The resulting yellow mixture was allowed to stir at room temperature for 17 hours. The solvent was then removed *in vacuo* and the residue dissolved in EtOAc (20 ml). The residue was filtered through a plug of silica to remove the palladium catalyst, and the organic layer was washed with distilled water (2 x 30 ml). The organics were dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow oil (0.187 g). This crude material was purified by column chromatography ($SiO_2$, $Et_2O$ : P.E. 40-60; 4 : 6) to afford a mixture of isomers of the desired furan **116** as a colourless oil (0.182 g, 0.63 mmol 63 %); $\nu_{max}$ (thin film)/$cm^{-1}$ 2984s, 2938m, 2906m (C-H str), 1734s (C=O str); $\delta_H$ (400 MHz; $CDCl_3$) 2.20 (1H, dd, *J* 8.0 and 12.0 Hz, 4-C(H)H), 2.49 (1H, dd, *J* 8.0 and 12.0 Hz, 4-C'(H)H), 2.77 (1H, dd, *J* 12.0 and 14.0 Hz, 4-C'(H)H), 3.10 (1H, dd, *J* 8.0 and 12.0 Hz, 4-C(H)H), 3.11 (3H, s, OC'$H_3$), 3.17 (3H, s, O$CH_3$), 3.77 (3H, s, O$CH_3$), 3.80 (3H, s, OC'$H_3$), 4.41 (1H, m, 5-C'H), 5.05 (1H, m, 5-CH), 5.25-5.43 (4H, m, $CH_2$=CH and C'$H_2$=C'H), 5.68 (1H, s, 2-C'H), 5.79 (1H, s, 2-CH), 5.90 (1H, m, $CH_2$=CH), 6.10 (1H, m, C'$H_2$=C'H), 7.24-7.41 (10H, m, 5 x Ph-H and 5 x Ph'-H); $\delta_C$ (100 MHz; $CDCl_3$) 40.37, 40.54 (4-C'$H_2$ and 4-$CH_2$), 52.15, 52.17, 52.82, 52.98 (2 x OC'$H_3$ and 2 x O$CH_3$), 66.22, 66.22 (3-C and 3-C'), 79.24 (5-C'H), 79.96 (5-CH), 83.51 (2-CH), 84.24 (2-C'H), 116.10 ($CH_2$=CH), 117.68 (C'$H_2$=C'H), 126.52,

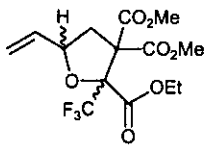
126.97, 127.81, 127.87, 127.99, 128.13 (Ph-CH and Ph-C'H), 136.48 ($C'H_2$=C'H), 137.79 ($CH_2$=CH), 138.15, 138.28 (*ipso*-C and *ipso*-C'), 168.97, 169.14, 170.42, 171.22 (2 x C=O and 2 x C'=O); *m/z* (EI) 290 ($M^+$, 25 %), 236 (81 %), 184 (67 %), 152 (82 %), 124 (53 %), 105 (100 %), 93 (19 %), 71 (39 %), (Found 290.1158, $C_{16}H_{18}O_5$ requires 290.1154).

**5-Vinyldihydrofuran-2,2,3,3-tetracarboxylic acid diethyl ester dimethyl ester (124)**




To a stirred solution of 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** (0.184 g, 1.00 mmol) in anhydrous THF (5 ml), was added diethyl ketomalonate **123** (0.174 g, 1.00 mmol) and zinc bromide (0.450 g, 2.00 mmol) at room temperature. The mixture was left to stir under nitrogen for 20 minutes before the addition of a catalytic amount of tetrakis (triphenylphosphine) palladium (0.115 g, 0.10 mmol). The resulting yellow solution was stirred for 20 hours at room temperature. The solvent was removed *in vacuo* to afford a yellow solid, which was dissolved in EtOAc (20 ml) and residue was passed through a plug of silica to remove the palladium catalyst. The organic layer was washed with distilled water (2 x 20 ml) and the yellow organics were dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow oil (0.665 g). The crude oil was purified by flash chromatography ($SiO_2$, EtOAc : P.E. 40-60; 2 : 8) to afford the desired furan **124** as a yellow oil (0.272 g, 0.76 mmol, 76 %); $\nu_{max}$ (thin film)/$cm^{-1}$ 3458w, 2994m (C-H), 1738s (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 1.19-1.25 (6H, m, 2 x $CH_2C\underline{H}_3$), 2.65-2.72 (2H, m, 4-C($\underline{H}$)$\underline{H}$), 3.69 (6H, s, $OC\underline{H}_3$), 4.12-4.23 (4H, m, 2 x $C\underline{H}_2CH_3$), 4.87 (1H, m, 5-C$\underline{H}$), 5.14 (1H, d, *J* 10.5 Hz, $C\underline{H}_2$=CH), 5.27 (1H, d, *J* 14.5 Hz, $C\underline{H}_2$=CH), 5.82 (1H, m, $CH_2$=C$\underline{H}$); $\delta_C$ (100 MHz; $CDCl_3$) 14.15, 14.26 (2 x $CH_2\underline{C}H_3$), 41.92 (4-$\underline{C}H_2$), 53.37, 53.59 (2 x $O\underline{C}H_3$), 62.57, 62.80 (2 x $\underline{C}H_2CH_3$), 67.40 (3-$\underline{C}$), 82.37 (5-$\underline{C}$H), 90.32 (2-$\underline{C}$), 118.60 ($\underline{C}H_2$=CH), 136.91 ($CH_2$=$\underline{C}$H), 167.66, 168.07, 168.88, 169.86 (4 x $\underline{C}$=O); *m/z* (FAB) 359 ($MH^+$, 72 %), 299, 285, 197, 183, 153, 121, (Found $MH^+$ 359.1348, $C_{16}H_{22}O_9$ requires 359.1342).

**Trifluoromethyl-5-vinyldihydrofuran-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (126)** (7 : 1; *trans* : *cis*)



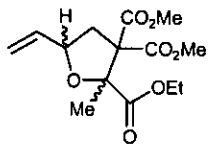

To a stirred solution of 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** (0.184 g, 1.00 mmol) in anhydrous THF (5 ml) was added ethyltrifluoropyruvate **125** (0.133 g, 1.00 mmol) and zinc bromide (0.450 g, 2.00 mmol) at room temperature. This mixture was left to stir for 20 minutes under nitrogen before a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.115 g, 0.10 mmol) was added. The resulting mixture was allowed to stir at room temperature for 18 hours. The solvent was then removed *in vacuo* and the residue dissolved in EtOAc (20 ml). The residue was passed through a plug of silica to remove the palladium catalyst. The organic layer was washed with distilled water (2 x 20 ml). The organics were dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow oil (0.316 g). This crude material was purified by column chromatography ($SiO_2$, $Et_2O$ : P.E. 40-60; 4 : 6) to afford the desired furan **126** as a yellow oil. Early fractions contained the *cis* diastereoisomer (0.028 g, 0.08 mmol, 8 %) and later fractions contained the *trans* diastereoisomer as the major (0.213 g, 0.60 mmol, 60 %).

*Cis* isomer:- $\nu_{max}$ (thin film)/$cm^{-1}$ 2985 (C-H w), 1744 (C=O s), 1685 (C=C w); $\delta_H$ (400 MHz; $CDCl_3$) 1.25-1.28 (3H, t, *J* 8.0 Hz, C'$H_2$C'$H_3$), 2.60 (1H, dd, *J* 8.0 and 12.0 Hz, 4-C'(H)H), 3.05 (1H, dd, *J* 8.0 and 12.0 Hz, 4-C'(H)H), 3.66 (3H, s, OC'$H_3$), 3.74 (3H, s, OC'$H_3$), 4.24 (2H, q, *J* 8.0 Hz, C'$H_2$C'$H_3$), 4.98 (1H, m, 5-C'H), 5.13 (1H, m, C'H=C'(H)H), 5.31 (1H, m, C'H=C'(H)H), 5.79 (1H, m, C'H=C'$H_2$); $\delta_C$ (100 MHz; $CDCl_3$) 12.73 (C'$H_2$C'$H_3$), 39.53 (4-C'$H_2$), 52.27, 52.71 (2 x OC'$H_3$), 61.58 (C'$H_2$C'$H_3$), 64.79 (3-C'), 81.74 (5-C'H), 87.06 (2-C'), 117.00 (C'$H_2$=C'H), 123.09 (C'$F_3$, $J_{C\text{-}F}$ 242 Hz), 135.45 (C'$H_2$=C'H), 164.79, 165.84, 166.98 (3 x C'=O);

*m/z* (FAB) 355 ($MH^+$, 80 %), 295, 281, 221, 201, 191, 165, 154, (Found $MH^+$ 355.1008, $C_{14}H_{17}O_7F_3$ requires 355.1005).

*Trans* isomer:- $\nu_{max}$ (thin film)/$cm^{-1}$ 2984 (C-H w), 1742 (C=O s), 1647 (C=C); $\delta_H$ (400 MHz; $CDCl_3$), 1.28 (3H, t, *J* 8.0 Hz, $CH_2CH_3$), 2.60 (1H, m, 4-C(H)H), 2.88 (1H, m, 4-C(H)H), 3.72 (3H, s, $OCH_3$), 3.77 (3H, s, $OCH_3$), 4.24-4.30 (2H, m, $CH_2CH_3$), 4.63 (1H, m, 5-CH), 5.19 (1H, d, *J* 10.0 Hz, CH=C(H)H), 5.29 (1H, d, *J* 16.0 Hz, CH=C(H)H), 5.84 (1H, m, $CH=CH_2$); $\delta_C$ (100 MHz; $CDCl_3$) 14.15 ($CH_2CH_3$), 41.32 (4-$CH_2$), 53.88, 53.95 (2 x $OCH_3$), 63.04 ($CH_2CH_3$), 66.05 (3-C), 81.40 (5-CH), 87.82 (2-C), 119.42 ($CH_2$=CH), 124.29 ($CF_3$, $J_{C-F}$ 287 Hz), 135.58 ($CH_2$=CH), 165.49, 165.67, 166.30 (3 x C=O); *m/z* (FAB) 355 ($MH^+$, 88 %), 295, 281, 221, 201, 191, 185, 147, 121, (Found $MH^+$ 355.0999, $C_{14}H_{17}O_7F_3$ requires 355.1005).

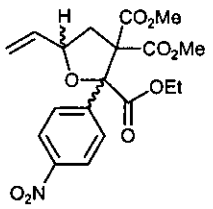
**2-Methyl-5-vinyldihydrofuran-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (129)** (1 : 1.5; *trans* : *cis*)




To a stirred solution of 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** (0.184 g, 1.00 mmol) in anhydrous THF (5 ml) was added ethylpyruvate **128** (0.116 g, 1.00 mmol) and zinc bromide (0.450 g, 2.00 mmol) at room temperature. This mixture was left to stir for 20 minutes under nitrogen before a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.115 g, 0.10 mmol) was added. The resulting mixture was allowed to stir at room temperature for 18 hours. The solvent was then removed *in vacuo* and the residue dissolved in EtOAC (20 ml). The residue was passed through a plug of silica to remove the palladium catalyst. The organic layer was washed with distilled water (2 x 20 ml). The organics were dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow oil (0.313 g). The crude material was

purified by column chromatography ($SiO_2$, EtOAc : P.E. 40-60; 3 : 7) to afford the desired furan **129** as a yellow oil (0.126 g, 0.42 mmol, 42 %); $\nu_{max}$ (thin film)/$cm^{-1}$ 2955w (C-H), 1738s (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 1.19-1.24 (6H, m, C'$H_2$C'$H_3$ and $CH_2CH_3$), 1.49 (6H, s, 2-$CH_3$ and 2-C'$H_3$), 2.42 (1H, dd, *J* 6.0 and 13.0 Hz, 4-C(H)H), 2.61-2.74 (2H, m, 4-C'(H)H and 4-C'(H)H), 2.90 (1H, m, 4-C(H)H), 3.65 (3H, s, OC'$H_3$), 3.67 (3H, s, $CH_3$), 3.71 (3H, s, $OCH_3$), 3.72 (3H, s, OC'$H_3$), 4.06-4.15 (4H, m, $CH_2CH_3$ and C'$H_2$C'$H_3$), 4.58 (1H, m, 5-CH), 4.86 (1H, m, 5-C'H), 5.03-5.12 (2H, m, C'H=C'$H_2$), 5.15-5.21 (2H, m, CH=C$H_2$), 5.80 (1H, m, C'H=C'$H_2$), 5.98 (1H, m, CH=$CH_2$); $\delta_C$ (100 MHz; $CDCl_3$) 14.27 (C'$H_2$C'$H_3$), 14.34 ($CH_2CH_3$), 20.62 (2-C'$H_3$), 20.88 (2-$CH_3$), 40.42 (4-$CH_2$), 40.55 (4-C'$H_2$), 52.98, 53.03 (2 x OC'$H_3$), 53.21, 53.25 (2 x $OCH_3$), 61.88 (C'$H_2$C'$H_3$), 61.90 ($CH_2CH_3$), 66.85 (3-C), 67.53 (3-C'), 80.37 (5-CH), 81.96 (5-C'H), 86.83 (2-C'), 87.51 (2-C), 117.27 (C'$H_2$=C'H), 117.71 ($CH_2$=CH), 138.20 ($CH_2$=CH), 138.53 (C'$H_2$=C'H), 169.56, 170.09, 170.20, 170.53, 170.79, 171.66 (3 x C=O and 3 x C'=O); *m/z* (FAB) 301 ($MH^+$, 22 %), 289, 241, 227, 213, 195, 183, 167, 153, (Found $MH^+$ 301.1290, $C_{14}H_{20}O_7$ requires 301.1287).

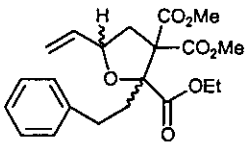
**2-(4-Nitro-phenyl)-5-vinyldihydrofuran-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (134)** (4 : 1; *trans* : *cis*)




To a stirred solution of 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** (0.184 g, 1.00 mmol) in anhydrous THF (5 ml) was added ethyl 4-nitrophenylglyoxylate **133** (0.223 g, 1.00 mmol) and zinc bromide (0.450 g, 2.00 mmol) at room temperature. This mixture was left to stir for 20 minutes under nitrogen before a catalytic amount of tetrakis(triphenylphosphine) palladium(0)

(0.115 g, 0.10 mmol) was added. The resulting mixture was allowed to stir at room temperature for 17 hours. The solvent was then removed *in vacuo* and the residue dissolved in EtOAc (20 ml). The residue was passed through a plug of silica to remove the palladium catalyst. The organic layer was washed with distilled water (2 x 20 ml). The organics were dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow oil (0.587 g). This crude material was purified by column chromatography twice ($SiO_2$, $Et_2O$ : P.E. 40-60; 4 : 6) followed by ($SiO_2$, DCM) to afford the desired furan **134** as a yellow oil (0.297 g, 0.73 mmol, 73 %); $\nu_{max}$ (thin film)/$cm^{-1}$ 2955m (C-H), 1736s (C=O), 1646w (C=C), 1523s ($NO_2$); $\delta_H$ (400 MHz; $CDCl_3$), 1.14-1.18 (6H, m, C'$H_2$C'$H_3$ and $CH_2CH_3$), 2.56 (1H, dd, *J* 5.5 and 13.0, 4-C(H)H), 2.67 (1H, dd, *J* 5.6 and 13.0, 4-C'(H)H), 2.92 (1H, m, 4-C'(H)H), 3.09-3.14 (7H, m, 4-C(H)H and $OCH_3$ and OC'$H_3$), 3.74 (6H, s, $OCH_3$ and OC'$H_3$), 4.08-4.21 (4H, m, $CH_2CH_3$ and C'$H_2$C'$H_3$), 4.82 (1H, m, 5-CH), 5.20-5.23 (2H, m, 5-C'H and CH=C(H)H), 5.29-5.33 (3H, m, CH=C(H)H and C'H=C'(H)H), 5.92 (1H, m, C'$H_2$=C'H), 6.17 (1H, m, $CH_2$=CH), 7.88-7.93 (4H, m, Ph-H and Ph-H'), 8.07-8.10 (4H, m, Ph-H and Ph-H'); $\delta_C$ (100 MHz; $CDCl_3$) 14.20 (C'$H_2$C'$H_3$), 14.26 ($CH_2CH_3$), 40.88 (4-$CH_2$), 41.75 (4-C'$H_2$), 53.03 ($OCH_3$), 53.07 (OC'$H_3$), 53.47 ($OCH_3$), 53.50 (OC'$H_3$), 62.73 (C'$H_2$C'$H_3$), 62.77 ($CH_2CH_3$), 69.41 (3-C), 70.45 (3-C'), 81.37 (5-CH), 83.64 (5-C'H), 90.75 (2-C and 2-C'), 118.30 (C'$H_2$=C'H), 118.47 ($CH_2$=CH), 122.52, 122.57 (Ph-CH), 123.84 128.71 (Ph-C), 129.13, 129.36 (Ph-CH), 137.52 ($CH_2$=CH), 137.79 (C'$H_2$=C'H), 143.71 (ipso-C), 144.77 (ipso-C'), 168.93, 169.16, 169.59, 169.66, 170.14, 170.22 (3 x C=O and 3 x C'=O); *m/z* (FAB) 408 ($MH^+$, 15 %), 334, 318, 193, 185, 150, 121, (Found $MH^+$ 408.1300, $C_{19}H_{21}NO_9$ requires 408.1300).

**2-Phenethyl-5-vinyl-dihydro-furan-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (138)** (1 : 1; *trans*: *cis*)



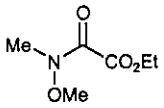

To a stirred solution of 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** (0.184 g, 1.00 mmol) in anhydrous THF (5 ml) was added ethyl 2-oxo-4-phenylbutyrate **137** (0.206 g, 1.00 mmol) and zinc bromide (0.450 g, 2.00 mmol) at room temperature. This mixture was left to stir for 10 minutes under nitrogen before a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.115 g, 0.10 mmol) was added. The resulting mixture was allowed to stir at room temperature for 18 hours. The solvent was then removed *in vacuo* and the residue dissolved in EtOAc (20 ml). The residue was passed through a plug of silica to remove the palladium catalyst. The organic layer was washed with distilled water (2 x 20 ml). The organics were dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow oil (0.52 g). This crude material was purified by column chromatography ($SiO_2$, $Et_2O$ : P.E. 40-60; 4 : 6) to afford the desired furan **138** as a yellow oil (0.242 g, 0.62 mmol, 62 %). Early fractions contained the *cis* diastereoisomer (0.121 g) and later fractions contained the *trans* diastereoisomer (0.121 g).

*Cis* isomer:- $\nu_{max}$ (thin film)/$cm^{-1}$ 2987w (C-H str), 1731s (C=O str); $\delta_H$ (400 MHz; $CDCl_3$) 1.33 (3H, t, *J* 8.0 Hz, C'$H_2$C'$\underline{H}_3$), 2.14-2.29 (2H, m, 4-C'($\underline{H}$)$\underline{H}$), 2.59-2.67 (2H, m, C'$\underline{H}_2$C'$H_2$Ph), 2.78-2.89 (2H, m, C'$H_2$C'$\underline{H}_2$Ph), 3.73 (3H, s, OC'$\underline{H}_3$), 3.76 (3H, s, OC'$\underline{H}_3$), 4.19-4.32 (2H, m, C'$\underline{H}_2$C'$H_3$), 4.77 (1H, m, 5-C'$\underline{H}$), 5.18 (1H, d, *J* 8.0 Hz, C'H=C'($\underline{H}$)H), 5.32 (1H, d, *J* 16.0 Hz, C'H=C'(H)$\underline{H}$), 5.97 (1H, m, C'$\underline{H}$=C'$H_2$), 7.18-7.29 (5H, m, Ph'-$\underline{H}$); $\delta_C$ (100 MHz; $CDCl_3$) 14.13 (C'$H_2\underline{C}$'$H_3$), 30.48 (C'$H_2\underline{C}$'$H_2$Ph), 36.17 ($\underline{C}$'$H_2$C'$H_2$Ph), 40.29 (4-$\underline{C}$'$H_2$), 52.84, 53.07 (2 x O$\underline{C}$'$H_3$), 61.61 ($\underline{C}$'$H_2$C'$H_3$), 66.74 (3-$\underline{C}$'), 79.52 (5-$\underline{C}$'H), 88.85 (2-$\underline{C}$'), 117.34 ($\underline{C}$'$H_2$=C'H), 125.89, 128.39, 128.42 (Ph-$\underline{C}$'H), 137.75 (C'$H_2$=$\underline{C}$'H),

141.89 (*ipso*-C'), 168.95, 169.02, 171.13 (3 x C=O); *m/z* (FAB) 391 ($MH^+$, 32 %), 317, 286, 185, 153, 121, 105, 91, (Found $MH^+$ 391.1761, $C_{21}H_{26}O_7$ requires 391.1757).

*Trans* isomer:- $\nu_{max}$ (thin film)$cm^{-1}$ 2954 (C-H w), 1734 (C=O s); $\delta_H$ (400 MHz; $CDCl_3$) 1.33 (3H, t, *J* 8.0 Hz, $CH_2CH_3$), 2.02 (1H, m, 4-C(H)H), 2.49-2.64 (2H, m, $CH_2CH_2Ph$ and $CH_2CH_2Ph$), 2.72 (1H, m, 4-C(H)H), 2.88 (1H, m, $CH_2CH_2Ph$), 3.76 (3H, s, $OCH_3$), 3.77 (3H, s, $OCH_3$), 4.24-4.29 (2H, m, $CH_2CH_3$), 4.71 (1H, m, 5-CH), 5.21 (1H, d, *J* 12.0 Hz, CH=C(H)H), 5.35 (1H, d, *J* 20 Hz, CH=C(H)H), 5.93 (1H, m, $CH=CH_2$), 7.14-7.28 (5H, m, Ph-H); $\delta_C$ (100 MHz; $CDCl_3$) 14.18 ($CH_2CH_3$), 30.16 ($CH_2CH_2Ph$), 38.48 ($CH_2CH_2Ph$), 40.76 (4-$CH_2$), 53.04, 53.09 (2 x $OCH_3$), 61.50 ($CH_2CH_3$), 66.89 (3-C), 79.00 (5-CH), 88.46 (2-C), 117.43 ($CH_2$=CH), 125.96, 128.38, 128.69 (Ph-CH), 137.44 ($CH_2$=CH), 141.57 (*ipso*-C), 168.58, 169.61, 171.14 (3x C=O); *m/z* (FAB) 391 ($MH^+$, 32 %), 317, 286, 185, 153, 121, 105, 91, (Found $MH^+$ 391.1761, $C_{21}H_{26}O_7$ requires 391.1757).

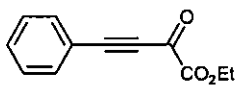
**Monoethyloxalic acid-*N*-methyoxy-*N*-methylamide[68] (141)**




Triethylamine (20 ml, 145 mmol) was added over 10 minutes to a solution of N,O-dimethylhydroxlamine hydrochloride (7.04 g, 79.60 mmol) and ethyl oxalyl chloride (8 ml, 72.20 mmol) in anhydrous DCM (120 ml) at 0°C and the mixture was stirred for 40 minutes. Methanol (20 ml, 0.12 M) was added and the mixture was concentrated *in vacuo*. THF (80 ml) was added and the precipitate was filtered under suction, washing with THF (2 x 40 ml). The filtrate was concentrated *in vacuo* and distilled by short path distillation to afford the desired Weinreb amide **141** as a colourless oil (8.98 g, 55.75 mmol, 78 %), bp 125°C (20 mbar Hg), lit. bp (55-60°C,

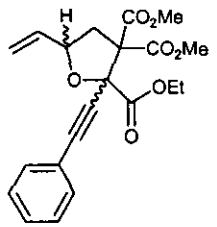
1.0 mm Hg); $\nu_{max}$ (thin film)/cm$^{-1}$ 2984, 2941, 1751 (C=Os), 1689 (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 1.28 (3H, t, *J* 7.0 Hz, $CH_2C\underline{H}_3$), 3.14 (3H, s, $C\underline{H}_3$), 3.67 (3H, s, $OC\underline{H}_3$), 4.26 (2H, q, *J* 7.0, $C\underline{H}_2CH_3$); $\delta_C$ (100 MHz; $CDCl_3$) 14.25 ($CH_2\underline{C}H_3$), 31.61 ($O\underline{C}H_3$), 62.33 ($\underline{C}H_2CH_3$), 62.53 ($\underline{C}H_3$), 162.30 ($\underline{C}$=O), 162.75 ($\underline{C}$=O); *m/z* (EI) 161 ($M^+$, 30 %), 102, 88, 74, 60, 58, 46, (Found $M^+$ 161.0685, $C_6H_{11}NO_4$ requires 161.0688).

**Ethyl 2-oxo-4-phenylbut-3-ynoate (142)**




A solution of *n*-butyllithium (2.48 ml of a 2.5 M solution in hexanes, 6.20 mmol) was added dropwise over 10 minutes to a stirred solution of phenylacetylene (0.68 ml, 6.20 mmol) in dry THF (15 ml) at –78°C. The solution was stirred for 35 minutes and added dropwise to a solution of monoethyloxalic acid-*N*-methyoxy-*N*-methylamide **141** (1.000 g, 6.21 mmol) in dry THF (30 ml) at –78°C. The mixture was stirred for 20 minutes, poured over ice (10 g), and partitioned between phosphoric acid (20 %, 30 ml) and $Et_2O$ (30 ml). The aqueous layer was further extracted with $Et_2O$ (2 x 25 ml) and the combined organic extracts were washed sequentially with phosphoric acid (10 %, 25 ml) and brine (25 ml), dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow oil (1.32 g). The crude material was purified by flash chromatography ($SiO_2$, EtOAc : P.E. 40-60; 1: 6) to afford the desired α-keto ester **142** as a yellow oil (0.380 g, 1.88 mmol, 30 %); $\nu_{max}$ (thin film)/cm$^{-1}$ 2984, 2201 (alkyne), 1735 (C=O), 1676 (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 1.34 (3H, t, *J* 7.2 Hz, $CH_2C\underline{H}_3$), 4.34 (2H, q, *J* 6.8 Hz, $C\underline{H}_2CH_3$), 7.32-7.36 (2H, m, *m*-Ph-$\underline{H}$), 7.44-7.46 (1H, m, *p*-Ph-$\underline{H}$), 7.58-7.60 (2H, m, *o*-Ph-$\underline{H}$); $\delta_C$ (100 MHz; $CDCl_3$) 14.37 ($CH_2\underline{C}H_3$), 63.72 ($\underline{C}H_2$-$CH_3$), 87.55 ($\underline{C}$), 98.44 ($\underline{C}$), 119.44 (Ph-$\underline{C}$), 129.19 (Ph-$\underline{C}$H), 132.26 (Ph-$\underline{C}$H), 134.20 (Ph-$\underline{C}$H), 159.60 ($\underline{C}$=O), 169.99 ($\underline{C}$=O); *m/z* (EI) 202 ($M^+$, 4 %), 129, 105, 77, 51, (Found $M^+$ 202.0632, $C_{12}H_{10}O_3$ requires 202.0630).

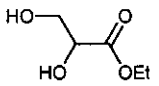
**2-Phenylethynyl-5-vinyldihydrofuran-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (143)** (1 : 3.3; *trans*: *cis*)




To a stirred solution of 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** (0.184 g, 1.00 mmol) in anhydrous THF (5 ml) was added ethyl 2-oxo-4-phenylbut-3-ynoate **142** (0.202 g, 1.00 mmol) and zinc bromide (0.450 g, 2.00 mmol) at room temperature. This mixture was left to stir for 10 minutes under nitrogen before a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.115 g, 0.10 mmol) was added. The resulting mixture was allowed to stir at room temperature for 18 hours. The solvent was then removed *in vacuo* and the residue dissolved in EtOAc (20 ml). The residue was passed through a plug of silica to remove the palladium catalyst. The organic layer was washed with distilled water (2 x 20 ml). The organics were dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow oil (0.505 g). The crude material was purified by column chromatography ($SiO_2$, EtOAc : P.E. 40-60; 4 : 6) to afford the desired furan **143** as a yellow oil (0.255 g, 0.66 mmol, 66 %); $\nu_{max}$ (thin film)/$cm^{-1}$ 2953w (C-H), 2238w (alkyne), 1737s (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 1.19-1.29 (6H, m, C'$H_2$C'$\underline{H}_3$ and $CH_2C\underline{H}_3$), 2.58 (1H, m, 4-C($\underline{H}$)H), 2.68 (1H, m, 4-C'($\underline{H}$)H), 2.83-2.89 (2H, m, 4-C'(H)$\underline{H}$ and 4-C(H)$\underline{H}$), 3.67 (3H, s, $OC\underline{H}_3$), 3.69 (3H, s, OC'$\underline{H}_3$), 3.71 (3H, s, OC'$\underline{H}_3$), 3.74 (3H, s, $OC\underline{H}_3$), 4.21-4.26 (4H, m, C'$H_3$C'$\underline{H}_2$ and $CH_3C\underline{H}_2$), 4.73 (1H, m, 5-C'$\underline{H}$), 5.05 (1H, m, 5-C$\underline{H}$), 5.16-5.18 (3H, m, C'H=C'($\underline{H}$)H and CH=C($\underline{H}$)$\underline{H}$), 5.25 (1H, m, C'H=C'(H)$\underline{H}$), 5.78 (1H, m, $CH_2$=C$\underline{H}$), 6.08 (1H, m, C'$H_2$=C'$\underline{H}$), 7.20-7.27 (6H, m, Ph-$\underline{H}$ and Ph-$\underline{H}$'), 7.36-7.38 (4H, m, Ph-$\underline{H}$ and Ph-$\underline{H}$'); $\delta_C$ (100 MHz; $CDCl_3$) 14.28 (C'$H_2\underline{C}$'$H_3$), 14.33 ($CH_2\underline{C}H_3$), 40.14 (4-$\underline{C}$'$H_2$), 41.22 (4-

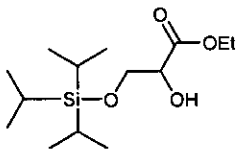
$\underline{C}H_2$), 53.32, 53.45, 53.61 (4 x O$\underline{C}H_3$), 60.79 ($\underline{C}H_2CH_3$), 62.96 ($\underline{C}'H_2C'H_3$), 69.07 (3-$\underline{C}$'), 69.70 (3-$\underline{C}$), 81.52 (5-$\underline{C}$'H), 82.28 (5-$\underline{C}$H), 83.88 ($\underline{C}$), 84.32 ($\underline{C}$'), 88.55 ($\underline{C}$), 88.64 ($\underline{C}$'), 118.38 ($\underline{C}'H_2$=C'H and $\underline{C}H_2$=CH), 122.17 (Ph-$\underline{C}$), 128.63, 128.65, 129.36, 129.28, 132.34 (Ph-$\underline{C}$H), 137.39 ($CH_2$=$\underline{C}$H), 137.82 (C'$H_2$=$\underline{C}$'H), 167.21, 168.09, 168.99, 169.16, 169.21, 169.27 (6 x $\underline{C}$=O); *m/z* (EI) 386 ($M^+$, 3 %), 313 (50 %), 249 (10 %), 129 (100 %), 84 (46 %), (Found $M^+$ 386.1373, $C_{21}H_{22}O_7$ requires 386.1366).

**2,3-Dihydroxy-propionic acid ethyl ester[69] (145)**



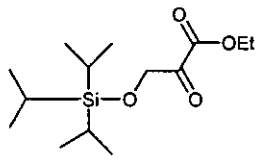

Potassium permanganate (5.217 g, 33.00 mmol) was dissolved in water (50 ml) and acetone (100 ml) and the resulting purple mixture was cooled to –78°C. Ethyl acrylate **144** (3.003 g, 30.00 mmol) was added slowly with stirring. The reaction mixture was allowed to warm to 0 °C. The brown inorganic salts were removed by filtration and washed with acetone (3 x 50 ml). The combined filtrates were concentrated *in vacuo* at a temperature below 40°C. The resulting brown solution was extracted with EtOAc (3 x 50 ml), dried ($Na_2SO_4$) and the solvent was removed *in vacuo* to afford the desired diol **145** as a colourless oil (2.052 g, 15.31 mmol, 51 %); $\nu_{max}$ (thin film)/$cm^{-1}$ 3385 (O-H b), 2982 (C-H s), 1737 (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 1.30 (3H, t, *J* 7.0 Hz, $CH_2C\underline{H}_3$), 3.30 (1H, br s, O$\underline{H}$), 3.83 (1H, dd, *J* 4.0 and 11.5 Hz, C($\underline{H}$)HOH), 3.90 (1H, dd, *J* 4.0 and 11.5 Hz, C(H)$\underline{H}$OH), 4.00 (1H, br s, O$\underline{H}$), 4.23-4.29 (3H, m, C$\underline{H}$OH and $C\underline{H}_2CH_3$); $\delta_C$ (100 MHz; $CDCl_3$) 14.07 ($CH_2\underline{C}H_3$), 61.88 ($\underline{C}H_2CH_3$), 64.11 ($\underline{C}H_2$OH), 71.86 ($\underline{C}$HOH), 172.99 ($\underline{C}$=O); *m/z* (EI) 135 ($MH^+$, 10 %), 104, 76, 61, (Found $MH^+$ 135.0655, $C_5H_{10}O_4$ requires 135.0657).

**2-Hydroxy-3-triisopropylsilanyloxy-propionic acid ethyl ester[70] (146)**



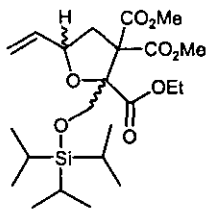

To diol **145** (0.590 g, 4.40 mmol), in dry DMF (15 ml) was added imidazole (0.300 g, 4.40 mmol) and triiospropylsilyl chloride (0.850 g, 4.40 mmol). The resulting reaction mixture was stirred at room temperature for 17 hours. Saturated aqueous $NH_4Cl$ (30 ml) was added and the solution was extracted with $Et_2O$ (3 x 50 ml). The combined organic layers were washed with brine (20 ml), dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the crude mixture ($SiO_2$, EtOAc : hexane; 4 : 96) afforded the desired protected diol **146** as a colourless oil (0.870 g, 3.00 mmol, 68 %); $\nu_{max}$ (thin film)/$cm^{-1}$ 3463 (O-H br), 2982 (C-H s) 1739 (C=O), 1384w; $\delta_H$ (400 MHz; $CDCl_3$) 1.02-1.10 (21H, m, Si(CH-($C\underline{H}_3)_2)_3$ and $CH_2C\underline{H}_3$), 1.24-1.34 (3H, m, Si($C\underline{H}$-$(CH_3)_2)_3$), 3.08 (1H, d, *J* 8.5 Hz, O$\underline{H}$), 3.96 (1H, dd, *J* 4.0 and 8.0 Hz, C($\underline{H}$)HOH), 4.05 (1H, dd, *J* 4.0 and 8.0 Hz, C(H)$\underline{H}$OH), 4.19-4.27 (3H, m, $C\underline{H}$OH and $C\underline{H}_2CH_3$); $\delta_C$ (100 MHz; $CDCl_3$) 11.85 (Si-$\underline{C}$H), 14.13 ($CH_2\underline{C}H_3$), 17.69 (CH-($\underline{C}H_3)_2$), 61.50 ($\underline{C}H_2CH_3$), 65.58 ($\underline{C}H_2OH$), 72.08 ($\underline{C}$HOH), 172.99 ($\underline{C}$=O); *m/z* (FAB) 291 ($MH^+$, 36 %), 247, 173, 157, 131, 103, 75, 59, (Found $MH^+$ 291.1988, $C_{14}H_{30}O_4Si$ requires 291.1992).

**2-Oxo-3-triisopropylsilanyloxy-propionic acid ethyl ester (147)**



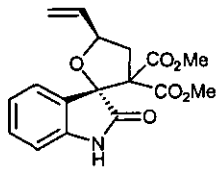

To a solution of 2-hydroxy-3-triisopropylsilanyloxy-propionic acid ethyl ester **146** (0.810 g, 2.80 mmol) in dry DCM (20 ml), was added Dess-Martin periodinane (2.370 g, 5.58 mmol). After stirring for 17 hours at room temperature, $Na_2S_2O_3$ (2.300 g) and saturated $NaHCO_3$ (50 ml) were added and the mixture was left top stir for 0.5 h. The mixture was extracted with DCM (3 x 20 ml). The combined organic layers were washed with brine (20 ml), dried ($MgSO_4$) and concentrated *in vacuo* to afford the desired keto ester **147** as a colourless oil which was unstable on standing. The oil was carried onto the next reaction without further purification; $\nu_{max}$ (thin film)/$cm^{-1}$ 2943s (C-H), 1757s (C=O), 1725 (C=O), 1464s, 1369s, 1260s; $\delta_H$ (400 MHz; $CDCl_3$) 1.05-1.17 (18H, m, Si-(CH-($C\underline{H}_3$)$_2$)$_3$), 1.26-1.31 (3H, m, Si-($C\underline{H}$-($CH_3$)$_2$)$_3$), 1.37 (3H, t, *J* 7.0 Hz, $CH_2C\underline{H}_3$), 4.32 (2H, q, *J* 7.2 Hz, $C\underline{H}_2CH_3$), 4.80 (2H, s, $C\underline{H}_2CO$); $\delta_C$ (100 MHz; $CDCl_3$) 11.94 (Si-$\underline{C}$H), 13.99 ($CH_2\underline{C}H_3$), 17.72 (CH-($\underline{C}H_3$)$_2$), 62.34 ($\underline{C}H_2CH_3$), 67.79 ($O\underline{C}H_2$), 162.65 ($\underline{C}$=O), 171.43 ($\underline{C}$=O); *m/z* (EI) 289 ($MH^+$, 7 %), 261, 245, 217, 199, 173, 131, 103, 75, (Found $MH^+$ 289.1829, $C_{14}H_{28}O_4Si$ requires 289.1835).

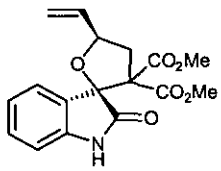
**2-Triisopropylsilanyloxymethyl-5-vinyl-dihydro-furan-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (148)** (*cis* isomer exclusively)




To a stirred solution of 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** (0.100 g, 0.54 mmol) in anhydrous THF (5 ml) was added 2-oxo-3-triisopropylsilanyloxy-propionic acid ethyl ester **147** (0.157 g, 0.54 mmol) and zinc bromide (0.240 g, 1.09 mmol) at room temperature. This mixture was left to stir for 20 minutes under argon before a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.060 g, 0.05 mmol) was added. The resulting mixture was allowed to stir at room temperature for 18 hours. The solvent was removed *in vacuo* and the residue dissolved in EtOAc (20 ml). The residue was passed through a plug of silica to remove the palladium catalyst. The organic layer was washed with distilled water (2 x 20 ml). The organics were dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow oil (0.316g). This crude material was purified by column chromatography ($SiO_2$, $Et_2O$ : hexanes; 1 : 1) to afford the desired furan **148** as the cis diastereoisomer selectively as a yellow oil (0.144 g, 0.30 mmol, 56 %); $\nu_{max}$ (thin film)/$cm^{-1}$ 2945w (C-H), 1747s (C=O), 1707s (C=O), 1462, 1266; $\delta_H$ (400 MHz; $CDCl_3$) 1.02-1.09 (21H, m, Si-(C'H-(C'$H_3$)$_2$), 1.28 (3H, t, *J* 8.0 Hz, C'$H_2$C'$H_3$), 2.48 (1H, m, 4-C'(H)H), 2.62 (1H, m, 4-C'(H)H), 3.73 (3H, s, OC'$H_3$), 3.77 (3H, s, OC'$H_3$), 3.93 (1H, d, *J* 8 Hz, C(H)HOSi), 4.18-4.21 (2H, m, C'$H_2$C'$H_3$), 4.31 (1H, d, *J* 8.0 Hz, C(H)HOSi), 4.77 (1H, m, 5-C'H), 5.17 (1H, d, *J* 12.0 Hz, C'H=C'(H)H), 5.32 (1H, m, C'H=C'(H)H), 5.89 (1H, m, C'H=C'$H_2$); $\delta_C$ (100 MHz; $CDCl_3$) 11.66 (Si-CH-($CH_3$)$_2$), 14.01 (C'$H_2$C'$H_3$), 17.63 (Si-(CH-(C'$H_3$)$_2$), 41.67 (4-C'$H_2$), 52.78, 53.43 (2 x OC'$H_3$), 60.40 (C'$H_2$C'$H_3$), 65.86 (3-C'), 66.69 (C'$H_2$OSi), 79.27 (5-C'H), 90.34 (2-C'), 117.48 (C'$H_2$=C'H), 137.08 (C'$H_2$=C'H), 168.32, 170.36, 170.67 (3 x C=O); *m/z* (FAB) 473 ($MH^+$, 13 %), 429, 399, 299, 217, 173, 157, 131, 103, 115, 75, 59, (Found $MH^+$ 473.2565, $C_{23}H_{40}O_8Si$ requires 473.2571).

**Dimethyl-2'-oxo-5-vinyl-1',2',4,5-tetrahydro-3*H*-spiro[furan-2,3'-indole]-3,3-dicarboxylate** (1.5 : 1; *trans* **(163a)** : *cis* **(163b)**)

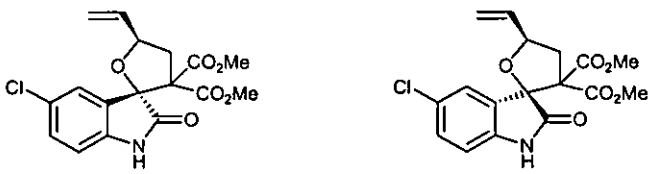



To a stirred solution of 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** (0.184 g, 1.00 mmol) in anhydrous THF (5 ml) was added isatin **157a** (0.147 g, 1.00 mmol) and zinc bromide (0.450 g, 2.00 mmol) at room temperature. This mixture was left to stir for 10 minutes under nitrogen before a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.115 g, 0.10 mmol) was added. The resulting mixture was allowed to stir at 37°C for 48 hours. The solvent was removed *in vacuo* and the residue dissolved in EtOAc (20 ml). The palladium catalyst was filtered through a plug of silica, and the organic layer was washed with distilled water (2 x 20 ml). The organics were dried ($MgSO_4$) and concentrated *in vacuo* to afford an orange oil (0.505 g). This crude material was purified by column chromatography twice ($SiO_2$, EtOAc : P.E. 40-60; 1 : 1) followed by $Et_2O$ to afford the desired furan **163a** and **164a** as an orange solid (0.098 g, 0.30 mmol, 30 %), m.p. 70-74°C; $\nu_{max}$ (thin film)/$cm^{-1}$ 3319w (N-H broad), 2954 (C-H w), 1735 (C=O s); $\delta_H$ (400 MHz, $CDCl_3$) 2.59 (1H, dd, *J* 5.0 and 13.0 Hz, 4-C(H)H), 2.79 (1H, q, *J* 6.5 Hz, 4-C'(H)H), 3.01 (1H, m, 4-C'(H)H), 3.20 (1H, m, 4-C(H)H), 3.60 (3H, s, $OCH_3$), 3.60 (3H, s, $OCH_3$), 3.61 (3H, s, $OC'H_3$), 3.68 (3H, s, $OC'H_3$), 5.12-5.28 (6H, m, 5-CH and 5-C'H and C'H=C'(H)H and CH=C(H)H), 6.05 (1H, m, $C'H_2$=C'H), 6.18 (1H, m, $CH_2$=CH), 6.76-6.78 (2H, m, Ph-H), 6.91-6.92 (2H, m, Ph-H), 6.99-7.01 (2H, m, Ph-H), 7.19-7.20 (2H, m, Ph-H), 8.53 (1H, s, NH), 8.58 (1H, s, NH); $\delta_C$ (100 MHz, $CDCl_3$) 39.13 (4-$CH_2$), 39.36 (4-C'$H_2$), 53.26, 53.23, 53.84 (2 x $OCH_3$ and 2 x OC'$H_3$), 66.65 (3-C), 67.91 (3-C'), 79.83 (5-CH), 83.32 (5-C'H), 85.82 (2-C') 86.63 (2-C), 110.76 (Ph-C'H and Ph-CH), 118.31 ($CH_2$=CH and C'$H_2$=C'H), 123.02 (Ph-CH), 125.09 (Ph-C), 125.34, 125.38 (Ph-CH), 125.70 (Ph-C), 131.15, 131.21 (Ph-

CH), 138.01 ($CH_2$=CH), 138.96 (C'$H_2$=C'H), 142.54 (ipso-C' and ipso-C), 168.98, 169.53, 169.59 (3 x C'=O) 177.15 (C=O), 178.18 (C=O); *m/z* (EI) 331 ($M^+$, 40 %), 240, 212, 184, 146, 120, (Found 331.1061, $C_{17}H_{17}O_6N$ requires 331.1056).

**Dimethyl-5'-chloro-2'-oxo-5-vinyl-1',2',4,5-tetrahydro-3*H*-spiro[furan-2,3'-indole]-3,3-dicarboxylate** (1 : 1; *trans* **(163b)** : *cis* **(164b))**

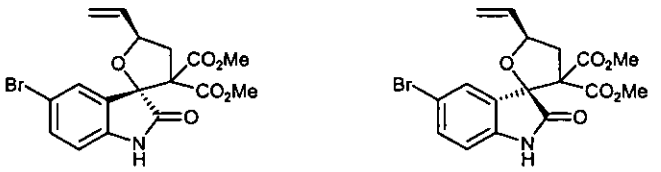



To a stirred solution of 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** (0.184 g, 1.00 mmol) in anhydrous THF (5 ml) was added 5-chloroisatin **157b** (0.182 g, 1.00 mmol) and zinc bromide (0.450 g, 2.00 mmol) at room temperature. This mixture was left to stir for 10 minutes under nitrogen before a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.115 g, 0.10 mmol) was added. The resulting mixture was allowed to stir at 37°C for 17 hours. The solvent was removed *in vacuo* and the residue dissolved in EtOAc (20 ml). The palladium catalyst was filtered through a plug of silica, and the organic layer was washed with distilled water (2 x 20 ml). The organics were dried ($MgSO_4$) and concentrated *in vacuo* to afford an orange solid (0.42 g). This crude material was purified by column chromatography ($Al_2O_3$, EtOAc : P.E. 40-60; 6 : 4) and then ($Al_2O_3$, $Et_2O$ : P.E. 40-60; 1 : 1) to afford the desired spiro furan **163b** and **164b** as a white solid (0.216 g, 0.59 mmol, 59 %), m.p. 148-152°C; $\nu_{max}$ (thin film)/$cm^{-1}$ 3322w (N-H), 2953w (C-H), 1736s (C=O), 1697s (N-C=O), 731w (C-Cl); $\delta_H$ (400 MHz, $CDCl_3$) 2.59 (1H, dd, *J* 5.0 and 13.5 Hz, 4-C(H)H), 2.78 (1H, q, *J* 6.5 Hz, 4-C'(H)H), 2.98 (1H, m, 4-C'(H)H), 3.17 (1H, m, 4-C(H)H), 3.60 (6H, s, $OCH_3$ and $OCH_3$), 3.61 (3H, s, OC'$H_3$), 3.72 (3H, s, OC'$H_3$), 5.11-5.28 (6H, m, C'H=C'(H)H and CH=C(H)H and 5-CH and 5-C'H), 6.03 (1H, m, C'$H_2$=C'H), 6.20 (1H, m, $CH_2$=CH), 6.71 (2H, q, *J* 4.4 Hz, Ph-H), 6.99 (2H, s, Ph-H),

7.15-7.20 (2H, m, Ph-H), 8.22-8.26 (2H, bs, NH); $\delta_C$ (100 MHz, $CDCl_3$) 38.92 (4-$CH_2$), 39.24 (4-C'$H_2$), 53.40 (2 x O$CH_3$ and 2 x OC'$H_3$), 66.79 (3-C), 68.11 (3-C'), 80.11 (5-CH), 83.62 (5-C'H), 85.68 (2-C'), 86.46 (2-C), 111.77 (Ph-CH), 118.55 (C'$H_2$=C'H), 118.55 ($CH_2$=CH), 126.01, 126.03 (Ph-CH), 126.67, 127.41, 128.37, 128.39 (Ph-CH), 130.98, 131.06 (Ph-CH), 137.74 ($CH_2$=CH), 138.65 (C'$H_2$=C'H), 141.12 (ipso-C'), 141.18 (ipso-C), 168.82, 169.23, 169.44, 169.96 (C'=O), 176.66 (C=O), 177.69 (C=O); *m/z* (EI) 365, 367 ($M^+$, 80 %, 22 %), 306, 274, 246, 180, 164, 153, 124, 93, 77, 71, 59, (Found 365.0663, $C_{17}H_{16}O_6N^{35}Cl$ requires 365.0666).

*Cis* isomer **164b** isolated: $\nu_{max}$ (thin film)/$cm^{-1}$ 3321w (N-H), 2953w (C-H), 1736s (C=O), 1697s (N-C=O), 731w (C-Cl); $\delta_H$ (400 MHz; $CDCl_3$) 2.77 (1H, q, *J* 6.4 Hz, 4-C'(H)H), 2.98 (1H, m, 4-C'(H)H), 3.62 (3H, s, OC'$H_3$), 3.72 (3H, s, OC'$H_3$), 5.11-5.27 (3H, m, C'H=C'(H)H and 5-C'H), 6.03 (1H, m, C'$H_2$=C'H), 6.71 (1H, d, *J* 4 Hz, Ph-H), 6.99 (1H, s, Ph-H), 7.19 (1H, m, Ph-H), 7.78 (1H, s, NH); $\delta_C$ (100 MHz; $CDCl_3$) 39.19 (4-C'$H_2$), 53.39 (2 x OC'$H_3$), 68.14 (3-C'), 83.66 (5-C'H), 85.57 (2-C'), 111.63 (Ph-C'H), 118.56 (C'$H_2$=C'H), 126.08 (Ph-C'H), 127.40 (Ph-C'), 127.40, 128.42 (Ph-C'), 130.99 (Ph-C'H), 138.65 (C'$H_2$=C'H), 140.94 (ipso-C'), 168.78, 169.22 (C'=O), 177.35 (C'=O); *m/z* (EI) 365, 367 ($M^+$, 80 %, 22 %), 306, 274, 246, 180, 164, 153, 124, 93, 77, 71, 59, (Found 365.0663, $C_{17}H_{16}O_6N^{35}Cl$ requires 365.0666).

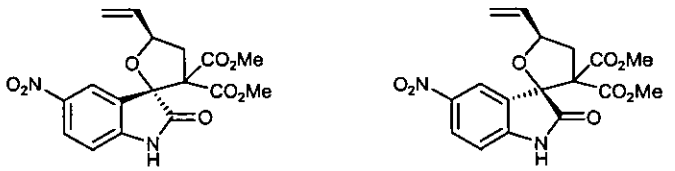
**Dimethyl-5'-bromo-2'-oxo-5-vinyl-1',2',4,5-tetrahydro-3*H*-spiro[furan-2,3'-indole]-3,3-dicarboxylate** (1.2 : 1; *trans* **(163c)** : *cis* **(164c))**



To a stirred solution of 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** (0.184 g, 1.00 mmol) in anhydrous THF (5 ml) was added 5-bromoisatin **157c** (0.226 g, 1.00 mmol) and zinc bromide (0.450 g, 2.00 mmol) at room temperature. This mixture was left to stir for 10 minutes under nitrogen before a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.115 g, 0.10 mmol) was added. The resulting mixture was allowed to stir at 37°C for 17 hours. The solvent was removed *in vacuo* and the residue dissolved in EtOAC (20 ml). The palladium catalyst was filtered through a plug of silica, and the organic layer was washed with distilled water (2 x 20 ml). The organics were dried ($MgSO_4$) and concentrated *in vacuo* to afford an orange solid (0.41 g). This crude material was purified by column chromatography ($Al_2O_3$, EtOAc : P.E. 40-60; 6 : 4) and then ($Al_2O_3$, $Et_2O$ : P.E. 40-60; 1 : 1) to afford the desired spiro furan **163c** and **164c** as a brown solid (0.254 g, 0.62 mmol, 62 %), m.p. 153-157°C; $\nu_{max}$ (thin film)/$cm^{-1}$ 3314w (N-H), 2952w (C-H), 1735s (C=O), 1679 (N-C=O), 1436, 1272, 1212 650w (C-Br); $\delta_H$ (400 MHz; $CDCl_3$) 2.59 (1H, dd, *J* 5.0 and 13.5 Hz, 4-C(H)H), 2.77 (1H, q, *J* 6.5 Hz, 4-C'(H)H), 2.97 (1H, m, 4-C'(H)H), 3.17 (1H, m, 4-C(H)H), 3.61 (6H, s, $OCH_3$ and $OCH_3$), 3.69 (3H, s, $OC'H_3$), 3.72 (3H, s, $OC'H_3$), 5.11-5.27 (6H, m, C'H=C'(H)H and CH=C(H)H and 5-CH and 5-C'H), 6.03 (1H, m, $C'H_2$=C'H), 6.20 (1H, m, $CH_2$=CH), 6.64-6.70 (2H, q, *J* 4.5 Hz, Ph-H), 7.11 (2H, m, Ph-H), 7.30-7.33 (2H, m, Ph-H), 8.24 (1H, s, NH), 8.28 (1H, s, NH); $\delta_C$ (100 MHz; $CDCl_3$) 38.83 (4-$CH_2$), 39.17 (4-C'$H_2$), 53.45 (2 x $OCH_3$ and 2 x $OC'H_3$), 66.76 (3-C), 68.10 (3-C'), 80.13 (5-CH), 83.68 (5-C'H), 85.63 (2-C'), 86.40 (2-C), 112.30, 112.31 (Ph-CH), 115.22, 115.54 (Ph-C), 118.68 (C'$H_2$=C'H), 118.72 ($CH_2$=CH), 126.90, 127.68 (Ph-C), 128.74, 128.76 (Ph-CH), 133.88, 133.97 (Ph-CH),

137.69 ($CH_2$=$\underline{C}$H), 138.62 (C'$H_2$=$\underline{C}$'H), 141.61, 141.69 (Ph-$\underline{C}$), 168.85, 169.24, 169.48, 169.98 ($\underline{C}$'=O), 176.58 ($\underline{C}$=O), 177.61 ($\underline{C}$=O); *m/z* (EI) 409, 411 ($M^+$, 40 %, 40 %), 350, 318, 226, 199, 184, 170, 152, 124, 84, 71, 59, (Observed 409.0154, $C_{17}H_{16}O_6N^{79}Br$ requires 409.0160).

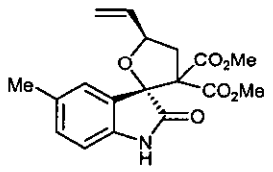
**Dimethyl-5'-nitro-2'-oxo-5-vinyl-1',2',4,5-tetrahydro-3*H*-spiro[furan-2,3'-indole]-3,3-dicarboxylate** (1.5 : 1; *trans* **(163d)** : *cis* **(164d))**

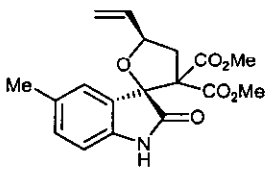


To a stirred solution of 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** (0.184 g, 1.00 mmol) in anhydrous THF (5 ml) was added 5-nitroisatin **157d** (0.192 g, 1.00 mmol) and zinc bromide (0.450 g, 2.00 mmol) at room temperature. This mixture was left to stir for 10 minutes under nitrogen before a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.115 g, 0.10 mmol) was added. The resulting mixture was allowed to stir at 37°C for 17 hours. The solvent was removed *in vacuo* and the residue dissolved in EtOAc (20 ml). The palladium catalyst was filtered through a plug of silica, and the organic layer was washed with distilled water (2 x 20 ml). The organics were dried ($MgSO_4$) and concentrated *in vacuo* to afford an orange solid (0.43 g). This crude material was purified by column chromatography ($Al_2O_3$, EtOAc : P.E. 40-60; 6 : 4) and then ($Al_2O_3$, EtOAc : P.E. 40-60; 7 : 3) to afford the desired spiro furan **163d** and **164d** as a cream solid (0.252 g, 0.67 mmol, 67 %), m.p. 174-176°C; $\nu_{max}$ (thin film)/$cm^{-1}$ 3321w (N-H), 2954w (C-H), 1734s (C=O), 1605m ($NO_2$), 1526, 1340; $\delta_H$ (400 MHz; $CDCl_3$) 2.59 (1H, dd, *J* 5.0 and 13.5 Hz, 4-C($\underline{H}$)H), 2.84 (1H, q, *J* 6.4 Hz, 4-C'($\underline{H}$)H), 2.98 (1H, m, 4-C'(H)$\underline{H}$), 3.29 (1H, m, 4-C(H)$\underline{H}$), 3.63 (6H, s, OC$\underline{H_3}$ and OC$\underline{H_3}$), 3.75 (3H, s, OC'$\underline{H_3}$), 3.80 (3H, s, OC'$\underline{H_3}$), 5.14-5.30 (6H, m, C'H=C'($\underline{H}$)$\underline{H}$ and CH=C($\underline{H}$)$\underline{H}$ and 5-C$\underline{H}$ and 5-C'$\underline{H}$), 6.01

(1H, m, C'$H_2$=C'H), 6.20 (1H, m, $CH_2$=CH), 6.89 (2H, q, *J* 4.4 Hz, Ph-H), 7.90 (2H, s, Ph-H), 8.15-8.20 (2H, m, Ph-H), 8.73 (2H, bs, NH); $\delta_C$ (100 MHz; $CDCl_3$) 37.13 (4-$CH_2$), 37.55 (4-C'$H_2$), 52.23, 52.45 (4 x O$CH_3$), 66.90 (3-C), 66.96 (3-C'), 82.66 (5-CH), 83.59 (5-C'H), 84.32 (2-C'), 86.46 (2-C), 109.32, 109.32 (Ph-C'H), 117.71 (C'$H_2$=C'H and $CH_2$=CH), 120.33 (Ph-CH), 124.39, 125.21 (Ph-CH), 126.60, 126.69 (Ph-CH), 135.94 ($CH_2$=CH), 136.84 (C'$H_2$=C'H), 147.13, 147.22 (Ph-C), 167.45, 167.47, 168.08, 168.21 (C'=O), 175.66 (C=O), 176.80 (C=O); *m/z* (EI) 376 ($M^+$, 8 %), 317, 285, 257, 191, 175, 165, 153, 121, 84, 71, 59, (Observed 376.0899, $C_{17}H_{16}O_8N_2$ requires 376.0907).

**Dimethyl-5'-methyl-2'-oxo-5-vinyl-1',2',4,5-tetrahydro-3*H*-spiro[furan-2,3'-indole]-3,3-dicarboxylate** (1: 1; *trans* **(163e)** : *cis* **(164e))**

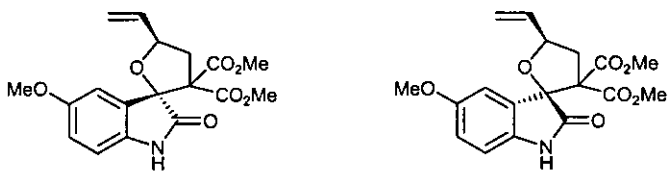



To a stirred solution of 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** (0.184 g, 1.00 mmol) in anhydrous THF (5 ml) was added 5-methylisatin **157e** (0.161 g, 1.00 mmol) and zinc bromide (0.450 g, 2.00 mmol) at room temperature. This mixture was left to stir for 10 minutes under nitrogen before a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.115 g, 0.10 mmol) was added. The resulting mixture was allowed to stir at 37°C for 17 hours. The solvent was removed *in vacuo* and the residue dissolved in EtOAc (20 ml). The palladium catalyst was filtered through a plug of silica, and the organic layer was washed with distilled water (2 x 20 ml). The organics were dried ($MgSO_4$) and concentrated *in vacuo* to afford an orange solid (0.39 g). This crude material was purified by column chromatography ($Al_2O_3$, EtOAc : P.E. 40-60; 6 : 4) and then ($Al_2O_3$, EtOAc : P.E. 40-60; 8 : 2) to afford the desired spiro furan **163e** and **164e** as a white solid (0.183 g, 0.53 mmol,

53 %), m.p. 118-122°C; $\nu_{max}$ (thin film)/cm$^{-1}$ 3325w (N-H), 2953w (C-H), 1733s (C=O), 1684 (N-C=O), 1627, 1496, 1436, 1436; $\delta_H$ (400 MHz, $CDCl_3$) 2.20 (6H, s, C'$\underline{H}_3$ and C$\underline{H}_3$), 2.59 (1H, dd, *J* 5.0 and 13.0 Hz, 4-C($\underline{H}$)H), 2.80 (1H, q, *J* 6.5 Hz, 4-C'($\underline{H}$)H), 3.04 (1H, m, 4-C'(H)$\underline{H}$), 3.22 (1H, m, 4-C(H)$\underline{H}$), 3.60 (6H, s, OC$\underline{H}_3$ and OC$\underline{H}_3$), 3.66 (3H, s, OC'$\underline{H}_3$), 3.68 (3H, s, OC'$\underline{H}_3$), 5.09-5.27 (6H, m, C'H=C'($\underline{H}$)$\underline{H}$ and CH=C($\underline{H}$)$\underline{H}$ and 5-C$\underline{H}$ and 5-C'$\underline{H}$), 6.06 (1H, m, C'$H_2$=C'$\underline{H}$), 6.20 (1H, m, $CH_2$=C$\underline{H}$), 6.65-6.67 (2H, m, Ph-$\underline{H}$), 6.81 (2H, s, Ph-$\underline{H}$), 7.00 (2H, d, *J* 8.0 Hz, Ph-$\underline{H}$), 7.78 (2H, bs, N$\underline{H}$); $\delta_C$ (100 MHz, $CDCl_3$) 21.45 ($\underline{C}H_3$), 21.45 ($\underline{C}'H_3$), 39.12 (4-$\underline{C}H_2$), 39.36 (4-$\underline{C}'H_2$), 53.13, 53.26 (4 x O$\underline{C}H_3$), 66.57 (3-$\underline{C}$), 67.85 (3-$\underline{C}'$), 79.76 (5-$\underline{C}$H), 83.29 (5-$\underline{C}'$H), 85.90 (2-$\underline{C}'$), 86.73 (2-$\underline{C}$), 110.42, 110.45 (Ph-$\underline{C}$H), 118.15 ($\underline{C}H_2$=CH), 118.29 ($\underline{C}'H_2$=C'H), 124.98, 125.66 (Ph-$\underline{C}$), 126.03, 126.09 (Ph-$\underline{C}$H), 131.43, 131.48 (Ph-$\underline{C}$H), 132.46 (Ph-$\underline{C}$), 138.07 ($CH_2$=$\underline{C}$H), 139.03 (C'$H_2$=$\underline{C}'$H), 140.01, 140.06 (ipso-$\underline{C}$), 168.94, 169.55, 169.59, 170.33 ($\underline{C}'$=O), 176.74 ($\underline{C}$=O), 177.74 ($\underline{C}$=O); *m/z* (EI) 345 ($M^+$, 87 %), 254, 184, 160, 152, 133, 124, 104, 77, 71, 59, (Observed 345.1212, $C_{19}H_{19}O_6N$ requires 345.1212).

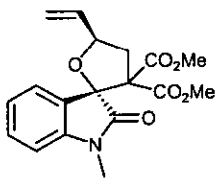
**Dimethyl-5'-methoxy-2'-oxo-5-vinyl-1',2',4,5-tetrahydro-3*H*-spiro[furan-2,3'-indole]-3,3-dicarboxylate** (1: 1; *trans* **(163f)** : *cis* **(164f)**)

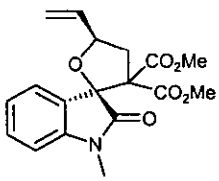



To a stirred solution of 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** (0.184 g, 1.00 mmol) in anhydrous THF (5 ml) was added 5-methoxyisatin **157f** (0.177 g, 1.00 mmol) and zinc bromide (0.450 g, 2.00 mmol) at room temperature. This mixture was left to stir for 10 minutes under nitrogen before a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.115 g, 0.10 mmol) was added. The resulting mixture was allowed to stir at 37°C for 18 hours. The solvent was then

removed *in vacuo* and the residue dissolved in EtOAc (20 ml). The palladium catalyst was filtered through a plug of silica, and the organic layer was washed with distilled water (2 x 20 ml). The organics were dried ($MgSO_4$) and concentrated *in vacuo* to afford an orange solid (0.39 g). This crude material was purified by column chromatography ($Al_2O_3$, EtOAc : P.E. 40-60; 7: 3) and then ($Al_2O_3$, EtOAc) to afford the desired spiro furan as a white solid (0.116 g, 0.32 mmol, 32 %), m.p. 91-94°C; $\nu_{max}$ (thin film)/$cm^{-1}$ 3317w (N-H), 2953w (C-H), 1732s (C=O), 1687 (N-C=O); $\delta_H$ (400 MHz; $CDCl_3$) 2.59 (1H, dd, *J* 5.0 and 13.0 Hz, 4-C(H)H), 2.76 (1H, q, *J* 6.4 Hz, 4-C'(H)H), 3.03 (1H, m, 4-C'(H)H), 3.17 (1H, m, 4-C(H)H), 3.61 (6H, s, $OCH_3$ and $OCH_3$), 3.68 (9H, s, $OCH_3$ and 2 x $OC'H_3$), 3.71 (3H, s, $OC'H_3$), 5.09-5.30 (6H, m, C'H=C'(H)H and CH=C(H)H and 5-CH and 5-C'H), 6.05 (1H, m, $C'H_2$=C'H), 6.20 (1H, m, $CH_2$=CH), 6.63-6.75 (6H, m, Ph-H), 7.71 (2H, bs, NH); $\delta_C$ (100 MHz; $CDCl_3$) 39.21 (4-$CH_2$), 39.41 (4-C'$H_2$), 53.35, 53.38, 56.17 (4 x $OCH_3$), 66.64 (3-C), 67.93 (3-C'), 79.92 (5-CH), 83.40 (5-C'H), 86.04 (2-C'), 86.46 (2-C), 111.13, 111.16 (Ph-CH), 112.30, 112.50 (Ph-CH), 115.97, 116.07 (Ph-CH), 118.35 (C'$H_2$=C'H), 118.40 ($CH_2$=CH), 126.14, 126.77, 135.76, 135.80 (Ph-C), 137.98 ($CH_2$=CH), 138.92 (C'$H_2$=C'H), 156.25, 156.25 (ipso-C), 168.95, 169.54, 170.28 (C'=O), 176.73 (C=O), 177.79 (C=O); *m/z* (EI) 361 ($M^+$, 100 %), 275, 184, 176, 160, 149, 121, 106, 84, 71, 59, (Observed 361.1160, $C_{18}H_{19}O_7N$ requires 361.1162).

**Dimethyl-1'-methyl-2'-oxo-5-vinyl-1',2',4,5-tetrahydro-3*H*-spiro[furan-2,3'-indole]-3,3-dicarboxylate** (1 : 1; *trans* **(163g)** : *cis* **(164g))**

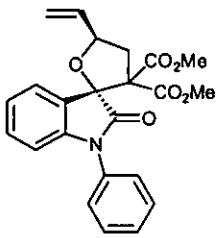


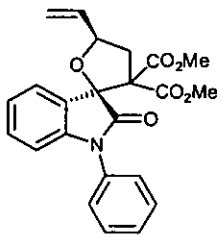




To a stirred solution of 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** (0.184 g, 1.00 mmol) in anhydrous THF (5 ml) was added 1-methylisatin **157g** (0.161

g, 1.00 mmol) and zinc bromide (0.450 g, 2.00 mmol) at room temperature. This mixture was left to stir for 10 minutes under nitrogen before a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.115 g, 0.10 mmol) was added. The resulting mixture was allowed to stir at 37°C for 17 hours. The solvent was then removed *in vacuo* and the residue dissolved in EtOAc (20 ml). The palladium catalyst was filtered through a plug of silica, and the organic layer was washed with distilled water (2 x 20 ml). The organics were dried ($MgSO_4$) and concentrated *in vacuo* to afford an orange solid (0.48 g). This crude material was purified by column chromatography ($Al_2O_3$, EtOAc : P.E. 40-60; 6 : 4) and then ($Al_2O_3$, EtOAc : P.E. 40-60; 8 : 2) to afford the desired spiro furan **163g** and **164g** as a white solid (0.242 g, 0.70 mmol, 70 %), m.p. 85-89°C; $\nu_{max}$ (thin film)/$cm^{-1}$ 2953w (C-H), 1733s (C=O) 1653 (N-C=O), 1472, 1267, 1031; $\delta_H$ (400 MHz, $CDCl_3$) 2.59 (1H, dd, *J* 5.0 and 13.0 Hz, 4-C(H)H), 2.78 (1H, q, *J* 6.5 Hz, 4-C'(H)H), 3.00-3.09 (7H, m, 4-C'(H)H and 2 x NC'$H_3$), 3.20 (1H, m, 4-C(H)H), 3.56 (6H, s, $OCH_3$ and $OCH_3$), 3.62 (3H, s, OC'$H_3$), 3.66 (3H, s, OC'$H_3$), 5.08-5.25 (6H, m, C'H=C'(H)H and CH=C(H)H and 5-CH and 5-C'H), 6.08 (1H, m, $C'H_2$=C'H), 6.21 (1H, m, $CH_2$=CH), 6.65-6.67 (2H, q, *J* 4.0 Hz, Ph-H), 6.92-6.93 (2H, m, Ph-H), 6.99-7.01 (2H, d J 6 Hz, Ph-H), 7.25-7.26 (2H, m, Ph-H); $\delta_C$ (100 MHz, $CDCl_3$) 26.43 ($CH_3$), 26.56 (C'$H_3$), 39.15 (4-$CH_2$), 39.34 (4-C'$H_2$), 53.23, 53.26 (2 x $OCH_3$), 66.65 (3-C), 67.99 (3-C'), 79.80 (5-CH), 83.31 (5-C'H), 85.60 (2-C'), 86.39 (2-C), 109.08, 109.08 (Ph-CH), 118.29 ($CH_2$=CH), 118.32 (C'$H_2$=C'H), 123.00, 123.03 (Ph-CH), 124.45, 125.18 (Ph-C), 124.81, 124.90 (Ph-CH), 131.26, 131.34 (Ph-CH), 138.12 ($CH_2$=CH), 139.12 (C'$H_2$=C'H), 145.42, 145.47 (ipso-C), 168.87, 169.52, 169.59, 170.32 (C'=O), 175.06 (C=O), 176.02 (C=O); *m/z* (EI) 345 ($M^+$, 68 %), 286, 254, 244, 226, 184, 152, 133, 124, 105, 77, 71, 59, (Observed 345.1220, $C_{18}H_{19}O_6N$ requires 345.1212).

**Dimethyl-1'-phenyl-2'-oxo-5-vinyl-1',2',4,5-tetrahydro-3*H*-spiro[furan-2,3'-indole]-3,3-dicarboxylate** (1.5 : 1; *trans* **(163h)** : *cis* **(164h))**




To a stirred solution of 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** (0.184 g, 1.00 mmol) in anhydrous THF (5 ml) was added 1-phenylisatin **157h** (0.223 g, 1.00 mmol) and zinc bromide (0.450 g, 2.00 mmol) at room temperature. This mixture was left to stir for 10 minutes under nitrogen before a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.115 g, 0.10 mmol) was added. The resulting mixture was allowed to stir at 37°C for 17 hours. The solvent was removed *in vacuo* and the residue dissolved in EtOAc (20 ml). The palladium catalyst was filtered through a plug of silica, and the organic layer was washed with distilled water (2 x 20 ml). The organics were dried ($MgSO_4$) and concentrated *in vacuo* to afford an orange solid (0.43 g). This crude material was purified by column chromatography ($Al_2O_3$, EtOAc : P.E. 40-60; 6 : 4) and then ($Al_2O_3$, EtOAc : P.E. 40-60; 8 : 2) to afford the desired furan **163h** and **164h** as a white solid (0.31 g, 0.76 mmol, 76 %), m.p. 132-135°C; $\nu_{max}$ (thin film)/$cm^{-1}$ 2953w (C-H), 1732s (C=O), 1500, 1373, 1271, 1210; $\delta_H$ (400 MHz, $CDCl_3$) 2.63 (1H, dd, *J* 5.0 and 13.0 Hz, 4-C(H)H), 2.80 (1H, q, *J* 6.5 Hz, 4-C'(H)H), 3.04 (1H, m, 4-C'(H)H), 3.23 (1H, m, 4-C(H)H), 3.62 (6H, s, $OCH_3$ and $OCH_3$), 3.67 (3H, s, $OC'H_3$), 3.69 (3H, s, $OC'H_3$), 5.09-5.29 (6H, m, C'H=C'(H)H and CH=C(H)H and 5-CH and 5-C'H), 6.09 (1H, m, $C'H_2$=C'H), 6.24 (1H, m, $CH_2$=CH), 6.70-6.72 (2H, m, Ph-H), 6.96-6.97 (2H, m, Ph-H) 7.07-7.10 (2H, m, Ph-H), 7.18-7.21 (2H, m, Ph-H), 7.36-7.39 (6H, m, Ph-H), 7.42-7.45 (4H, m, Ph-H); $\delta_C$ (100 MHz, $CDCl_3$) 39.06 (4-$CH_2$), 39.29 (4-C'$H_2$), 53.22, 53.35 (4 x $OCH_3$), 67.10 (3-C), 68.54 (3-C'), 79.90 (5-CH), 83.56 (5-C'H), 85.76 (2-C'), 86.51

(2-C), 110.32 (Ph-C'H and Ph-CH), 118.29 ($\underline{C}H_2$=CH), 118.34 ($\underline{C}'H_2$=C'H), 123.33, 123.37 (Ph-CH), 124.19, 124.96 (Ph-C), 125.18, 125.26 (Ph-CH), 126.98, 127.03 (Ph-CH), 128.56, 128.65 (Ph-CH), 129.98, 130.03 (Ph-CH), 131.09, 131.18 (Ph-CH), 134.40, 134.54 (Ph-C), 138.11 ($CH_2$=CH), 139.20 (C'$H_2$=C'H), 145.54, 145.68 (ipso-C), 168.95, 169.57, 169.61, 170.31 (C'=O), 174.52 (C=O), 175.60 (C=O); *m/z* (EI) 407 ($M^+$, 45 %), 316, 306, 288 , 204, 195, 167, 152, 124, 84, 77, 71, 49, (Observed 407.1362, $C_{23}H_{21}O_6N$ requires 407.1369).

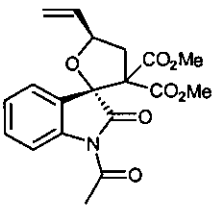
**Dimethyl-1'-phenyl-2'-oxo-5-vinyl-1',2',4,5-tetrahydro-3*H*-spiro[furan-2,3'-indole]-3,3-dicarboxylate** (5.7 : 1; *trans* **(163h)** : *cis* **(164h)** in DCM)

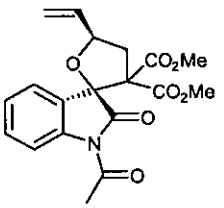
The *trans* diastereoisomer **163h** was isolated exclusively after column chromatography as a white solid (0.21 g, 0.52 mmol, 52 %), m.p. 132-135°C; $\nu_{max}$ (thin film)/$cm^{-1}$ 2953w (C-H), 1732s (C=O), 1644 (N-C=O), 1614, 1500, 1272, 1121; $\delta_H$ (400 MHz, $CDCl_3$) 2.63 (1H, dd, *J* 5.0 and 13.0 Hz, 4-C(H)H), 3.22 (1H, m, 4-C(H)H), 3.60 (3H, s, $OCH_3$), 3.66 (3H, s, $OCH_3$), 5.14-5.30 (3H, m, CH=C(H)H and 5-CH), 6.20-6.27 (1H, m, $CH_2$=CH), 6.70 (1H, d, *J* 7.5 Hz, Ph-H), 6.96 (1H, m, Ph-H), 7.18 (1H, d, *J* 7.6 Hz, Ph-H), 7.18-7.20 (1H, m, Ph-H), 7.32-7.38 (3H, m, Ph-H), 7.42-7.44 (2H, m, Ar-H); $\delta_C$ (100 MHz, $CDCl_3$) 39.03 (4-$CH_2$), 53.22, 53.35 (4 x $OCH_3$), 67.10 (3-C), 79.93 (5-CH), 86.49 (2-C), 110.35 (Ph-CH), 118.42 ($CH_2$=CH), 123.42 (Ph-CH), 124.11 (Ph-C), 125.24, 127.02, 128.70, 130.07, 131.24 (Ph-CH), 134.35 (Ph-C), 138.08 ($CH_2$=CH), 145.65 (ipso-C), 169.65, 170.33 (C=O), 174.53 (C=O); *m/z* (EI) 407 ($M^+$, 45 %), 316, 306, 288, 204, 195, 167, 152 , 124, 84, 77, 71, 49, (Observed 407.1362, $C_{23}H_{21}O_6N$ requires 407.1369).

**Dimethyl-1'-phenyl-2'-oxo-5-vinyl-1',2',4,5-tetrahydro-3*H*-spiro[furan-2,3'-indole]-3,3-dicarboxylate** (1 : 4.5; *trans* **(163h)** : *cis* **(164h)** in $CH_3CN$)

The *cis* **164h** isomer was isolated as the major diastereoisomer as a white solid (0.25 g, 0.61 mmol, 61 %), m.p. 132-135°C; $\nu_{max}$ (thin film)/$cm^{-1}$ 2952w (C-H), 1736s (C=O), 1684 (N-C=O), 1500, 1373, 1271, 1211; $\delta_H$ (400 MHz, $CDCl_3$) 2.63 (1H, dd, *J* 5.0 and 13.0 Hz, 4-C(H)H), 2.80 (1H, q, *J* 6.5 Hz, 4-C'(H)H), 3.04 (1H, m, 4-C'(H)H), 3.23 (1H, m, 4-C(H)H), 3.61 (6H, s, $OCH_3$ and $OCH_3$), 3.67 (3H, s, $OC'H_3$), 3.69 (3H, s, $OC'H_3$), 5.09-5.29 (6H, m, C'H=C'(H)H and CH=C(H)H and 5-CH and 5-C'H), 6.09 (1H, m, $C'H_2$=C'H), 6.23 (1H, m, $CH_2$=CH), 6.70-6.72 (2H, m, Ph-H), 7.07 (2H, m, Ph-H), 7.18 (2H, m, Ph-H), 7.36-7.39 (6H, m, Ph-H), 7.42-7.45 (4H, m, Ph-H); $\delta_C$ (100 MHz, $CDCl_3$) 39.02 (4-$CH_2$), 39.25 (4-C'$H_2$), 53.29, 53.32, 53.41, 53.88 ($OCH_3$), 67.06 (3-C), 68.52 (3-C'), 79.90 (5-CH), 83.60 (5-C'H), 85.73 (2-*C*'), 86.48 (2-C), 110.35 (Ph-C'H), 118.42 ($CH_2$=CH), 118.46 (C'$H_2$=CH), 123.38, 123.41 (Ph-CH), 124.11 (Ph-C), 125.16, 125.24, 126.97, 127.02, 128.60, 128.69, 130.02, 130.07, 131.14, 131.24 (Ph-CH), 134.34, 134.48 (Ph-C), 138.08 ($CH_2$=CH), 139.18 (C'$H_2$=C'H), 145.51 (ipso-C'), 145.65 (ipso-C), 168.98, 169.58, 169.65, 170.33 (C'=O), 174.53 (C=O), 175.61 (C'=O); *m/z* (EI) 407 ($M^+$, 45 %), 316, 306, 288, 204, 195, 167, 152, 124, 84, 77, 71, 49, (Observed 407.1362, $C_{23}H_{21}O_6N$ requires 407.1369).

**Dimethyl-1'-phenyl-2'-oxo-5-vinyl-1',2',4,5-tetrahydro-3*H*-spiro[furan-2,3'-indole]-3,3-dicarboxylate** (1.5 : 1 *trans* **(163i)** : *cis* **(164i))**

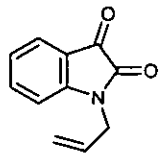



To a stirred solution of 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** (0.184 g, 1.00 mmol) in anhydrous THF (5 ml) was added 1-acetylisatin **157i** (0.189 g, 1.00 mmol) and zinc bromide (0.450 g, 2.00 mmol) at room temperature. This mixture was left to stir for 10 minutes under nitrogen before a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.115 g, 0.10 mmol) was added. The resulting mixture was allowed to stir at 37°C for 17 hours. The solvent was then removed *in vacuo* and the residue dissolved in EtOAc (20 ml). The palladium catalyst was filtered through a plug of silica, and the organic layer was washed with distilled water (2 x 20 ml). The organics were dried ($MgSO_4$) and concentrated *in vacuo* to afford an orange solid (0.42 g). This crude material was purified by column chromatography to afford the desired furan **163i** and **164i** as a white solid ($Al_2O_3$, EtOAc : P.E. 40-60; 1 : 1), m.p. 87-91°C; $\nu_{max}$ (thin film)/$cm^{-1}$ 2953w (C-H), 1734s, 1715s (C=O), 1644 (N-C=O), 1606, 1479, 1371, 1279; $\delta_H$ (400 MHz, $CDCl_3$) 2.55 (6H, s, C'$\underline{H}_3$ and C$\underline{H}_3$), 2.67 (1H, dd, *J* 4.0 and 12.0 Hz, 4-C($\underline{H}$)H), 2.83-2.87 (2H, m, 4-C'($\underline{H}$)H and 4-C'(H)$\underline{H}$), 3.09 (1H, m, 4-C(H)$\underline{H}$), 3.58 (3H, s, OC$\underline{H}_3$), 3.59 (3H, s, OC$\underline{H}_3$), 3.61 (3H, s, OC'$\underline{H}_3$), 3.65 (3H, s, OC'$\underline{H}_3$), 5.12-5.28 (6H, m, C'H=C'($\underline{H}$)$\underline{H}$ and CH=C($\underline{H}$)$\underline{H}$ and 5-C$\underline{H}$ and 5-C'$\underline{H}$), 6.05 (1H, m, C'$H_2$=C'$\underline{H}$), 6.19 (1H, m, $CH_2$=C$\underline{H}$), 7.05-7.09 (4H, m, Ph-$\underline{H}$), 7.29-7.33 (2H, m, Ph-$\underline{H}$), 8.19-8.21 (2H, d *J* 8.0 Hz, Ph-$\underline{H}$); $\delta_C$ (100 MHz, $CDCl_3$) 24.58 ($\underline{C}H_3$), 25.35 ($\underline{C}'H_3$), 37.59 (4-$\underline{C}H_2$), 38.03 (4-$\underline{C}'H_2$), 51.88, 52.02 (4 x O$\underline{C}H_3$), 66.56 (3-$\underline{C}$), 68.08 (3-$\underline{C}'$), 79.10 (5-$\underline{C}$H), 82.28 (5-$\underline{C}'$H), 84.34 (2-$\underline{C}'$), 85.03 (2-$\underline{C}$), 115.94, 115.99 (Ph-$\underline{C}$H), 117.03 ($\underline{C}H_2$=CH), 117.22 ($\underline{C}'H_2$=C'H), 122.45, 123.18 (Ph-$\underline{C}$), 123.23, 123.26 (Ph-$\underline{C}$H), 123.87, 123.88,

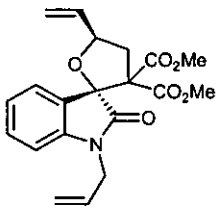
(Ph-CH), 130.13, 130.22 (Ph-CH), 136.39 ($CH_2$=CH), 137.04 (C'$H_2$=C'H), 140.39, 140.49 (ipso-C), 167.51, 167.52, 168.17, 168.20, 169.24, 169.28 (C=O), 175.18 (C=O), 176.46 (C'=O); *m/z* (EI) 373 ($M^+$, 57 %), 331, 282, 240, 212, 184, 146, 124, 90, 77, (Observed 373.1169, $C_{19}H_{19}O_7N$ requires 373.1161).

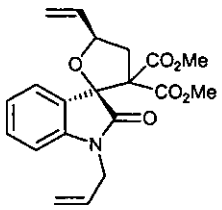
**1-Allyl isatin (157j)**



To a dry flask was weighed sodium hydride (0.300 g, 7.48 mmol) and THF (25 ml). The flask was cooled to 0°C and isatin **157a** (1 g, 6.80 mmol) was added. The mauve solution was stirred for 30 minutes at 0°C before the addition of allyl bromide **165** (0.820 g, 6.80 mmol). The flask was warmed to room temperature and stirred for 17 hours. The resulting red solution was poured over ice (20 g) and extracted with EtOAc (2 x 25 ml) and the organics were washed with $NaHCO_3$ (25 ml), dried ($MgSO_4$) and concentrated *in vacuo* to afford an orange solid (0.73 g). The crude material was purified by column chromatography ($SiO_2$, DCM) to afford the desired isatin **157j** as an orange solid (0.56 g, 3.00 mmol, 44 %), m.p. 87-89°C (Lit[98] m.p. 87-88°C); $\nu_{max}$ (thin film)/$cm^{-1}$ 2928 (C-H w), 1732s (C=O), 1689 (N-C=O); $\delta_H$ (400 MHz, $CDCl_3$) 4.28-4.31 (2H, m, $CH_2$-CH=$CH_2$), 5.20-5.28 (2H, m, $CH_2$=CH), 5.77 (1H, m, $CH_2$=CH), 6.84 (1H, d, *J* 6.0 Hz, Ph-H), 7.05 (1H, t, *J* 7.0 Hz, Ph-H), 7.48-7.53 (2H, m, Ph-H); $\delta_C$ (100 MHz, $CDCl_3$) 42.85 ($CH_2$), 111.32 (Ph-CH), 117.90 (Ph-C), 118.99 (CH=$CH_2$), 124.18, 125.68, 130.71 (Ph-CH), 138.77 (CH=$CH_2$), 151.18 (*ipso-C*), 158.27 (*C*=O), 183.63 (C=O); *m/z* (EI) 187 ($M^+$, 57 %), 159, 146, 130, 104, 90, 84, 77, 51, (Observed 187.0633, $C_{11}H_9O_2N$ requires 187.0633).

**Dimethyl-1'-phenyl-2'-oxo-5-vinyl-1',2',4,5-tetrahydro-3*H*-spiro[furan-2,3'-indole]-3,3-dicarboxylate** (1 : 1; *trans* **(163j)** : *cis* **(164j))**

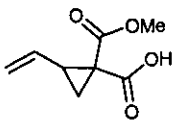



To a stirred solution of 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** (0.184 g, 1.00 mmol) in anhydrous THF (5 ml) was added 1-allylisatin **157j** (0.187 g, 1.00 mmol) and zinc bromide (0.450 g, 2.00 mmol) at room temperature. This mixture was left to stir for 10 minutes under nitrogen before a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.115 g, 0.10 mmol) was added. The resulting mixture was allowed to stir at 37 °C for 18 hours. The solvent was then removed *in vacuo* and the residue dissolved in ethyl acetate (20 ml). The palladium catalyst was filtered through a plug of silica, and the organic layer was washed with distilled water (2 x 20 ml). The organics were dried ($MgSO_4$) and concentrated *in vacuo* to afford an orange solid (0.43 g). The crude material was purified by column chromatography ($Al_2O_3$, EtOAc : DCM; 1 : 9) followed by ($Al_2O_3$, $Et_2O$ : P.E. 40-60; 1 : 1) to afford the desired furan **163j** and **164j** as a white solid (0.249 g, 0.67 mmol, 67 %), m.p. 95-99°C; $\nu_{max}$ (thin film)/$cm^{-1}$ 2953w (C-H), 1733s (C=O), 1648 (N-C=O) 1613, 1490, 1468, 1366,1269; $\delta_H$ (400 MHz, $CDCl_3$) 2.59 (1H, dd *J* 5.0 and 13.0 Hz, 4-C(H)H), 2.77 (1H, q, *J* 6.5 Hz, 4-C'(H)H), 3.04 (1H, m, 4-C'(H)H), 3.23 (1H, m, 4-C(H)H), 3.57 (3H, s, $OCH_3$), 3.58 (3H, s, $OCH_3$), 3.63-3.71 (6H, m, 2 x $OC'H_3$), 4.01-4.10 (2H, m, $CH_2$-CH=$CH_2$), 4.32-4.37 (2H, m, C'$H_2$-C'H=C'$H_2$), 5.11-5.32 (10H, m, C'H=C'(H)H (vinyl) and CH=C(H)H (vinyl) and C'H=C'(H)H (allyl) and CH=C(H)H (allyl) and 5-CH and 5-C'H), 5.74-5.81 (2H, m, C'H=C'$H_2$ (allyl) and CH=$CH_2$ (allyl)), 6.08 (1H, m, C'$H_2$=C'H (vinyl)), 6.25 (1H, m, $CH_2$=CH (vinyl)), 6.74-6.75 (2H, d, *J* 7.5 Hz, Ph-H), 6.89-6.94 (2H, m, Ph-H), 6.70-7.02 (2H, m, Ph-H), 7.20-7.22 (2H, m, Ph-H); $\delta_C$ (100 MHz, $CDCl_3$) 39.21 (4-$CH_2$), 39.44 (4-

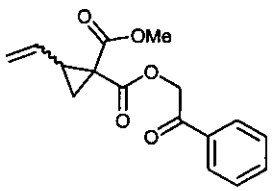
C'$H_2$), 42.70 (C$H_2$ (allyl)), 42.93 (C'$H_2$ (allyl)), 53.41, 53.20 (2 x OC$H_3$), 66.60 (3-C), 67.90 (3-C'), 79.74 (5-CH), 83.24 (5-C'H), 85.51 (2-C'), 86.32 (2-C), 109.97 (Ph-CH), 118.15 ($CH_2$=CH vinyl), 118.31 (C'$H_2$=C'H vinyl), 118.38 (2 x C'$H_2$=C'H (allyl)), 122.89, 122.92 (Ph-CH), 124.59 (Ph-C), 124.90, 124.96 (Ph-CH), 125.26 (Ph-C), 131.02, 131.09 (Ph-CH), 131.51 (CH=$CH_2$ (allyl)), 131.62 (C'H=C'$H_2$ (allyl)), 138.14 ($CH_2$=CH (vinyl)), 139.19 (C'$H_2$=C'H (vinyl)), 144.72, 144.75 (ipso-C), 168.76, 169.39, 169.57, 170.26 (4 x C'=O) 174.77 (C=O), 175.77 (C=O); *m/z* (EI) 371 ($M^+$, 70 %), 312, 280, 270, 184, 146, 130, 84, (Observed 371.1370, $C_{20}H_{21}O_6N$ requires 371.1369).

**2-Vinylcyclopropane-1,1-dicarboxylic acid monomethyl ester (166)**



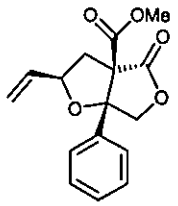
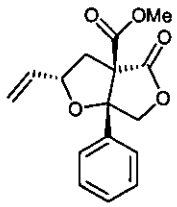

To a stirred solution of 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** (1.000 g, 5.43 mmol), THF (20 ml) and water (20 ml), LiOH (0.130 g, 5.43 mmol) was added and the reaction was stirred at room temperature for 17 hours. The reaction mixture was acidified to pH 2 with 1M HCl. The aqueous mixture was extracted with EtOAc (2 x 30 ml) and the combined organic extracts were washed with brine (30 ml), dried ($MgSO_4$) and concentrated *in vacuo* to afford a colourless oily residue. The resulting residue was re-dissolved in EtOAc (20 ml) and extracted with $NaHCO_3$ (20 ml). The aqueous layer was acidified to pH 2 with 1M HCl and extracted with $Et_2O$ (2 x 20 ml). The combined $Et_2O$ layers were dried ($MgSO_4$) and concentrated *in vacuo* to afford the desired acid **166** as a colourless oily residue (0.632 g, 3.70 mmol, 68 %); $\nu_{max}$ (thin film)/$cm^{-1}$ 3583s (C-H), 3019s (O-H br), 1734s (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 1.93-2.09 (2H, m, 3-C(H)H), 2.72 (1H, q, *J* 8.5 Hz, 2-CH), 3.81 (3H, s, $OCH_3$), 5.22 (1H, d, *J* 8.4 Hz, C(H)H=CH), 5.35 (1H, d, *J* 15 Hz, C(H)H=CH), 5.56 (1H, m, $CH_2$=CH); $\delta_C$ (100 MHz; $CDCl_3$) 22.91 (3-$CH_2$), 33.89 (1-C), 37.42 (2-CH), 53.07 ($OCH_3$), 120.47 ($CH_2$=CH), 132.26 ($CH_2$=CH), 171.84 (C=O), 172.08 (COOH); *m/z* (EI) 170 ($M^+$, 4 %), 152, 124, 110, 94, 79, 71, 66, 59, (Found 170.0577, $C_8H_{10}O_4$ requires 170.0579).

**2-Vinylcyclopropane-1,1-dicarboxylic acid methyl ester 2-oxo-2-phenyl-ethyl ester (171)**




A mixture of 2- vinylcyclopropane-1,1-dicarboxylic acid monomethyl ester **166** (0.100 g, 0.59 mmol), 2-bromoacetophenone **170** (0.470 g, 2.35 mmol), anhydrous potassium carbonate (0.200 g, 1.47 mmol) and acetone (10 ml) was stirred at room temperature for 17 hours. The solvent was removed *in vacuo* to afford a yellow solid, which was partitioned between DCM (30 ml) and 1M HCl (30 ml). The organic layer was washed with saturated $NaHCO_3$ (2 x 30 ml), dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow oil (0.540 g). The crude oil was purified by flash chromatography ($SiO_2$, DCM) to afford the desired cyclopropane **171** a yellow oil (0.159 g, 0.55 mmol, 94 %); $\nu_{max}$ (thin film)/$cm^{-1}$ 2950w (C-H), 1734s (C=O), 1700 (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 1.72 (1H, dd, *J* 5.0 and 9.0 Hz, 3-C(H)H), 1.78 (1H, dd, *J* 5.0 and 7.5 Hz, 3-C(H)H), 2.65 (1H, m, 2-CH), 3.67 (3H, s, $OCH_3$), 5.08 (1H, d, *J* 8.4 Hz, C(H)H=CH), 5.22 (3H, m, C(H)H=CH and $CH_2COPh$), 5.29 (1H, m, $CH_2$=CH), 7.38-7.42 (2H, m, Ph-H), 7.51 (1H, m, Ph-H), 7.80-7.83 (2H, m, Ph-H); $\delta_C$ (100 MHz; $CDCl_3$) 21.43 (3-$CH_2$), 32.85 (2-CH), 36.07 (1-C), 53.00 ($OCH_3$), 67.13 ($CH_2COPh$), 119.35 ($CH_2$=CH), 128.14, 129.34, 133.16 (Ph-CH), 134.50 ($CH_2$=CH), 134.61 (Ph-C), 167.92 (C=OR), 169.31 (C=O), 191.97 (C(O)Ar); *m/z* (EI) 288 ($M^+$, 6 %), 257, 152, 121, 105, 91, 77, (Found 288.1001, $C_{16}H_{16}O_5$ requires 288.0998).

**4-Oxo-6a-phenyl-2-vinyltetrahydro-furo[3,4-b]furan-3a-carboxylic acid methyl ester (172)** (*cis* : *trans*; 1 : 1)

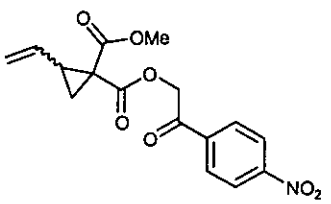



2-Vinylcyclopropane-1,1-dicarboxylic acid methyl ester 2-oxo-2-phenyl-ethyl ester **171** (0.077g, 0.27 mmol) was stirred with dry THF (2 ml) under nitrogen for 20 minutes before tetrakis (triphenyl phosphine) palladium (0) (0.03 g, 0.03 mmol) was added. The yellow solution was stirred at 35°C for 16 hours. The solvent was removed *in vacuo* and re-dissolved in EtOAc (5 ml) and the green solution was passed through a plug of silica to remove the catalyst. The solvent was removed *in vacuo* to afford a green oil (0.133 g). The crude oil was purified by flash chromatography ($SiO_2$, $Et_2O$ : P.E. 40-60; 4 : 6) to afford the desired bicylic furan **172**. A small amount of the *cis* diastereoisomer was isolated (0.008 g) from the mixture of the two diastereoisomers (0.043 g). Total yield (0.051 g, 0.18 mmol, 66 %).

*Cis* isomer:- $\nu_{max}$ (thin film)/$cm^{-1}$ 2951 (C-H w), 1782 (C=O s), 1748 (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 2.50 (1H, m, 5-C'(H)H), 2.61 (1H, dd, *J* 5.2 and 12.8 Hz, 5-C(H)H), 3.44 (3H, s, OC'$H_3$), 4.51-4.60 (2H, m, 2-C'(H)H and 6-C'H), 4.94 (1H, d, *J* 10.5 Hz, 2-C'(H)H), 5.20 (1H, d, *J* 10 Hz, C'H=C'(H)H), 5.39 (1H, d, *J* 17.0 Hz, C'H=C'(H)H), 5.98 (1H, m, C'H=C'$H_2$), 7.19-7.38 (5H, m, Ph-H); $\delta_C$ (100 MHz; $CDCl_3$) 38.91 (5-C'$H_2$), 53.25 (4a-OC'$H_3$), 67.96 (1a-C'), 77.71 (2-C'$H_2$), 80.76 (6-C'H), 91.92 (4a-C'), 119.27 (C'$H_2$=C'H), 126.36, 128.89, 129.31 Ph-CH), 135.84 (Ph-C'), 136.57 (C'$H_2$=C'H), 166.54 (C'=O), 174.56 (C'=O); *m/z* (EI) 288 ($M^+$, 8 %), 256, 230, 197, 125, 115, 105, 91, 77, 65, 57, 49, (Found 288.0993, $C_{16}H_{16}O_5$ requires 288.0998).

*Cis* and *Trans* isomer: $\nu_{max}$ (thin film)/cm$^{-1}$ 2953 (C-H w), 1782 (C=O), 1746 (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 2.44-2.52 (2H, m, 5-C(H)H and 5-C'(H)H), 2.59 (1H, dd, *J* 5.2 Hz, 5-C'(H)H), 2.98 (1H, m, 5-C(H)H), 3.44 (3H, s, OC'$H_3$), 3.56 (3H, s, O$CH_3$), 4.49-4.58 (3H, m, 2-C'(H)H and 2-C(H)H and 6-C'H), 4.74 (1H, d *J* 10.4 Hz, 2-C(H)H), 4.92-4.95 (2H, m, 2-C'(H)H, and 6-CH), 5.13 (1H, m, CH=C(H)H), 5.26-5.36 (2H, m, CH=C(H)H and C'H=C'(H)H), 5.41 (1H, d *J* 17.0 Hz, C'H=C'(H)H), 5.79 (1H, m, $CH_2$=CH), 5.98 (1H, m, C'H=C'$H_2$), 7.19-7.36 (10H, m, Ph-H and Ph-H), $\delta_C$ (400 MHz; $CDCl_3$) 38.20 (5-$CH_2$), 38.91 (5-C'$H_2$), 53.26 (4a-OC'$H_3$), 53.50 (4a-O$CH_3$), 67.30 (1a-C), 67.97 (1a-C'), 76.00 (2-$CH_2$), 77.09 (2-C'$H_2$), 80.76 (6-C'H), 80.86 (6-CH), 91.92 (4a-C'), 93.55 (4a-C), 117.32 ($CH_2$=CH), 119.28 (C'$H_2$=C'H), 125.91, 126.27, 126.37, 128.90, 129.18, 129.32 (Ph-CH), 129.39 (Ph-C and Ph-C'), 135.84 ($CH_2$=CH), 136.57 (C'$H_2$=C'H), 166.40 (C=O), 166.54 (C'=O), 174.65 (C=O), 174.94 (C'=O); *m/z* (EI) 288 ($M^+$, 8 %), 256, 230, 197, 125, 115, 105, 91, 77, 59, 49, (Found 288.1003, $C_{16}H_{16}O_5$ requires 288.0998).

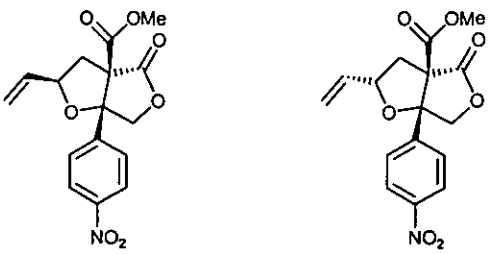
**2-Vinyl-cyclopropane-1,1-dicarboxylic acid methyl ester-2-(4-nitro-phenyl)-2-oxo-ethyl ester (174)**




A solution of 2- vinylcyclopropane-1,1-dicarboxylic acid monomethyl ester **166** (1.00 g, 5.88 mmol), 2-bromo-4'-nitroacetophenone **173** (1.43 g, 5.88 mmol), anhydrous potassium carbonate (0.81 g, 5.88 mmol) and acetone (20 ml) was stirred at room temperature for 17 hours. The solvent was removed *in vacuo* to afford a

yellow solid, which was partitioned between DCM (30 ml) and 1M HCl (30 ml). The organic layer was washed with saturated $NaHCO_3$ (2 x 30 ml), dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow oil (0.58 g). The crude oil was purified by flash chromatography ($SiO_2$, DCM) followed by ($SiO_2$, $Et_2O$ : P.E. 40-60; 1 : 1) to afford the desired cyclopropane **174** as an off white solid (0.695 g, 2.09 mmol, 35 %), m.p.156-158°C; $\nu_{max}$ (thin film)/$cm^{-1}$ 2952w (C-H), 1733s (C=O), 1717 (C=O), 1527, 1347, 1211, 1132; $\delta_H$ (400 MHz; $CDCl_3$) 1.67-1.70 (1H, dd, *J* 5.0 and 9.0 Hz, 3-C(H)H), 1.77-1.80 (1H, dd, *J* 5.2 and 7.6 Hz, 3-C(H)H), 2.62-2.64 (1H, m, 2-CH), 3.68 (3H, s, $OCH_3$), 5.10 (1H, d, *J* 8.4 Hz, C(H)H=CH), 5.23-5.38 (3H, m, C(H)H=CH and $CH_2COPh$), 5.33 (1H, m, $CH_2$=CH), 7.99-8.02 (2H, d, *J* 5.2 Hz, Ph-H), 8.25-8.27 (2H, d, *J* 5.2 Hz, Ph-H); $\delta_C$ (100 MHz; $CDCl_3$) 21.55 (3-$CH_2$), 32.92 (2-CH), 35.90 (1-C), 53.09 ($OCH_3$), 67.16 ($CH_2COPh$), 119.62 ($CH_2$=CH), 124.48, 129.47, (Ph-CH), 132.91 ($CH_2$=CH), 138.82 (Ph-C), 151.08 (Ph-C), 167.69 (C=O), 169.29 (C=O), 191.01 (C(O)Ar); *m/z* (EI) 333 ($M^+$, 11 %), 302, 220, 152, 121, 104, 93, 71, 65, (Found 333.0845, $C_{16}H_{15}NO_7$ requires 333.0849).

**6*a*-(4-Nitro-phenyl)-4-oxo-2-vinyl-tetrahydro-furo[3,4-*b*]furan-3a-carboxylic acid methyl ester (175)** (1.5 : 1; *cis* : *trans*)




2-Vinyl-cyclopropane-1,1-dicarboxylic acid methyl ester-2-(4-nitro-phenyl)-2-oxo-ethyl ester **174** (0.400 g, 1.20 mmol) was stirred with dry THF (10 ml) under nitrogen for 20 minutes before tetrakis (triphenyl phosphine) palladium (0) (0.139 g, 0.120 mmol) was added. The yellow solution was stirred at 35°C for 16 hours. The solvent

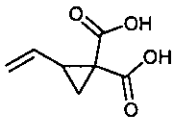
was removed *in vacuo* and re-dissolved in EtOAc (5 ml) and the green solution was passed through a plug of silica to remove the catalyst. The solvent was removed *in vacuo* to afford a yellow solid (0.420 g). The crude solid was purified by flash chromatography three times ($SiO_2$, $Et_2O$ : DCM; 1 : 1) followed by ($SiO_2$, $Et_2O$) then ($SiO_2$, $Et_2O$ : P.E. 40-60; 2 : 8) to afford the desired furan **175** as an off white solid, m.p. 101 °C. A small amount of the *cis* diastereoisomer was isolated (0.020 g) from the mixture of the two diastereoisomers (0.300 g). Total yield (0.320 g, 80 %).

*Cis* isomer:- $\nu_{max}$ (thin film)/$cm^{-1}$ 2951 (C-H w), 1784s (C=O), 1749s (C=O), 1351, 1251; $\delta_H$ (400 MHz; $CDCl_3$) 2.47 (1H, m, 5-C'(H)H), 2.66 (1H, dd, *J* 5.0 and 13.0 Hz, 5-C'(H)H), 3.51 (3H, s, OC'$H_3$), 4.57-4.60 (2H, m, 2-C'(H)H and 6-C'H), 4.91 (1H, d, *J* 11.0 Hz, 2-C'(H)H), 5.34 (1H, d, *J* 8.5 Hz, C'H=C'(H)H), 5.42 (1H, d *J* 15.0 Hz, C'H=C'(H)*H*), 5.99 (1H, m, C'H=C'$H_2$), 7.57-7.60 (2H, d, *J* 5.0 Hz, Ph-H), 8.16-8.19 (2H, d, *J* 5.0 Hz, Ph-H); $\delta_C$ (100 MHz; $CDCl_3$) 39.01 (5-C'$H_2$), 53.71 (4a-OC$H_3$), 68.21 (1a-C'), 77.10 (2-C'$H_2$), 81.18 (6-C'H), 91.33 (4a-C'), 120.02 (C'$H_2$=C'H), 124.00, 127.66, (Ph-C'H), 135.14 (C'$H_2$=C'H), 143.76 (Ph-C'), 148.52 (Ph-C'), 166.09 (C'=O), 173.68 (C'=O); *m/z* (EI) 333 ($M^+$, 31 %), 302, 275, 264, 243, 215, 169, 150, 125, 115, 104, 93, 76, 71, 59, (Observed 333.0851, $C_{16}H_{15}NO_7$ requires 333.0849).

*Cis* and *Trans* isomer: $\nu_{max}$ (thin film)/$cm^{-1}$ 2951w (C-H), 1784s (C=O), 1749s (C=O), 1351, 1251; $\delta_H$ (400 MHz; $CDCl_3$) 2.42-2.48 (2H, m, 5-C(H)H and 5-C'(H)H), 2.63 (1H, dd, *J* 5.0 and 13.0 Hz, 5-C'(H)H), 2.95 (1H, m, 5-C(H)H), 3.49 (3H, s, OC'$H_3$), 3.60 (3H, s, OC$H_3$), 4.58 (3H, m, 2-C'(H)H and 2-C(H)H and 6-C'H), 4.73 (1H, d, *J* 10.4 Hz, 2-C(H)H), 4.91 (1H, d, *J* 11.0 Hz, 2-C'(H)H), 4.92 (1H, m, 6-CH), 5.16 (1H, d, *J* 10.5 Hz, CH=C(H)H), 5.28-5.43 (2H, m, CH=C(H)H and C'H=C'(H)H), 5.42 (1H, d *J* 16.0 Hz, C'H=C'(H)H), 5.81 (1H, m, CH=$CH_2$), 5.98 (1H, m, C'H=C'$H_2$), 7.47-7.49 (2H, m, Ph-H), 7.57-7.60 (2H, m, Ph-H), 8.15-8.19 (4H, m, Ph-H and Ph-H); $\delta_C$ (400 MHz; $CDCl_3$) 38.16 (5-C$H_2$), 38.99 (5-C'$H_2$), 53.71 (4a-OC'$H_3$), 53.91 (4a-OC$H_3$), 67.58 (1a-C), 68.21 (1a-C'), 75.88 (2-C$H_2$), 77.78 (2-C'$H_2$), 81.17 (6-C'H), 81.40 (6-CH), 91.34 (4a-C'), 93.05 (4a-C), 117.82 (C$H_2$=CH), 119.99 (C'$H_2$=C'H), 123.99, 124.29, 127.26, 127.68 (Ph-CH and Ph-C'H), 135.16 (C'$H_2$=C'H), 137.06 ($CH_2$=CH), 143.31 (Ph-C), 143.77 (Ph-C'), 148.49 (Ph-C'),

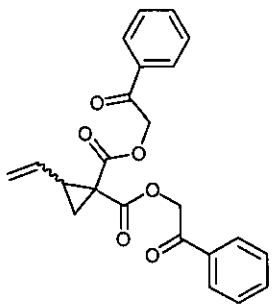
148.54 (Ph-C), 166.09 (C=O), 166.24 (C'=O), 173.70 (C'=O), 174.03 (C=O); *m/z* (EI) 333 ($M^+$, 31 %), 302, 275, 264, 243, 215, 169, 150, 125, 115, 104, 93, 76, 71, 59, (Found 333.0851, $C_{16}H_{15}NO_7$ requires 333.0849).

**2-Vinylcyclopropane-1,1-dicarboxylic acid (176)**



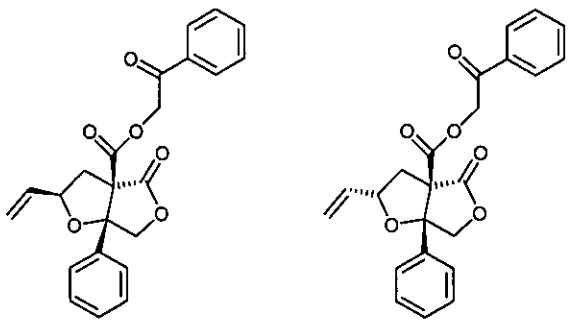

To a stirred solution of 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** (0.350 g, 1.90 mmol), THF (7 ml) and water (7 ml), LiOH (0.456 g, 19.00 mmol) was added and the reaction was left stirring for 18 hours. The resulting mixture was acidified to pH 2 with 1M HCl and extracted with $Et_2O$ (2 x 30 ml). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo* to afford the desired cyclopropane diacid **176** as an oily residue (0.290 g, 1.86 mmol, 98 %); $\nu_{max}$ (thin film)$cm^{-1}$ 2990s (O-H broad), 2360m (C-H) 1735s (C=O), 1637, 1438; $\delta_H$ (400 MHz; $CDCl_3$) 2.11-2.15 (1H, dd, *J* 5.0 and 9.0 Hz, 3-C(H)H), 2.22 (1H, dd, *J* 4.5 and 9.0 Hz, 3-C(H)H), 2.87 (1H, m, 2-CH), 5.29 (1H, d, *J* 9.5 Hz, C(H)H=CH), 5.43 (1H, d, *J* 16.5 Hz, C(H)H=CH), 5.84 (1H, m, $CH_2$=CH); $\delta_C$ (100 MHz; $CDCl_3$) 25.44 (3-$CH_2$), 32.56 (1-C), 40.64 (2-CH), 121.26 ($CH_2$=CH), 131.84 ($CH_2$=CH), 173.51 (C=O), 175.46 (C=O); *m/z* (EI) 156 ($M^+$, 5 %), 152 (11 %), 138 (35 %), 110 (100 %), 94 (62 %), 82 (51 %), 66 (78 %), (Found 156.0421, $C_7H_8O_4$ requires 156.0423).

**2-Vinylcyclopropane-1,1-dicarboxylic acid bis-(2-oxo-2-phenyl-ethyl) ester (177)**



A solution of 2- vinylcyclopropane-1,1-dicarboxylic acid **176** (0.200 g, 1.28 mmol), 2-bromoacetophenone **170** (1.020 g, 5.12 mmol), anhydrous potassium carbonate (0.890 g, 6.41 mmol) and acetone (20 ml) was stirred at room temperature for 17 hours. The solvent was removed *in vacuo* to afford a yellow solid, which was partitioned between DCM (30 ml) and 1M HCl (30 ml). The organic layer was washed with saturated $NaHCO_3$ (2 x 30 ml), dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow oil (0.954 g). The crude oil was purified by flash chromatography ($SiO_2$, DCM : P.E. 40-60; 2 : 8) and then ($SiO_2$, EtOAc : DCM; 2 : 8) to afford the desired alkylated cyclopropane **177** as a yellow oil (0.452 g, 1.15 mmol, 90 %); $\nu_{max}$ (thin film)/$cm^{-1}$ 2936w (C-H str), 1733s (C=O), 1700s (C=O), 1597, 1449, 1373, 1230, 1132; $\delta_H$ (400 MHz; $CDCl_3$) 1.76-1.87 (2H, m, 3-C(H)H), 2.74 (1H, q *J* 8.5 Hz, 2-CH), 5.14-5.20 (2H, m, $CH_2$=CH), 5.29-5.33 (4H, m, 2 x $CH_2$COPh), 5.63 (1H, m, $CH_2$=CH), 7.34-7.42 (4H, m, Ph-H), 7.50-7.52 (2H, m, Ph-H), 7.80-7.83 (4H, m, Ph-H); $\delta_C$ (100 MHz; $CDCl_3$) 21.97 (3-$CH_2$), 33.32 (2-CH), 35.81 (1-C), 67.15, 67.35 ($CH_2$COPh), 119.40 ($CH_2$=CH), 128.17, 128.25, 129.08, 129.23, 129.28, 133.54 (Ph-CH), 134.23, ($CH_2$=CH), 134.49, 134.61 (Ph-C), 167.05, 169.12 (C=O), 191.99, 192.04 (C(O)Ar); *m/z* (EI) 392 ($M^+$, 12 %), 273, 257, 175, 121, 105, 91, 65, 51, (Found 391.9844, $C_{23}H_{20}O_6$ requires 391.9851).

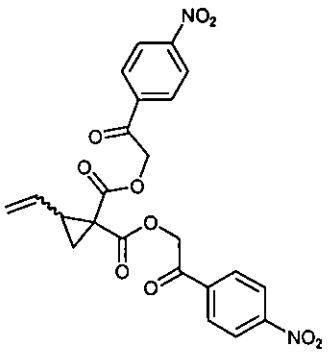
**4-Oxo-6a-phenyl-2-vinyltetrahydro-furo[3,4-*b*]furan-3a-carboxylic acid 2-oxo-2-phenyl-ethyl ester (178)** (*cis* : *trans*; 1.7 : 1)



2-Vinylcyclopropane-1,1-dicarboxylic acid bis-(2-oxo-2-phenyl-ethyl) ester **177** (0.203 g, 0.52 mmol) was stirred with dry THF (5 ml) under nitrogen for 20 minutes before tetrakis(triphenylphosphine) palladium (0) (0.060 g, 0.05 mmol) was added. The yellow solution was stirred at 35°C for 16 hours. The solvent was removed *in vacuo* and re-dissolved in EtOAc (5 ml) and the green solution was passed through a plug of silica to remove the catalyst. The solvent was removed *in vacuo* to afford a green oil (0.350 g). The crude oil was purified by flash chromatography ($SiO_2$, DCM) followed by ($SiO_2$, $Et_2O$ : P.E. 40-60; 4 : 6) to afford the desired bicyclic furan **178** as a mixture of diastereoisomers as a yellow oil (0.195 g, 0.50 mmol, 96 %); $\nu_{max}$ (thin film)/$cm^{-1}$ 2921 (C-H w), 1783 (C=O s), 1755 (C=O), 1704 (C=O); $\delta_H$ (400 MHz; $CDCl_3$) 2.59-2.66 (2H, m, 5-C(H)H and 5-C'(H)H), 2.79 (1H, dd *J* 5.0 and 13.0 Hz, 5-C'(H)H), 3.11 (1H, m, 5-C(H)H), 4.62-4.71 (3H, m, 2-C'(H)H and 2-C(H)H and 6-C'H), 4.99-5.07 (3H, m, 2-C(H)H and 2-C'(H)H and 6-CH), 5.15-5.25 (4H, m, OC'$H_2$ and O$CH_2$), 5.34-5.49 (4H, m, C'H=C'(H)H and CH=C(H)H), 5.89 (1H, m, $CH_2$=CH), 6.09 (1H, m, C'$H_2$=C'H), 7.31-7.86 (20H, m, Ph-H and Ph-H'); $\delta_C$ (400 MHz; $CDCl_3$) 38.32 (5-$CH_2$), 38.88 (5-C'$H_2$), 67.05 (1a-C), 67.23 (OC'$H_2$), 67.39 (O$CH_2$), 67.83 (1a-C'), 75.71 (2-$CH_2$), 77.71 (2-C'$H_2$), 80.68 (6-C'H), 80.90 (6-CH), 92.13 (4a-C'), 93.74 (4a-C), 117.48 ($CH_2$=CH), 119.44 (C'$H_2$=C'H), 126.32, 126.70, 128.15, 128.16, 128.94, 129.20, 129.36, 129.39, 129.42 (Ph-CH and Ph-C'H), 134.18, 134.18 (Ph-C), 134.57 ($CH_2$=CH), 134.62 (C'$H_2$=C'H), 135.64, 136.33 (Ph-C), 174.13 (C=O), 174.68 (C'=O), 190.69 (C=O), 190.87 (C'=O); *m/z* (EI) 392 ($M^+$, 7

%), 323, 273, 229, 215, 199, 121, 105, 91, 77, 71, 65, (Observed 392.1253, $C_{23}H_{20}O_6$ requires 392.1260).

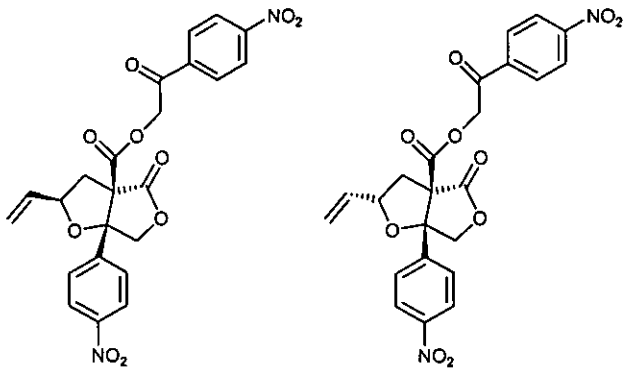
**2-Vinyl-cyclopropane-1,1-dicarboxylic acid bis-[2-(4-nitro-phenyl)-2-oxo-ethyl] ester (179)**




A solution of 2- vinylcyclopropane-1,1-dicarboxylic acid **176** (1.000 g, 6.41 mmol), 2-bromo-4'nitroacetophenone **173** (3.440 g, 14.09 mmol), anhydrous potassium carbonate (1.95 g, 14.09 mmol) and acetone (50 ml) was stirred at room temperature for 17 hours. The solvent was removed *in vacuo* to afford a yellow solid, which was partitioned between DCM (60 ml) and 1M HCl (60 ml). The organic layer was washed with saturated $NaHCO_3$, dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow solid (3.902 g). The crude oil was purified by flash chromatography ($SiO_2$, DCM : P.E. 40-60; 2 : 8) followed by ($SiO_2$, $Et_2O$ : P.E. 40-60; 1 : 1) and then ($SiO_2$, EtOAc : P.E. 40-60; 1 :1) to afford the desired alkylated cyclopropane **179** as a white solid (1.03 g, 2.14 mmol, 33 %), m.p. 187-189°C; $\nu_{max}$ (thin film)/$cm^{-1}$ 1737 (C=O), 1711 (C=O), 1525, 1346, 1130; $\delta_H$ (400 MHz; $CDCl_3$) 1.83 (1H, dd, *J* 5.0 and 9.0 Hz, 3-C(H)H), 1.89 (1H, dd J 5.2 and 8.8 Hz, 3-C(H)H), 2.76 (1H, m, 2-CH), 5.18 (1H, d, *J* 9.0 Hz, C(H)H=CH), 5.31-5.34 (5H, m, 2 x $CH_2$COPh and C(H)H=CH), 5.52-5.61 (1H, m, $CH_2$=CH), 8.00-8.03 (4H, m, Ph-H), 8.26-8.29 (4H, m, Ph-H); $\delta_C$ (100 MHz; $CDCl_3$) 22.15 (3-$CH_2$), 33.69 (2-CH), 35.59 (1-C), 67.22, 67.47 ($CH_2$COPh), 119.96 ($CH_2$=CH), 124.50, 124.56, 129.37, 129.47 (Ph-CH), 132.94 ($CH_2$=CH), 138.77,

138.92 (Ph-C), 151.12, 151.17 (Ph-C), 166.83, 168.87 (C=O), 190.84, 190.96 (C(O)Ar); *m/z* (EI) 482 ($M^+$, 3 %), 430, 337, 301, 273, 220, 150, 120, 104, 92, 76, 57, (Found 482.0969, $C_{23}H_{18}N_2O_{10}$ requires 482.0961).

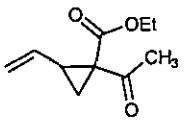
**6a-(4-Nitrophenyl)-4-oxo-2-vinyltetrahydrofuro[3,4-*b*]furan-3a-carboxylic acid 2-(4-nitrophenyl)-2-oxo-ethyl ester (180)**



2-Vinyl-cyclopropane-1,1-dicarboxylic acid bis-[2-(4-nitro-phenyl)-2-oxo-ethyl] ester **179** (0.482 g, 1.00 mmol) was stirred with dry THF (10 ml) under nitrogen for 20 minutes before tetrakis(triphenylphosphine) palladium (0) (0.115 g, 0.10 mmol) was added. The yellow solution was stirred at 35°C for 16 hours. The solvent was removed *in vacuo* and re-dissolved in EtOAc (5 ml) and the green solution was passed through a plug of silica to remove the catalyst. The solvent was removed *in vacuo* to afford a green oil (0.560 g). The crude oil was purified by flash chromatography ($SiO_2$, DCM) followed by ($SiO_2$, $Et_2O$ : P.E. 40-60; 4 : 6) to afford the desired bicyclic furan **180** as a mixture of diastereoisomers as a white solid (0.420 g, 0.87 mmol, 87 %), m.p. 179-181°C; $\nu_{max}$ (thin film)/$cm^{-1}$ 2930w (C-H), 1783s (C=O), 1755 (C=O), 1712 (C=O), 1524, 1350; $\delta_H$ (400 MHz; $(CD_3)_2CO$) 2.43-2.47 (2H, m, 5-C(H)H and 5-C'(H)H), 2.66 (1H, dd, *J* 5.2 and 12.8, 5-C'(H)H), 3.12 (1H, m, 5-C(H)H), 4.62-4.69 (3H, m, 2-C'(H)H and 2-C(H)H and 6-C'H), 5.01-5.02 (3H, m, 2-C'(H)H and 2-C(H)H and 6-CH), 5.17-5.26 (4H, m, OC'$H_2$ and OC$H_2$), 5.39-5.57 (4H, m, CH=C(H)H and C'H=C'(H)H), 5.68 (1H, m, $CH_2$=CH), 6.15 (1H, m, C'$H_2$=C'H), 7.76-8.27

(16H, m, Ph-C<u>H</u> and Ph-C'<u>H</u>); $\delta_C$ (400 MHz; $(CD_3)_2CO$) 38.29 (5-<u>C</u>$H_2$), 39.31 (5-<u>C</u>'$H_2$), 68.31 (1a-<u>C</u>' and 1a-<u>C</u>), 68.68 (O<u>C</u>'$H_2$), 68.87 (O<u>C</u>$H_2$), 75.39 (2-<u>C</u>$H_2$), 77.46 (2-<u>C</u>'$H_2$), 81.25 (6-<u>C</u>'H), 82.69 (6-<u>C</u>H), 92.12 (4a-<u>C</u>'), 93.78 (4a-<u>C</u>), 116.80 (<u>C</u>$H_2$=CH), 119.38 (<u>C</u>'$H_2$=C'H), 124.30, 124.51, 124.74, 128.66, 128.99, 130.13, 130.17, 132.48 (Ph-<u>C</u>H and Ph-<u>C</u>'H), 136.66 ($CH_2$=<u>C</u>H), 138.57 (C'$H_2$=<u>C</u>'H), 139.33, 144.36 (Ph-<u>C</u>), 149.01, 151.69 (Ph-<u>C</u>), 173.38 (<u>C</u>=O), 174.68 (<u>C</u>'=O), 191.01 (<u>C</u>=O), 191.01 (<u>C</u>'=O); *m/z* (EI) 482 ($M^+$, 2 %), 452, 424, 318, 277, 227, 196, 150, 121, 104, 91, 84, 67, 57, (Observed 482.0969, $C_{23}H_{18}N_2O_{10}$ requires 482.0961).

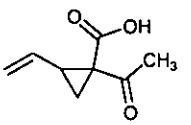
**1-Acetyl-2-vinyl-cyclopropanecarboxylic acid ethyl ester [83] (182)**




A stirred solution of ethyl sodioacetate, prepared from sodium (1.150 g, 50.00 mmol) ethanol (40 ml) and ethylacetoacetate **181** (3.250 g, 25.00 mmol), was introduced to a refluxing solution of *trans*-1,4-dibromobut-2-ene **121** (5.340 g, 25.00 mmol) in ethanol (40 ml). The mixture was left to reflux for 6 hours and then stirred at room temperature for a further 17 hours. The white precipitate was filtered off and the filtrate was concentrated *in vacuo* to give an oily residue. The residue was partitioned between $Et_2O$ (30 ml) and distilled water (30 ml). The layers were separated and the organics were washed with water (2 x 30 ml), dried ($MgSO_4$) and concentrated *in vacuo* to afford a pale yellow oil (5.067 g). The product was purified by flash chromatography ($SiO_2$, graded 0-10 % $Et_2O$ : P.E. 40-60). The desired cyclopropane **182** was isolated as a mixture of diastereoisomers as a colourless oil (2.650 g, 14.55 mmol, 58 %); $\nu_{max}$ (thin film)/$cm^{-1}$ 2982w (C-H), 1703s (C=O), 1644 (C=C), 1383, 1313, 1266, 1224, 1121; $\delta_H$ (400 MHz; $CDCl_3$) 1.23-1.29 (6H, m, $CH_2C\underline{H}_3$ both diastereoisomers), 1.50 (1H, dd, *J* 4.5 and 9.0 Hz, 3-C(<u>H</u>)H), 1.82 (1H, dd, *J* 4.5 and 7.5 Hz, 3-C(H)<u>H</u>), 2.18 (3H, s, C<u>H</u>$_3$CO), 2.30 (3H, s, C<u>H</u>$_3$CO), 2.63 (1H, m, 2-C<u>H</u>), 3.04 (1H, m, 2-C<u>H</u>), 4.11-4.28 (4H, m, C<u>H</u>$_2$CH$_3$ both diastereoisomers), 4.98-5.29

(5H, m, 2 x C'$\underline{H}_2$=C'H both diastereoisomers and $CH_2$=C$\underline{H}$), 5.86-5.94 (1H, m, $CH_2$=C$\underline{H}$); $\delta_C$ (100 MHz; $CDCl_3$) 14.05, 14.41 ($\underline{C}H_3CH_2$), 20.06 (3-$\underline{C}H_2$), 30.26, 30.49 (2-$\underline{C}$H), 33.44 ($\underline{C}H_3CO$), 37.63, 42.64 (1-$\underline{C}$), 59.39, 61.47 ($CH_3\underline{C}H_2$), 116.48, 118.84 ($\underline{C}H_2$=CH), 132.80, 136.94 ($CH_2$=$\underline{C}$H), 167.45, 170.33, 200.88 ($\underline{C}$=O); *m/z* (EI) 182 ($M^+$, 11 %), 153, 137, 121, 109, 94, 83, 77, 66, 54, 43, (Found 182.0947, $C_{10}H_{14}O_3$ requires 182.0943).

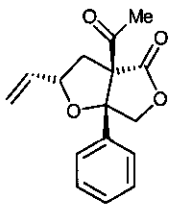
**1-Acetyl-2-vinyl-cyclopropanecarboxylic acid (183)**




To a stirred solution of 1-acetyl-2-vinylcyclopropanecarboxylic acid ethyl ester **182** (1.00 g, 5.49 mmol), THF (20 ml) and water (20 ml), LiOH (0.145 g, 6.04 mmol) was added and the reaction was stirred for 17 hours. The reaction mixture was then acidified to pH 1 with 1M HCl. The aqueous mixture was extracted with ether (2 x 30 ml) and the combined extracts were washed with brine (30 ml), dried ($MgSO_4$) and concentrated *in vacuo* to afford a colourless oily residue. The residue was then re-dissolved in ether and washed with $NaHCO_3$. The aqueous layer was acidified to pH 1, extracted with ethyl acetate (30 ml) and the organics washed with brine (30 ml), dried ($MgSO_4$) and concentrated *in vacuo* to afford a colourless oil as a mixture of diastereoisomers (0.44 g, 2.86 mmol, 52 %); $\nu_{max}$ (thin film)/$cm^{-1}$ 3583s (C-H str), 3019s (O-H br str), 1734s (C=O str); $\delta_H$ (400 MHz; $CDCl_3$) 1.70 (1H, dd, *J* 5.0 and 9.0 Hz, 3-C'($\underline{H}$)H), 1.80-1.83 (1H, dd, *J* 5.0 and 9.0 Hz, 3-C($\underline{H}$)H), 1.94-1.97 (2H, m, 3-C'(H)$\underline{H}$ and 3-C(H)$\underline{H}$), 2.32 (3H, s, $COC\underline{H}_3$), 2.37 (3H, s, $COC\underline{H}_3$), 2.65-2.70 (2H, m, 2-C'$\underline{H}$ and 2-C$\underline{H}$), 5.15-5.30 (5H, m, C'$\underline{H}_2$=C'H and $C\underline{H}_2$=CH and $CH_2$=C$\underline{H}$), 5.67 (1H, m, $C'H_2$=C'$\underline{H}$); $\delta_C$ (100 MHz; $CDCl_3$) 20.62 (3-$\underline{C}'H_2$), 24.26 (3-$\underline{C}H_2$), 28.63 (1-$\underline{C}$'), 31.00 (1-$\underline{C}$), 35.82 ($\underline{C}'H_3$), 37.30 ($\underline{C}H_3$), 42.71 (2-$\underline{C}$H), 43.13 (2-$\underline{C}$'H), 120.15 ($\underline{C}H_2$=CH), 120.52 ($\underline{C}'H_2$=C'H), 132.64 ($CH_2$=$\underline{C}$H), 132.76 ($C'H_2$=$\underline{C}$'H),

172.87 (<u>C</u>OCH$_3$), 177.22 (<u>C</u>OCH$_3$), 201.53 (<u>C</u>OOH), 201.93 (<u>C</u>OOH); *m/z* (EI) 154 ($M^+$, 5 %), 136, 121, 111, 94, 71, 66, (Found 154.0632, $C_8H_{10}O_3$ requires 154.0630).

**3a-Acetyl-6a-phenyl-2-vinyl-tetrahydro-furo[3,4-*b*]furan-4-one (184)**

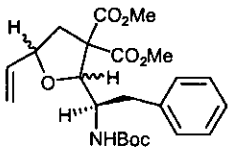



A solution of 1-acetyl-2-vinylcyclopropanecarboxylic acid **183** (0.154g, 1.00 mmol), 2-bromoacetophenone **170** (0.796 g, 4 mmol), anhydrous potassium carbonate (0.346 g, 2.5 mmol) and acetone (10 ml) was stirred at room temperature for 17 hours. The solvent was removed *in vacuo* to afford a yellow solid, which was partitioned between DCM (30 ml) and 1M HCl. The organic layer was washed with saturated $NaHCO_3$, dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow oil (0.832 g). The crude oil was purified by flash chromatography ($SiO_2$, DCM : P.E. 40-60; 2 : 8) to afford a yellow oil (0.252 g, 57 %). The desired cyclopropane, 1-acetyl-2-vinyl-cyclopropanecarboxylic acid 2-oxo-2-phenyl-ethyl ester, was isolated as a mixture of diastereoisomers and an unintractable mixture of starting material and product. The mixture was reacted without further purification.

1-Acetyl-2-vinyl-cyclopropanecarboxylic acid 2-oxo-2-phenyl-ethyl ester (0.057 g) was stirred with dry THF (2 ml) under nitrogen for 20 minutes before tetrakis(triphenylphosphine) palladium (0) (0.042 g, 0.02 mmol) was added. The yellow solution was stirred at 35 °C for 16 hours. The solvent was removed *in vacuo* and re-dissolved in EtOAc (5 ml) and the green solution was passed through a plug of silica to remove the palladium catalyst. The solvent was removed *in vacuo* to afford a green oil (0.072 g). The crude oil was purified by flash chromatography ($SiO_2$, DCM) followed by ($SiO_2$, $Et_2O$ : P.E. 40-60; 4 : 6) to afford the *trans* diastereoisomer as a yellow oil (0.031 g, 0.11 mmol, 54 %); $\nu_{max}$ (thin film)/$cm^{-1}$ 3387 (C-H w), 1696

(C=O), 1640 (C=C); $\delta_H$ (400 MHz; $CDCl_3$) 2.19 (3H, s, $COC\underline{H}_3$), 2.71 (1H, m, 5-C(H)H), 3.10 (1H, m, 5-C(H)H), 5.04 (1H, m, 6-C$\underline{H}$), 5.15-5.23 (2H, m, 2-C(H)H), 5.27 (2H, s, CH=C(H)H), 5.87 (1H, m, C$\underline{H}$=$CH_2$), 7.20-7.88 (5H, m, Ph-H); $\delta_C$ (100 MHz; $CDCl_3$) 14.71 ($\underline{C}H_3$), 35.75 (5-$\underline{C}H_2$), 65.74 (2-$\underline{C}H_2$), 83.43 (6-$\underline{C}$H), 101.30 (4a-$\underline{C}$), 117.37 ($\underline{C}H_2$=CH), 128.20, 129.03, 129.22, 134.17 (Ph-$\underline{C}$H), 134.17 ($CH_2$=$\underline{C}$H), 134.79 (Ph-$\underline{C}$), 169.84 ($\underline{C}$=O), 193.38 ($\underline{C}$=O); *m/z* (EI) 272 ($M^+$, 13 %), 229, 153, 137, 121, 105, 121, 77, 43, (Found 272,1047, $C_{16}H_{16}O_4$ requires 272.1049).

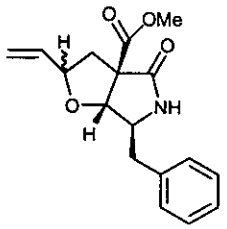
**2-(1-*tert*-Butoxycarbonylamino-2-phenyl-ethyl)-5-vinyl-dihydro-furan-3,3-dicarboxylic acid dimethyl ester (188)** (1 : 2; *trans* : *cis*)




To a stirred solution of 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** (0.184 g, 1.00 mmol) in anhydrous THF (5 ml) was added (S)-(-)-2-(*tert*-butoxycarbonylamino)-3-phenyl propanal **187** (0.249 g, 1.0 mmol) and zinc bromide (0.450 g, 2 mmol) at room temperature. This mixture was left to stir for 20 minutes under argon before a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.115 g, 0.10 mmol) was added. The resulting mixture was allowed to stir at room temperature for 17 hours. The solvent was then removed *in vacuo* and the residue dissolved in EtOAc (20 ml). The palladium catalyst was filtered off through a plug of silica, and the organic layer was washed with distilled water (2 x 20 ml). The organics were dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow oil (0.587 g). This crude material was purified by column chromatography ($SiO_2$, $Et_2O$ : hexane 2 : 3) followed by ($SiO_2$, DCM) to afford the desired furan **188** as a colourless oil (0.320 g, 0.74 mmol, 74 %); $\nu_{max}$ (thin film)/$cm^{-1}$ 3441br (N-H str), 2975 (C-H), 1734 (C=O ester str), 1716 (C=O amide); $\delta_H$ (400 MHz; $CDCl_3$) 1.36 (6H, s, 2 x $CC\underline{H}_3$), 1.37 (3H, s, $CC\underline{H}_3$), 1.90 (1H, dd, *J* 8.0 and 12.0 Hz, 4-C($\underline{H}$)H), 2.32 (1H, dd, *J* 8.0 and 12.0, 4-C'($\underline{H}$)H), 2.59 (1H, m, 4-C'(H)$\underline{H}$), 2.78-2.87 (2H, m, C'$\underline{H}_2$-Ph), 2.93-3.04 (3H, m, $C\underline{H}_2$-Ph and 4-C(H)$\underline{H}$), 3.57 (3H, s, $OC\underline{H}_3$), 3.64 (3H, s, OC'$\underline{H}_3$), 3.69 (3H, s, $OC\underline{H}_3$), 3.70 (3H, s, OC'$\underline{H}_3$), 4.22-4.34 (2H, m, 2-C'$\underline{H}$ and 5-C'$\underline{H}$), 4.38 (1H, s, N$\underline{H}$), 4.48 (1H, s, N'$\underline{H}$), 4.74-4.91 (2H, m, 2-C$\underline{H}$ and 5-C$\underline{H}$), 5.12-5.36 (4H, m, $C\underline{H}_2$=CH and C'$\underline{H}_2$=C'H), 5.76-5.84 (1H, m, $CH_2$=C$\underline{H}$), 5.96-6.04 (1H, m, $CH_2$=C$\underline{H}$), 7.26-7.29 (10H, m, Ph-$\underline{H}$); $\delta_C$ (100 MHz; $CDCl_3$) 28.33, 28.18 ($C(\underline{C}H_3)_3$), 40.41, 40.53, 40.89, 41.12 (Ph-$\underline{C}'H_2$ and Ph-$\underline{C}H_2$ and 4-$\underline{C}'H_2$ and 4-$\underline{C}H_2$), 51.05 (N$\underline{C}$H), 51.44 (N$\underline{C}$'H), 52.66, 52.93, 53.01, 53.19 ($O\underline{C}H_3$ and $O\underline{C}H_3$), 61.10, 61.62 (3-$\underline{C}$' and 3-$\underline{C}$), 78.67 (2-

C'H), 79.24 (2-C'H), 80.57 (5-CH), 81.65 (5-C'H), 115.68 ($CH_2$=CH), 117.77 ($C'H_2$=C'H), 126.32, 128.31, 128.45, 128.91, 129.35, 129.62 (Ph-CH), 137.91 ($C'H_2$=C'H), 137.91 ($CH_2$=CH), 137.93, 138.26 (*ipso*-C' and *ipso*-C), 154.99 (NHC'=O), 155.10 (NHC=O), 169.07, 169.55, 169.60, 170.89 (C=O); *m/z* (FAB) 434 ($MH^+$, 5 %), 400, 378, 334, 286, 242, 185, 153, 121, 91, 77, 57, (Found 434.2180, $C_{23}H_{32}NO_7$ requires 434.2179).

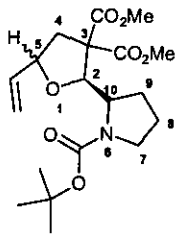
**6-Benzyl-4-oxo-2-vinyl-hexahydro-furo[2,3-*c*]pyrrole-3a-carboxylic acid methyl ester (189)** (1 : 2; *trans* : *cis*)




A solution containing furan 2-(1-*tert*-butoxycarbonylamino-2-phenyl-ethyl)-5-vinyl-dihydro-furan-3,3-dicarboxylic acid dimethyl ester **188** (0.100 g, 0.23 mmol), anisole (25 μl), trifluoroacetic acid (0.026 g, 0.23 mmol) and DCM (3 ml) was stirred for 17 hours at room temperature. Thin layer chromatography indicated that the furan had been de-protected. Saturated $NaHCO_3$ (3 ml) was added and the resulting solution was stirred for a further 17 hours at room temperature. The solvent was removed *in vacuo* and the residue was partitioned between saturated $NaHCO_3$ (20 ml) and EtOAc (2 x 20 ml). The organic phase was washed with $NaHCO_3$ (20 ml) followed by brine (20 ml), dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow oil. The yellow residue was purified by chromatography ($SiO_2$, $Et_2O$) to afford the desired lactam **189** as a pale yellow oil (0.059 g, 0.20 mmol, 85 %); $\nu_{max}$ (thin film)/$cm^{-1}$ 3238br (N-H w), 1746 (MeOC=O str), 1704 (NHC=O), 1435w, 1248w; $\delta_H$ (400 MHz; $CDCl_3$) 2.13 (1H, dd, *J* 8.5 and 13.0 Hz, 5-C'(H)H), 2.25 (1H, m, 5-C(H)H), 2.60 (1H, dd, *J* 7.5 and 13.0 Hz, 5-C(H)H), 2.75-2,84 (3H, m, 5-C'(H)H and Ph-C'$H_2$), 3.02-3.07 (2H,

m, Ph-C$\underline{H}_2$), 3.66 (3H, s, OC'$\underline{H}_3$), 3.66 (3H, s, OC$\underline{H}_3$), 3.96-4.00 (2H, m, 2-C'$\underline{H}$ and 2-C$\underline{H}$), 4.37-4.41 (3H, m, 1a-C'$\underline{H}$, 1a-C$\underline{H}$ and 6-C'$\underline{H}$), 4.68 (1H, m, 6-C$\underline{H}$), 5.13-5.30 (4H, m, C'$\underline{H}_2$=C'H and C$\underline{H}_2$=CH), 5.80-5.89 (2H, m, C'$\underline{H}$=C'$H_2$, C$\underline{H}$=$CH_2$), 6.29 (2H, s, N'$\underline{H}$), 6.39 (2H, s, N$\underline{H}$), 7.17-7.27 (10H, m, Ph-C$\underline{H}$); $\delta_C$ (100 MHz; $CDCl_3$) 35.29 (Ph$\underline{C}$'$H_2$), 35.51 (Ph$\underline{C}H_2$), 38.45 (5-$\underline{C}$'$H_2$), 38.53 (5-$\underline{C}H_2$), 53.13 (4a-O$\underline{C}$'$H_3$), 53.17 (4a-O$\underline{C}H_3$), 57.76 (2-$\underline{C}$'H), 59.55 (2-$\underline{C}$H), 64.46 (4a-$\underline{C}$'), 64.71 (4a-$\underline{C}$), 81.33 (6-$\underline{C}$'H), 81.76 (6-$\underline{C}$H), 81.97 (1a-$\underline{C}$H), 83.17 (1a-$\underline{C}$'H), 117.37 ($\underline{C}H_2$=CH), 117.33 ($\underline{C}$'$H_2$=C'H), 126.93, 128.85, 129.21 (Ph-$\underline{C}$H and Ph-$\underline{C}$'H), 136.58 ($CH_2$=$\underline{C}$H), 136.63 (C'$H_2$=$\underline{C}$'H), 137.59 (*ipso*-$\underline{C}$ and *ipso*-$\underline{C}$'), 168.90 ($\underline{C}$ONH), 169.33 ($\underline{C}$'ONH), 172.61 ($\underline{C}O_2$Me), 173.77 ($\underline{C}$'$O_2$Me); *m/z* (EI) 301 ($M^+$, 29 %), 270, 242, 210, 188, 178, 150, 135, 121, 91, (Found 301.1310, $C_{17}H_{19}NO_4$ requires 301.1310).

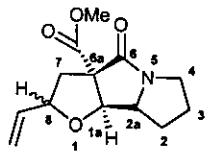
**2-(1-*tert*-Butoxycarbonyl-pyrrolidin-2-yl)-5-vinyl-dihydro-furan-3,3-dicarboxylic acid dimethyl ester (191)** (1 : 1.7; *trans* : *cis*)




To a stirred solution of 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** (0.924 g, 5.02 mmol) in anhydrous THF (20 ml) was added *N*-(tert-butoxycarbonyl)-*L*-prolinal **190** (0.50 g, 2.51 mmol) and zinc bromide (1.13 g, 5.02 mmol) at room temperature. This mixture was left to stir for 20 minutes under argon before a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.580 g, 0.50 mmol) was added. The resulting mixture was allowed to stir at room temperature for 17 hours. The solvent was removed *in vacuo* and the residue dissolved in EtOAc (50 ml).

The palladium catalyst was filtered off through a plug of silica, and the organic layer was washed with distilled water (2 x 50 ml). The organics were dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow oil (1.53 g). This crude material was purified by column chromatography ($SiO_2$, $Et_2O$ : P.E. 40-60; 4 : 6) followed by ($SiO_2$, $Et_2O$) to afford the desired furan **191** as a pale yellow oil (0.723 g, 1.89 mmol, 75 %); $\nu_{max}$ (thin film)/$cm^{-1}$ 2948w (C-H ), 1734s (C=O ester), 1681s (C=O amide); $\delta_H$ (400 MHz; $CDCl_3$) 1.38 (18H, s, $CH(C\underline{H}_3)_3$ and $C'H(C'\underline{H}_3)_3$), 1.61-1.66 (4H, m, 7-$C'\underline{H}_2$ and 7-$C\underline{H}_2$), 1.71-1.73 (4H, m, 8-$C'\underline{H}_2$ and 8-$C'\underline{H}_2$), 1.90 (1H, m, 4-$C(\underline{H})H$), 2.30 (1H, dd, J 5.9 and 13.4 Hz, 4-$C'(\underline{H})H$), 2.47 (1H, m, 4-$C'(H)\underline{H}$), 2.85 (1H, m, 4-$C(H)\underline{H}$), 3.25 (4H, m, 9-$C'\underline{H}_2$ and 9-$C\underline{H}_2$), 3.67 (3H, s, $OC\underline{H}_3$), 3.67 (3H, s, $OC'\underline{H}_3$), 3.70 (3H, s, $OC\underline{H}_3$), 3.71 (3H, s, $OC'\underline{H}_3$), 3.90 (1H, m, 10-$C'\underline{H}$), 4.01 (1H, m, 10-$C\underline{H}$), 4.11 (2H, m, 5-$C'\underline{H}$ and 5-$C\underline{H}$), 5.00-5.03 (2H, m, $C'(\underline{H})H$=C'H and $C(\underline{H})H$=CH), 5.09-5.13 (2H, m, C'(H)$\underline{H}$=C'H and C(H)$\underline{H}$=CH), 5.17-5.23 (2H, m 2-$C'\underline{H}$ and 2-$C\underline{H}$), 5.65 (1H, m $CH_2$=$C\underline{H}$), 5.83 (1H, m, $C'H_2$=$C'\underline{H}$); $\delta_C$ (100 MHz; $CDCl_3$) 24.27, 24.96 (8-$\underline{C}H_2$), 26.02, 27.88 (9-$\underline{C}H_2$), 28.53, 28.57 ($CH(\underline{C}H_3)_3$), 40.42, 40.77 (4-$\underline{C}H_2$ and 4-$\underline{C}'H_2$), 46.23, 46.71 (7-$\underline{C}H_2$ and 7-$\underline{C}H_2$), 52.77, 52.79, 52.88, 52.96 ($O\underline{C}H_3$), 53.07 (10-$\underline{C}H$), 62.16, 62.54 (3-$\underline{C}$), 78.46, 78.96 (2-$\underline{C}H$), 79.06, 82.71 ($\underline{C}H(\underline{C}H_3)_3$) 83.42, 82.83 (5-$\underline{C}H$), 115.66, 117.26 ($\underline{C}H_2$=CH), 136.30 ($CH_2$=$\underline{C}H$), 155.23 (NH$\underline{C}$=O), 169.54, 170.67 ($\underline{C}$=O); *m/z* (EI) 383 ($M^+$, 1 %), 327, 310, 252, 213, 170, 153, 114, 70, 57, (Found 383.1952, $C_{19}H_{29}O_7N$ requires 383.1945).

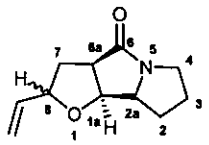
**7-Oxo-2-vinyl-hexahydro-3-oxa-6a-aza-cyclopenta[a]pentalene-7a-carboxylic acid methyl ester (192)** (1 : 9; *trans* : *cis*)




A solution containing furan **191** (0.710 g, 1.85 mmol), anisole (25 µl), trifluoroacetic acid (0.530 g, 4.63 mmol) and DCM (20 ml) was stirred for 17 hours at room temperature. Thin layer chromatography indicated that the furan had been de-protected. Saturated $NaHCO_3$ (6 ml) was added and the resulting solution was stirred for a further 17 hours at room temperature. The solvent was removed *in vacuo* and the residue was partitioned between $NaHCO_3$ (50 ml) and EtOAc (2 x 50 ml). The organic phase was washed with $NaHCO_3$ (50 ml) followed by brine (50 ml), dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow oil (0.511 g). The yellow residue was purified by chromatography ($SiO_2$, $Et_2O$) to afford the desired lactam **192** as a pale yellow oil (0.465 g, 1.85 mmol, 100 %); $\nu_{max}$ (thin film)/$cm^{-1}$ 2955 (C-H w), 1742 (C=O str), 1693 (NHC=O str), 1406w, 1251w, 1044w; $\delta_H$ (400 MHz; $CDCl_3$) 1.47-1.57 (2H, m, 2-C'$\underline{H}_2$), 1.95 (1H, m, 7-C'($\underline{H}$)H), 2.03-2.23 (6H, m, 3-C'$\underline{H}_2$ and 3-C$\underline{H}_2$ and 2-C$\underline{H}_2$), 2.45 (1H, m, 7-C($\underline{H}$)H), 2.76 (1H, dd *J* 4.0 and 8.0 Hz, 7-C(H)$\underline{H}$), 2.97 (1H, dd *J* 4.0 and 8.0 Hz, 7-C'(H)$\underline{H}$), 3.06-3.16 (2H, m, 4-C'$\underline{H}_2$), 3.56 (1H, m, 2a-C$\underline{H}$), 3.63-3.78 (9H, m, 2a-C'$\underline{H}$, OC'$\underline{H}_3$, OC$\underline{H}_3$, 4-C$\underline{H}_2$), 4.41-4.36 (2H, m, 8-C'$\underline{H}$), 4.57 (1H, s, 1a-C'$\underline{H}$), 4.74 (1H, s, 1a-C$\underline{H}$), 5.16-5.25 (2H, m, C($\underline{H}$)H=CH and C'($\underline{H}$)H=C'H), 5.29-5.37 (2H, m, C(H)$\underline{H}$=CH and C'(H)$\underline{H}$=C'H), 5.78-5.93 (2H, m, $CH_2$=C$\underline{H}$ and C'$H_2$=C'$\underline{H}$); $\delta_C$ (100 MHz; $CDCl_3$) 24.90 (3-C$\underline{H}_2$), 25.91 (3-C'$\underline{H}_2$), 28.41 (2-C'$\underline{H}_2$), 28.65 (2-C$\underline{H}_2$), 39.24 (7-C'$\underline{H}_2$), 39.34 (7-C$\underline{H}_2$), 42.48 (4-C'$\underline{H}_2$), 42.91 (4-C$\underline{H}_2$), 52.97 (OC$\underline{H}_3$), 53.15 (OC'$\underline{H}_3$), 64.27 (6a-C and 6a-C'), 67.07 (2a-C$\underline{H}$), 67.25 (2a-C'H), 80.09 (8-C'H), 80.72 (8-C$\underline{H}$), 81.65 (1a-C$\underline{H}$), 84.43 (1a-C'H), 117.77 (C$\underline{H}_2$=CH), 117.84 (C'$H_2$=C'H), 135.71 ($CH_2$=C$\underline{H}$), 136.18 (C'$H_2$=C'H), 170.33 (N-C=O), 170.55 (N-C'=O), 172.90 (C'=OMe), 173.20

(C'=OMe); *m/z* (EI) 251 ($M^+$, 24 %), 223, 208, 192, 182, 165, 150, 136, 122, 109, 94, 83, 70, (Found 251.1160, $C_{13}H_{17}O_4N$ requires 251.1158).

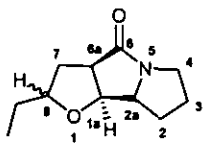
**2-Vinyl-octahydro-3-oxa-6a-aza-cyclopenta[a]pentalen-7-one (193)**



To a solution of 7-oxo-2-vinyl-hexahydro-3-oxa-6a-aza-cyclopenta[a]pentalene-7a-carboxylic acid methyl ester **192** (0.600 g, 2.39 mmol), in aqueous DMSO ($H_2O$ / 0.09 ml, 4.78 mmol in DMSO 50 ml) was added LiCl (0.152 g, 3.58 mmol). The resulting solution was heated under reflux conditions at 150°C for 48 hours. The resulting brown solution was partitioned between water (50 ml) and ethyl acetate (50 ml). The organics were washed with water (5 x 50 ml) to remove traces of DMSO, followed by brine (50 ml), dried ($MgSO_4$) and concentrated *in vacuo* to afford a brown oil (0.53 g). The brown residue was purified by chromatography ($SiO_2$, $Et_2O$) to afford the desired de-carboxylated lactam **193** as a brown oil (0.371 g, 1.92 mmol, 80 %); $\nu_{max}$ (thin film)/$cm^{-1}$ 2971 (C-H w), 1679 (NHC=O), 1396w, 1285w, 1111w; $\delta_H$ (400 MHz; $CDCl_3$) 1.15-1.28 (2H, m, 2-C'$\underline{H}_2$), 1.74-2.11 (7H, m, 2-C$\underline{H}_2$ and 3-C'$\underline{H}_2$ and 3-C$\underline{H}_2$ and 7-C'(<u>H</u>)H), 2.35 (1H, m, 7-C(<u>H</u>)H), 2.44-2.51 (2H, m, 6a-C'<u>H</u> and 6a-C<u>H</u>), 2.57 (1H, dd, *J* 4.0 and 8.0 Hz, 7-C(H)<u>H</u>), 3.03-3.10 (2H, m, 7-C'(H)<u>H</u>), 3.23-3.30 (2H, m, 4-C'$\underline{H}_2$), 3.62-3.79 (4H, m, 4-C$\underline{H}_2$ and 2a-C'<u>H</u> and 2a-C<u>H</u>), 4.35-4.41 (2H, m, 8-C'<u>H</u> and 8-C<u>H</u>), 4.45 (1H, dd, *J* 4.0 and 8.0 Hz, 1a-C'<u>H</u>), 4.60 (1H, dd, *J* 4.0 and 8.0 Hz, 1a-C<u>H</u>), 5.12-5.35 (4H, m, C'(<u>H</u>)<u>H</u>=C'H and C(<u>H</u>)<u>H</u>=CH), 5.75-5.94 (2H, m, C'$H_2$=C<u>H</u> and C'$H_2$=C<u>H</u>); $\delta_C$ (100 MHz; $CDCl_3$) 25.04 (3-<u>C</u>$H_2$), 25.30 (3-<u>C</u>'$H_2$), 29.04 (2-<u>C</u>'$H_2$), 29.24 (2-<u>C</u>$H_2$), 35.92 (7-<u>C</u>'$H_2$), 36.59 (7-<u>C</u>$H_2$), 41.92 (4-<u>C</u>'$H_2$), 42.19 (4-<u>C</u>$H_2$), 50.14 (6a-<u>C</u>'H), 50.37 (6a-<u>C</u>H), 68.38 (2a-<u>C</u>H), 69.65 (2a-<u>C</u>'H), 79.42 (8-<u>C</u>'H), 79.68 (8-<u>C</u>H), 80.89 (1a-<u>C</u>'H), 82.82 (1a-<u>C</u>H),

116.60 ($\underline{C}H_2$=CH), 117.32 ($\underline{C}'H_2$=C'H), 136.42 ($CH_2$=$\underline{C}$H), 137.12 (C'$H_2$=$\underline{C}$'H), 176.80 (N-$\underline{C}$=O), 177.00 (N-$\underline{C}$'=O); *m/z* (EI) 193 ($M^+$, 18 %), 165, 139, 124, 111, 96, 83, 70, 67, 55, (Found 193.1101 $C_{11}H_{15}NO_2$ requires 193.1103).

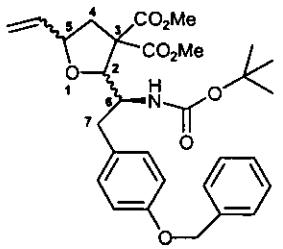
**2-Ethyl-octahydro-3-oxa-6a-aza-cyclopenta[*a*]pentalen-7-one (194)**



To a stirred solution of 2-vinyl-octahydro-3-oxa-6a-aza-cyclopenta[a]pentalen-7-one **193** (0.100 g, 0.518 mmol) in EtOAc (25 ml) was added palladium on carbon (0.006 g, 0.052 mmol). The reaction mixture was stirred under an atmosphere of hydrogen for 17 hours. The palladium was filtered off under suction and the residue was washed with EtOAC (3 x 50 ml) followed by DCM (50 ml). The combined organic phases were combined and concentrated *in vacuo* to afford the desired furan **194** as a colourless oil (0.096 g, 0.49 mmol, 95 %); $\nu_{max}$ (thin film)/$cm^{-1}$ 2961 (C-H w), 1685 (NHC=O), 1398w, 1212w, 1109w; $\delta_H$ (400 MHz; $CDCl_3$), 0.91 (3H, t, *J* 8.0 Hz, $C\underline{H}_3CH_2$), 0.96 (3H, t, *J* 8.0 Hz, C'$\underline{H}_3$C'$H_2$), 1.46-1.99 (7H, m, C'$H_3$C'$\underline{H}_2$ and $CH_3C\underline{H}_2$ and 2-C'$\underline{H}_2$ and 7-C'($\underline{H}$)H), 2.03-2.14 (6H, m, 3-C'$\underline{H}_2$ and 3-C$\underline{H}_2$ and 2-C$\underline{H}_2$), 2.27 (1H, m, 7-C($\underline{H}$)H), 2.36-2.43 (2H, m, 6a-C'$\underline{H}$ and 6a-C$\underline{H}$), 2.47 (1H, dd, *J* 4.0 and 8.0 Hz, 7-C'(H)$\underline{H}$), 3.00-3.09 (3H, m, 7-C'(H)$\underline{H}$ and 4-C'$\underline{H}_2$), 3.40-3.86 (6H, m, 2a-C'$\underline{H}$ and 2a-C$\underline{H}$, and 4-C$\underline{H}_2$ and 8-C$\underline{H}$ and 8-C'$\underline{H}$), 4.45 (1H, d. *J* 4.0 Hz, 1a-C'$\underline{H}$), 4.55 (1H, m, 1a-C$\underline{H}$); $\delta_C$ (100 MHz; $CDCl_3$) 10.14 ($\underline{C}H_3CH_2$), 10.14 ($\underline{C}'H_3C'H_2$), 25.05 (3-$\underline{C}H_2$), 25.29 (3-$\underline{C}'H_2$), 26.89 ($CH_3\underline{C}H_2$), 27.10 (C'$H_3\underline{C}'H_2$), 28.99 (2-$\underline{C}'H_2$), 29.31 (2-$\underline{C}H_2$), 35.15 (7-$\underline{C}'H_2$), 35.88 (7-$\underline{C}H_2$), 41.92 (4-$\underline{C}'H_2$), 42.18 (4-$\underline{C}H_2$), 50.13 (6a-$\underline{C}'$H), 52.80 (6a-$\underline{C}$H), 68.39 (2a-$\underline{C}$H), 69.74 (2a-$\underline{C}'$H), 79.45 (1a-$\underline{C}'$H), 79.88 (1a-$\underline{C}$H), 80.43 (8-$\underline{C}'$H), 81.50 (8-$\underline{C}$H), 177.38 (N-$\underline{C}$=O

and N-C'=O); *m/z* (EI) 195 ($M^+$, 13 %), 182, 166, 149, 136, 124, 111, 98, 83, 70, 55, 41, (Found 195.1262 $C_{11}H_{17}O_2N$ requires 195.1260).

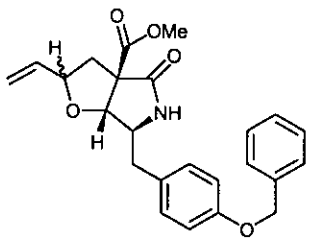
**2-[2-(4-Benzyloxy-phenyl)-1-*tert*-butoxycarbonylamino-ethyl]-5-vinyl-dihydro-furan-3,3-dicarboxylic acid dimethyl ester (196)** (1 : 3.3; *trans* : *cis* in THF) (1 : 8; *trans* : *cis* in $CH_3CN$)




To a stirred solution of 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** (0.184 g, 1.00 mmol) in anhydrous THF (5 ml) was added Boc-TYR (BZL)-aldehyde **195** (0.368 g, 1.00 mmol) and zinc bromide (0.450 g, 2.00 mmol) at room temperature. This mixture was left to stir for 20 minutes under argon before a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.115 g, 0.10 mmol) was added. The resulting mixture was allowed to stir at room temperature for 17 hours. The solvent was removed *in vacuo* and the residue dissolved in EtOAc (20 ml). The palladium catalyst was filtered off through a plug of silica, and the organic layer was washed with distilled water (2 x 20 ml). The organics were dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow oil (0.488 g). This crude material was purified by column chromatography twice ($SiO_2$, $Et_2O$ : hexane; 4 : 6) followed by ($SiO_2$, $Et_2O$ : hexane; 6 : 4) to afford the desired furan **196** as a yellow oil (0.362 g, 0.67 mmol, 67 %); $\nu_{max}$ (thin film)/$cm^{-1}$ 2948w (C-H ), 1735s (C=O ester); $\delta_H$ (400 MHz; $CDCl_3$) 1.36 (9H, s, C'H(C'$\underline{H}_3$)$_3$), 1.37 (9H, m, CH(C$\underline{H}_3$)$_3$), 1.87 (1H, m, 4-C($\underline{H}$)H), 2.34 (1H, m, 4-C'($\underline{H}$)H), 2.58 (1H, m, 4-C'(H)$\underline{H}$), 2.80-3.00 (5H, m, C(H)$\underline{H}$,

and C'$\underline{H}_2$-Ph and C$\underline{H}_2$-Ph), 3.56-3.63 (12H, m, 2 x OC'$\underline{H}_3$ and 2 x OC$\underline{H}_3$), 4.25 (4H, m, C'$\underline{H}$-C'$H_2$-Ph and C$\underline{H}$-C$H_2$-Ph and 5-C$\underline{H}$ and 5-C'$\underline{H}$), 4.25 (1H, s, N$\underline{H}$), 4.49 (1H, s, N'$\underline{H}$), 4.72-4.90 (2H, m, 2-C$\underline{H}$ and 2-C$\underline{H}$), 5.03 (4H, s, 2 x OC$\underline{H}_2$-Ph), 5.23-5.35 (4H, m, C'($\underline{H}$)$\underline{H}$=C'H and C($\underline{H}$)$\underline{H}$=CH), 5.75 (1H, m $CH_2$=C$\underline{H}$), 5.99 (1H, m, C'$H_2$=C'$\underline{H}$), 6.90-6.91 (4H, d, *J* 7 Hz, Ph-$\underline{H}$), 7.17-7.43 (14H, m, Ph-$\underline{H}$); $\delta_C$ (100 MHz; $CDCl_3$) 28.10, 28.35, 28.39 (C'H-($\underline{C}$'$H_3$)$_3$ and CH-($\underline{C}H_3$)$_3$), 40.19, 40.26 ($\underline{C}H_2$-Ph and $\underline{C}$'$H_2$-Ph), 40.43, 40.55 (4-$\underline{C}$'$H_2$ and 4-$\underline{C}H_2$), 51.09 ($\underline{C}$'H-C'$H_2$Ph), 51.52 ($\underline{C}$H-$CH_2$Ph), 52.62, 52.89, 52.97, 53.14 (4 x O$\underline{C}H_3$), 61.16, 61.71 (2 x 3-$\underline{C}$), 67.93 ($\underline{C}$H($CH_3$)$_3$), 69.99 (O$\underline{C}H_2$Ph and O$\underline{C}H_2$Ph), 78.62 (5-$\underline{C}$H), 79.19 (5-$\underline{C}$'H), 80.62 (2-$\underline{C}$H), 81.66 (2-$\underline{C}$'H), 114.72, 114.72 (Ph-$\underline{C}$H), 115.60 117.62 ($\underline{C}$'$H_2$=C'H and $\underline{C}H_2$=CH), 127.46, 127.86 128.54, 130.58, 130.62 (Ph-$\underline{C}$'H and Ph-$\underline{C}$H), 131.13, 137.28 (Ph-$\underline{C}$' and Ph-$\underline{C}$), 136.68 (C'$H_2$=$\underline{C}$'H), 138.32 ($CH_2$=$\underline{C}$H), 155.13, 157.45 (NH$\underline{C}$=O), 169.03, 169.54, 169.64, 170.91 (2 x $\underline{C}$=O and 2 x $\underline{C}$'=O); *m/z* (EI) 539 ($M^+$, 1 %), 466, 407, 342, 286, 242, 197, 178, 153, 121, 91, 57, (Found 539.2526 $C_{30}H_{37}NO_8$ requires 539.2519).

**1-(4-Benzyloxy-benzyl)-3-oxo-5-vinyl-hexahydro-cyclopenat[*c*]pyrrole-3a-carboxylic acid methyl ester (197)** (1 : 3; *trans* : *cis*)




A solution containing furan 2-[2-(4-benzyloxy-phenyl)-1-*tert*-butoxycarbonylamino-ethyl]-5-vinyl-dihydro-furan-3,3-dicarboxylic acid dimethyl ester **196** (0.135 g, 0.250 mmol), anisole (25 µl), trifluoroacetic acid (0.086 g, 0.75 mmol) and DCM (3 ml) was stirred for 17 hours at room temperature. Thin layer chromatography indicated that the furan had been de-protected. Saturated $NaHCO_3$ (6 ml) was added and the

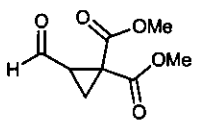
resulting solution was stirred for a further 17 hours at room temperature. The solvent was removed *in vacuo* and the residue was partitioned between saturated $NaHCO_3$ (20 ml) and EtOAc (2 x 20 ml). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow oil (0.250 g). The yellow residue was purified by chromatography ($SiO_2$, $Et_2O$ : hexane; 7 : 3) to afford the desired lactam **197** as a pale yellow oil (0.102 g, 0.250 mmol, 100 %); $\nu_{max}$ (thin film)/$cm^{-1}$ 2955 (C-H w), 1732 (MeOC=O str), 1708 (NHC=O), 1511, 1454, 1243w, 1026w; $\delta_H$ (400 MHz; $CDCl_3$) 2.20 (1H, dd, *J* 8.5 and 13.5 Hz, 5-C'(H)H), 2.34 (1H, m, 5-C(H)H), 2.78-2.89 (4H, m, 5-C'(H)H and 5-C(H)H and C'(H)H-Ph and C(H)H-Ph), 3.02-3.07 (2H, m, C(H)H-Ph and C(H)H-Ph), 3.74 (3H, s, C'$H_3$), 3.82 (3H, s, C$H_3$), 4.00-4.02 (2H, 1a-C'H and 1a-CH), 4.45-4.50 (5H, m, 2-C'H and 2-CH and 6-C'H), 4.65 (1H, m, 6-CH), 5.05 (4H, s, OC'$H_2$-Ph and OC$H_2$-Ph), 5.19-5.37 (4H, m, C'$H_2$=C'H and C$H_2$=CH), 5.87-6.00 (4H, m, C'$H_2$=C'H and $CH_2$=CH and 2 x NH), 6.92-7.44 (18H, m, 2 x Ph-H); $\delta_C$ (100 MHz; $CDCl_3$) 34.46 (5-C'$H_2$), 34.68 (5-C$H_2$), 38.47 (C$H_2$-Ph), 38.53 (C$H_2$-Ph), 53.13 (OC'$H_3$), 53.17 (OC$H_3$), 57.77 (2-C'H), 59.56 (2-CH), 64.45 (4a-C'), 64.71 (4a-C), 70.05 (2 x OC$H_2$Ph), 81.37 (1a-CH), 81.80 (1a-C'H), 82.01 (6-CH), 83.22 (6-C'H), 115.22 (Ph-C*H*), 115.30 (Ph-C'*H*), 117.41, 117.51 (C'$H_2$=C'H and C$H_2$=CH), 127.46, 128.03, 128.64, 129.75, 130.18 (Ph-CH), 136.55 (C'$H_2$=C'H), 136.61 ($CH_2$=CH), 136.95 (*ipso*-C' and *ipso*-C), 168.91 (NH-C=O), 169.34 (NH-C=O), 172.17 (C=O), 173.54 (C=O); *m/z* (EI) 407 ($M^+$, 10 %), 197, 178, 150, 107, 91, 57, (Found 407.1727 $C_{24}H_{25}NO_5$ requires 407.1733).

**1-(4-Benzyloxy-benzyl)-3-oxo-5-vinyl-hexahydro-cyclopenat[*c*]pyrrole-3a-carboxylic acid methyl ester (197)** (1 : 9; *trans* : *cis* with **196** in $CH_3CN$)

A solution containing furan 2-[2-(4-benzyloxy-phenyl)-1-*tert*-butoxycarbonylamino-ethyl]-5-vinyl-dihydro-furan-3,3-dicarboxylic acid dimethyl ester **196** (0.135 g, 0.250 mmol), anisole (25 µl), trifluoroacetic acid (0.086 g, 0.75 mmol) and DCM (3 ml) was stirred for 17 hours at room temperature. Thin layer chromatography indicated that the furan had been de-protected. Saturated $NaHCO_3$ (6 ml) was added and the

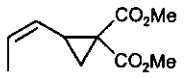
resulting solution was stirred for a further 17 hours at room temperature. The solvent was removed *in vacuo* and the residue was partitioned between saturated $NaHCO_3$ (20 ml) and EtOAc (2 x 20 ml). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow oil (0.488 g). The yellow residue was purified by chromatography ($SiO_2$, 70% $Et_2O$ in hexane) to afford the desired lactam **197** as the cis diastereoisomer as a pale yellow oil (0.102 g, 0.250 mmol, 100 %); $\nu_{max}$ (thin film)/$cm^{-1}$ 2955 (C-H w), 1732 (MeOC=O str), 1708 (NHC=O), 1511, 1454, 1243w, 1026w; $\delta_H$ (400 MHz; $CDCl_3$), 2.20 (1H, dd, *J* 8.5 and 13.5 Hz, 5-C'(H)H), 2.78-2.89 (2H, m, 5-C'(H)H and C'(H)H-Ph), 3.05 (1H, m,C'(H)H-Ph), 3.75 (3H, s, $C'H_3$), 4.01 (1H, 1a-C'H), 4.46-4.90 (2H, m, 2-C'H and 6-C'H), 5.07 (2H, s, $OC'H_2Ph$), 5.22 (1H, d *J* 10.5 Hz, C'(H)H=C'H), 5.33 (1H, m, C'(H)H=C'H), 5.51 (1H, s, NH), 5.90 (1H ,m, $C'H_2$=C'H), 6.92-7.44 (9H, m, Ph-H); $\delta_C$ (100 MHz; $CDCl_3$) 34.50 (5-$C'H_2$), 38.53 ($C'H_2Ph$), 53.11 ($OC'H_3$), 57.72 (2-C'H), 64.44 (4a-C'), 70.08 ($OCH_2Ph$), 81.78 (1a-C'H), 83.25 (6-C'H), 115.27 (Ph-C'H), 117.30, ($C'H_2$=C'H), 127.43, 127.99, 128.61, 129.77, 130.14 (Ph-C), 136.65 ($C'H_2$=C'H), 136.98 (*ipso*-C'), 169.34 (NH-C=O), 173.54 (C=O); *m/z* (EI) 407 ($M^+$, 10 %), 197, 178, 150, 107, 91, 57, (Found 407.1727 $C_{24}H_{25}NO_5$ requires 407.1733).

**2-Formyl-cyclopropane-1,1-dicarboxylic acid dimethyl ester (236)**



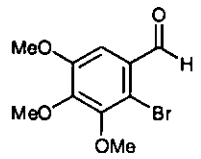

Oxygen was passed through a stirring solution of 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** (2.500 g, 13.58 mmol) in anhydrous DCM (30 ml). The colourless solution was cooled to –78°C. Ozone was bubbled through the resulting solution until a pale blue colour was observed. At this point oxygen was bubbled through the resulting blue solution for a further 10 minutes and the blue colour faded. Triphenylphosphine (3.560 g, 13.58 mmol) was added to the resulting colourless mixture, which was then left to stir at room temperature for 17 hours. The crude reaction mixture was concentrated *in vacuo* to afford a white solid. The crude mixture was purified by column chromatography ($SiO_2$, $Et_2O$ : P.E. 40-60; 1 : 1) to afford the desired cyclopropane **236** as a colourless oil (2.527 g, 13.58 mmol, quantitative yield); $\nu_{max}$ (thin film)/$cm^{-1}$ 2957w (C-H str), 1735s (C=O ester), 1715 (C=O aldehyde), 1438s, 1343s, 1271s, 1211s, 1133s; $\delta_H$ (400 MHz; $CDCl_3$) 1.83 (1H, dd, *J* 5.0 and 9.0 Hz, 3-C(H)H), 2.10 (1H, m, 3-C(H)H), 2.77 (1H, m, 2-CH), 3.77 (6H, s, 2 x $OCH_3$), 9.36 (1H, d, 4.0 Hz, CHO); $\delta_C$ (100 MHz; $CDCl_3$) 19.56 (3-$CH_2$), 34.76 (2-CH), 37.46 (1-C), 53.13, 53.30 (2 x $OCH_3$), 166.34, 168.30 (2 x C=O), 196.24 (CHO); *m/z* (EI) 185 (M-H, 2 %), 171, 155, 142, 126, 131, 98, 95, 68, 59, (Found 185.0448, $C_8H_9O_5$ requires 185.0450).

**2-Propenyl-cyclopropane-1,1-dicarboxylic acid dimethyl ester (234)** (1 : 4; *trans* : *cis*)



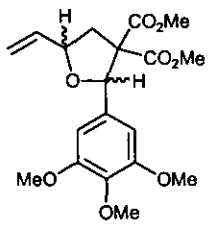

A stirred solution of (ethyl)triphenylphosphonium bromide (2.390 g, 6.44 mmol) in anhydrous $Et_2O$ (50 ml) under an atmosphere of nitrogen was treated with *n*-butyl lithium (2.6 ml of a 2.5M solution in hexanes, 2.58 mmol) at 0°C. The resulting orange solution was stirred under nitrogen for 10 minutes before the addition of 2-formyl-cyclopropane-1,1-dicarboxylic acid dimethyl ester **236** (1.000 g, 5.37 mmol) in anhydrous $Et_2O$ (20 ml) occurred. On addition of the aldehyde **236**, a white precipitate formed in solution and the mixture was stirred for a further 17 hours. The white precipitate was filtered and washed with $Et_2O$ (2 x 20 ml). The combined filtrate and $Et_2O$ washings were concentrated *in vacuo* to afford a crude oil, which was purified by column chromatography ($SiO_2$, $Et_2O$) to afford the desired cyclopropane **234** as a colourless oil (0.550 g, 2.78 mmol, 52 %); $\nu_{max}$ (thin film)/$cm^{-1}$ 2953s (C=C-H), 1728s (C=O ester), 1437s, 1329s, 1277s, 1212s, 1130s; $\delta_H$ (400 MHz; $CDCl_3$) 1.43-1.50 (3H, m, C<u>H</u>$_3$ *trans*), 1.54-1.65 (5H, m, C<u>H</u>$_3$ *cis* and 3-C(<u>H</u>)*H trans*), 1.71-1.74 (2H, m, 3-C(<u>H</u>)<u>H</u> *cis*), 2.48 (1H, m, 2-C<u>H</u> *trans*), 2.71-2.74 (1H, m, 2-C<u>H</u> *cis*), 3.70 (6H, s, 2 x OC<u>H</u>$_3$ *trans*), 3.72 (6H, s, 2 x OC<u>H</u>$_3$ *cis*), 4.90 (1H, m, CH=C<u>H</u>-CH$_3$ *cis*), 5.07 (1H, m, CH=C<u>H</u>-CH$_3$ *trans*), 5.61-5.65 (2H, m, C<u>H</u>-CH-CH$_3$ *cis* and *trans*); $\delta_C$ (100 MHz; $CDCl_3$) 13.38 (<u>C</u>H$_3$ *cis*), 17.91 (<u>C</u>H$_3$ *trans*), 20.68 (3-<u>C</u>H$_2$ *trans*), 21.76 (3-<u>C</u>H$_2$ *cis*), 26.88 (2-<u>C</u>H *cis*), 31.42 (2-<u>C</u>H *trans*), 35.41 (1-<u>C</u> *trans*), 35.46 (1-<u>C</u> *cis*), 52.44, 52.58 (2 x O<u>C</u>H$_3$ *trans*), 52.46, 52.66 (2 x O<u>C</u>H$_3$ *cis*), 125.11 (CH=<u>C</u>H-CH$_3$ *cis*), 125.40 (CH=<u>C</u>H-CH$_3$ *trans*), 130.07 (<u>C</u>H=CH-CH$_3$ *cis*), 132.78 (<u>C</u>H=CH-CH$_3$ *trans*),167.395, 168.06, 170.17, 170.27 (*C*=O); m/z (EI) 198 ($M^+$, 14 %), 166, 138, 107, 85, 79, 67, 59, (Found 198.0891, $C_{10}H_{14}O_4$ requires 198.0892).

**2-Bromo-3,4,5-trimethoxy-benzaldehyde[96] (233)**




To a 500 ml round bottomed flask was added 3,4,5-trimethoxybenzaldehyde **235** (7.000 g, 35.70 mmol), anhydrous DCM (150 ml) and acetic acid (0.2 ml). The flask was cooled to 0°C in an ice bath. Bromine (1.84 ml, 35.70 mmol) was dissolved in anhydrous DCM (10 ml) and was added dropwise *via* an addition funnel over 15 minutes. The orange mixture was left to stir at 0°C for 1 hour. Aqueous $Na_2S_2O_3$ was added (100 ml) and the mixture was extracted with DCM (3 x 100 ml). The combined organics were washed successively with saturated aqueous $NaHCO_3$ (3 x 100 ml), brine (100 ml) and dried ($Na_2SO_4$). The pale yellow solution was concentrated *in vacuo* to afford a pale yellow solid (8.55 g). The solid was recrystallized (EtOAc-Hexane) and the filtrate was purified further by column chromatography ($SiO_2$, $Et_2O$ : P.E. 40-60; 1 : 1) to afford the desired 2-bromo-3,4,5-trimethoxy-benzaldehyde **233** as colourless needles (7.281 g, 26.57 mmol, 74 %), m.p. 67-68°C (Lit. mp[96] 67.5-69.2 °C); $\nu_{max}$ (thin film)/$cm^{-1}$ 2939, 2959 (C-H w), 1686 (C=O str), 1686 (C=O str); $\delta_H$ (400 MHz, $CDCl_3$) 3.84 (3H, s, $OC\underline{H}_3$), 3.85 (3H, s, $OC\underline{H}_3$), 3.92 (3H, s, $OC\underline{H}_3$), 7.24 (1H, s, Ph-$\underline{H}$), 10.22 (1H, s, $C\underline{H}O$); $\delta_C$ (100 MHz, $CDCl_3$) 56.25 ($O\underline{C}H_3$), 61.03 ($O\underline{C}H_3$), 61.25 ($O\underline{C}H_3$), 107.51 (Ph-$\underline{C}H$), 115.61 (Ph-$\underline{C}$), 128.84 (Ph-$\underline{C}$), 148.74, 150.81, 153.05 (Ph-$\underline{C}$), 191.03 ($\underline{C}HO$); *m/z* (EI) 274, 276 ($M^+$, 100 %, 96 %), 259, 233, 203, 188, 165, 124, 109, 93, 77, (Found 273.9841, $C_{10}H_{11}O_4{}^{79}Br_2$ requires 273.9840).

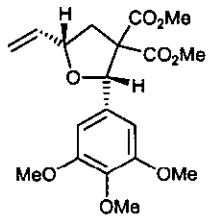
**2-(3,4,5-Trimethoxy-phenyl)-5-vinyl-dihydro-furan-3,3-dicarboxylic acid dimethyl ester (237)** (1: 3; *trans* : *cis* in THF with $ZnBr_2$, yield 75 %), (1 : 2; *trans* : *cis* in MeOH, no $ZnBr_2$, yield 40 %).




To a stirred solution of 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** (0.184 g, 1.00 mmol) in anhydrous MeOH (5 ml) was added 3,4,5-trimethoxybenzaldehyde **235** (0.199 g, 1.00 mmol) and zinc bromide (0.450 g, 2.00 mmol) at room temperature. This mixture was left to stir for 10 minutes under nitrogen before a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.115 g, 0.10 mmol) was added. The resulting mixture was allowed to stir at room temperature for 17 hours. The solvent was removed *in vacuo* and the residue dissolved in EtOAc (20 ml). The palladium catalyst was filtered through a plug of silica, and the organic layer was washed with distilled water (2 x 30 ml). The organics were dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow solid (0.310 g). This crude material was purified by column chromatography ($SiO_2$, gradient elution $Et_2O$ : P.E. 40-60; 0-4 : 6) to afford the desired furan **237** as a white solid (0.285 g, 0.75 mmol, 75 %), m.p. 121-126°C; $\nu_{max}$ (thin film)$cm^{-1}$ 2995, 2950, 2839 (C-H str), 1731s (C=O str); $\delta_H$ (400 MHz; $CDCl_3$) 2.18 (1H, dd, *J* 7.0 and 13.0 Hz, 4-C(H)H), 2.50 (1H, dd, *J* 6.0 and 13.5 Hz, 4-C'(H)H), 2.76 (1H, m, 4-C'(H)H), 3.03 (1H, m, 4-C(H)H), 3.23 (3H, s, OC'$H_3$), 3.27 (3H, s, O$CH_3$), 3.77 (3H,s, O$CH_3$), 3.81-3.86 (21H, m, OC'$H_3$ and PhOC'$H_3$ and PhO$CH_3$), 4.41 (1H, m, 5-C'H), 5.09 (1H, m, 5-CH), 5.18-5.44 (4H, m, $CH_2$=CH and C'$H_2$=CH), 5.60 (1H, s, 2-C'H), 5.67 (1H, s, 2-CH), 5.90 (1H, m, $CH_2$=CH), 6.10 (1H, m, C'$H_2$=C'H), 6.64 (2H, s, Ph'-H), 6.69 (2H, s, Ph-H); $\delta_C$ (100 MHz; $CDCl_3$) 40.22 (4-C'$H_2$), 40.52 (4-$CH_2$), 52.34, 52.39, 52.78,

52.97 (O<u>C</u>'$H_3$ and O<u>C</u>$H_3$), 56.10 (PhO<u>C</u>$H_3$ and PhO<u>C</u>'$H_3$), 66.03 (3-<u>C</u> and 3-<u>C</u>'), 79.12 (5-<u>C</u>'H), 79.64 (5-<u>C</u>H), 83.33 (2-<u>C</u>H), 84.21 (2-<u>C</u>'H), 103.59 (Ph-<u>C</u>H), 104.10 (Ph-<u>C</u>'H), 116.00 (<u>C</u>$H_2$=CH), 117.60 (<u>C</u>'$H_2$=C'H), 133.33, 133.64, 137.71, 138.14 (Ph-<u>C</u> and Ph-<u>C</u>'), 136.48 (C'$H_2$=<u>C</u>'H), 137.71 ($CH_2$=<u>C</u>H), 152.74, 152.80 (ipso-<u>C</u> and ipso-<u>C</u>'), 168.95, 169.18, 170.33, 171.15 (2 x <u>C</u>=O and 2 x <u>C</u>'=O); *m/z* (EI) 380 ($M^+$, 63 %), 349, 294, 220, 205, 196, 181, 152, 125, 57, (Found 380.1473, $C_{19}H_{24}O_8$ requires 380.1471).

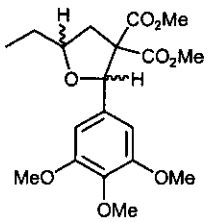
**2-(3,4,5-Trimethoxy-phenyl)-5-vinyl-dihydro-furan-3,3-dicarboxylic acid dimethyl ester (237)** (*cis* isomer, MeOH with $ZnBr_2$)




For the method previously described, the *cis* diastereoisomer was isolated exclusively after column ($SiO_2$, gradient elution $Et_2O$ : P.E. 40-60; 0-4 : 6) followed by ($SiO_2$, $Et_2O$ : P.E. 40-60; 1 : 9) and then ($SiO_2$ $Et_2O$) to afford the desired furan **237** as the *cis* diastereoisomer exclusively (0.278 g, 0.73 mmol, 73 %); $\nu_{max}$ (thin film)$cm^{-1}$ 2995, 2950, 2839 (C-H str), 1731s (C=O str); $\delta_H$ (400 MHz; $CDCl_3$) 2.52 (1H, dd, *J* 6.0 and 13.5 Hz, 4-C'(<u>H</u>)H), 2.78 (1H, m, 4-C'(H)<u>H</u>), 3.25 (3H, s, OC'<u>H</u>$_3$), 3.83-3.86 (6H, s, PhOC'<u>H</u>$_3$), 3.87-3.88 (6H, m, OC'<u>H</u>$_3$ and PhOC'<u>H</u>$_3$), 4.42 (1H, m, 5-C'<u>H</u>), 5.31 (1H, m, C'(<u>H</u>)H=C'H), 5.50 (1H, d, *J* 14.5 Hz, C'(H)<u>H</u>=C'H), 5.62 (1H, s, 2-C'<u>H</u>), 6.08-6.17 (1H, m, C'$H_2$=C'<u>H</u>), 6.66 (2H, s, Ph'-<u>H</u>); $\delta_C$ (100 MHz; $CDCl_3$) 40.25 (4-<u>C</u>'$H_2$), 52.40, 52.97 (O<u>C</u>'$H_3$), 56.10 (PhO<u>C</u>'$H_3$), 66.06 (3-<u>C</u>'), 79.12 (5-<u>C</u>'H), 84.24 (2-<u>C</u>'H), 104.15, 104.80 (Ph-<u>C</u>'H), 117.60 (<u>C</u>'$H_2$=C'H), 133.33, 137.72, (Ph-<u>C</u>'), 136.50 (C'$H_2$=<u>C</u>'H), 152.76, (ipso-<u>C</u>'), 168.96, 171.17 (2 x <u>C</u>'=O); *m/z* (EI)

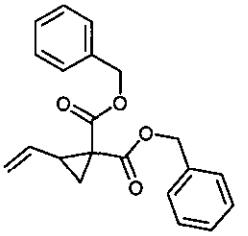
380 ($M^+$, 63 %), 349, 294, 220, 205, 196, 181, 152, 125, 57, (Found 380.1473, $C_{19}H_{24}O_8$ requires 380.1471).

**5-Ethyl-2-(3,4,5-trimethoxy-phenyl)-dihydro-furan-3,3-dicarboxylic acid dimethyl ester (238)**



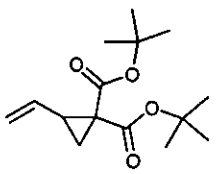

A solution of the furan **237** (0.190 g, 0.50 mmol) was stirred with 10 % palladium on carbon in EtOAc (30 ml) in an atmosphere of hydrogen for 17 hours at room temperature. The catalyst was filtered off through a pad of celite and washed with EtOAc (2 x 30 ml) and DCM (30 ml). The filtrate was concentrated *in vacuo* to afford a colourless crude oil. The crude material was purified by column chromatography ($SiO_2$, $Et_2O$ : P.E. 40-60; 1 : 9) to afford the desired compound **238** as a white solid (0.189 g, 0.49 mmol, 98 %), mp 125-128°C; $\nu_{max}$ (thin film)$cm^{-1}$ 2953 (C-H str), 1731s (C=O str), 1592, 1457, 1236, 1127; $\delta_H$ (400 MHz; $CDCl_3$) 0.90-1.01 (6H, m, C'$\underline{H}_3$ and C$\underline{H}_3$), 1.60-1.91 (5H, m, C'$\underline{H}_2$C'$H_3$ and C$\underline{H}_2$C$H_3$ and 4-C(\underline{H})H), 2.32 (1H, dd, *J* 6.0 and 13.0 Hz, 4-C'(\underline{H})H), 2.55 (1H, m, 4-C'(H)\underline{H}), 2.87 (1H, m, 4-C(H)\underline{H}), 3.13 (3H, s, OC'$\underline{H}_3$), 3.19 (3H, s, OC$\underline{H}_3$), 3.68-3.87 (25H, m, OC'$\underline{H}_3$ and OC$\underline{H}_3$ and PhOC'$\underline{H}_3$ and PhOC$\underline{H}_3$ and 5-C'\underline{H}), 4.46 (1H, m, 5-C\underline{H}), 5.47 (1H, s, 2-C'\underline{H}), 5.53 (1H, s, 2-C\underline{H}), 6.57 (2H, s, Ph'-\underline{H}), 6.61 (2H, s, Ph-\underline{H}); $\delta_C$ (100 MHz; $CDCl_3$) 10.02 (\underline{C}$H_3$), 10.25 (\underline{C}'$H_3$), 27.30 (\underline{C}'$H_2$), 28.95 (\underline{C}$H_2$), 39.88 (4-\underline{C}'$H_2$), 40.48 (4-\underline{C}$H_2$), 52.29, 52.36, 52.75, 52.89 (O\underline{C}'$H_3$ and O\underline{C}$H_3$), 56.11 (PhO\underline{C}$H_3$ and PhO\underline{C}'$H_3$), 66.00, 66.16 (3\underline{C} and 3'\underline{C}), 79.60 (5-\underline{C}'H), 80.57 (5-\underline{C}H), 82.93 (2-\underline{C}H), 84.27 (2-\underline{C}'H), 103.57 (Ph-\underline{C}H), 104.10 (Ph-\underline{C}'H), 132.44, 133.59, 137.63 (Ph-\underline{C} and Ph-\underline{C}'), 152.74, 152.80 (ipso-\underline{C} and ipso-\underline{C}'), 169.36, 171.52 (2 x \underline{C}=O and 2 x \underline{C}'=O); *m/z* (EI) 382 ($M^+$, 100 %), 291, 277, 262, 196, 122, 113, 77, (Found 382.1627, $C_{19}H_{26}O_8$ requires 382.1628).

**2-Vinyl-cyclopropane-1,1-dicarboxylic acid dibenzyl ester (243)**



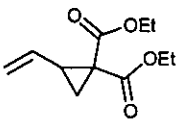
Sodium hydride (1.410 g, 35.20 mmol) was charged to a dry flask and washed successively with P.E. 40-60 (2 x 30 ml) followed by anhydrous THF (30 ml). To a stirred solution of sodium hydride (1.410 g, 35.20 mmol) in anhydrous THF (40 ml) was added dibenzylmalonate **240** (5.000 g, 17.60 mmol) at 0 °C. The resulting solution was stirred under nitrogen for a further 15 minutes followed by the addition of 1,4 dibromobut-2-ene **121** (3.760 g, 17.60 mmol) in anhydrous THF (20 ml). The resulting cream mixture was refluxed for 6 hours and then stirred at room temperature for 17 hours. The crude white suspension was partitioned with 1M HCl (50 ml) and the organic layer separated and washed with water (2 x 50 ml), dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude oil (5.620 g). This crude material was purified by column chromatography ($SiO_2$, $Et_2O$ : P.E. 40-60; 6 : 4) to afford the desired cyclopropane **243** as a colourless oil (4.320 g, 12.85 mmol, 73 %); $\nu_{max}$ (thin film)/$cm^{-1}$ 3032w (C-H str), 1751s (C=O str), 1455s, 1379s, 1268s, 1190s, 1126s; $\delta_H$ (400 MHz; $CDCl_3$) 1.64 (1H, dd, *J* 5.0 and 9.0 Hz, 3-C(H)H), 1.80 (1H, dd, J 5.0 and 7.5 Hz, 3-C(H)H), 2.67 (1H, m, 2-CH), 5.12-5.25 (5H, 2 x $CH_2$-Ph and C(H)H=CH), 5.27 (1H, d, *J* 12.0 Hz, C(H)H=CH), 5.37 (1H, m, $CH_2$=CH), 7.33-7.37 (10H, m, Ph-H); $\delta_C$ (100 MHz; $CDCl_3$) 20.82 (3-$CH_2$), 31.73 (2-CH), 35.97 (1-C), 67.36, 67.43 ($CH_2$-Ph), 118.86 ($CH_2$=CH), 128.07, 128.27, 128.29, 128.34, 128.48, 128.57 (Ph-CH), 132.86 ($CH_2$=CH), 135.44, 135.40 (ipso-C), 167.23, 169.44 (2 x $CO_2$Ph); *m/z* (EI) 336 ($M^+$, 2 %), 245, 201, 181, 139, 121, 91, 77, 65, (Found 336.1367, $C_{21}H_{20}O_4$ requires 336.1362).

**2-Vinyl-cyclopropane-1,1-dicarboxylic acid di-*tert*-butyl ester (244)**



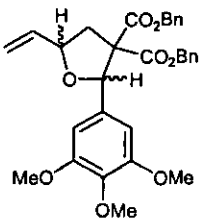
Sodium hydride (1.850 g, 46.20 mmol) was charged to a dry flask and washed successively with P.E. 40-60 (2 x 30 ml) followed by anhydrous THF (30 ml). To a stirred solution of sodium hydride (1.850 g, 46.20 mmol) in anhydrous THF (40 ml) was added di-tert-butylmalonate **241** (5.000 g, 23.12 mmol) at 0°C. The resulting solution was stirred under nitrogen for a further 15 minutes followed by the addition of 1,4 dibromobut-2-ene **121** (4.95 g, 23.12 mmol) in anhydrous THF (20 ml). The resulting cream mixture was refluxed for 6 hours and then stirred at room temperature for 17 hours. The crude white suspension was partitioned with 1M HCl (50 ml) and the organic layer separated and washed with water (2 x 50 ml), dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude oil which was purified by column chromatography twice ($SiO_2$, $Et_2O$ : P.E. 40-60; 6 : 4) followed by ($SiO_2$, DCM) to afford the desired cyclopropane **244** as a white solid (4.22 g, 15.74 mmol, 68 %), m.p. 110-113°C; $\nu_{max}$ (thin film)/$cm^{-1}$ 2977w (C-H str), 1719s (C=O str), 1477, 1367s, 1331s, 1283s, 1171s; $\delta_H$ (400 MHz; $CDCl_3$) 1.39 (1H, dd, *J* 4.5 and 9.0 Hz, 3-C(H)H), 1.47 (9H, s, $C(CH_3)_3$), 1.49 (9H, s, $C(CH_3)_3$), 1.55 (1H, dd, *J* 4.5 and 7.5 Hz, 3-C(H)H), 2.44-2.51 (1H, m, 2-CH), 5.12 (1H, dd, *J* 1.0 and 10.0 Hz, C(H)H=CH), 5.29 (1H, dd, *J* 1.0 and 17.0 Hz, C(H)H=CH), 5.31-5.39 (1H, m, $CH_2$=CH); $\delta_C$ (100 MHz; $CDCl_3$) 19.69 (3-$CH_2$), 28.00, 28.02 ($C(CH_3)_3$), 29.93 (2-CH), 37.62 (1-C), 81.25, 81.70 ($C(CH_3)_3$), 117.73 ($CH_2$=CH), 133.58 ($CH_2$=CH), 166.84, 169.09 (2 x C=O); *m/z* (FAB) 269 ($MH^+$, 5 %), 213, 157, 139, 121, 107, 89, 77, 65, 57, 41, (Found 269.1757, $C_{15}H_{27}O_4$ requires 269.1753).

**2-Vinylcyclopropane-1,1-dicarboxylic acid diethyl ester[67] (245)**



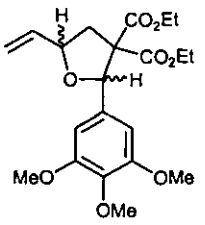

Sodium hydride (2.497 g, 62.40 mmol) was charged to a dry flask and washed successively with P.E. 40-60 (2 x 30 ml) followed by anhydrous THF (30 ml). To a stirred solution of sodium hydride (2.497 g, 62.40 mmol) in anhydrous THF (40 ml) was added diethylmalonate **242** (5.000 g, 31.22 mmol) at 0 °C. The resulting solution was stirred under nitrogen for a further 15 minutes followed by the addition of 1,4 dibromobut-2-ene **121** (6.670 g, 31.22 mmol) in anhydrous THF (20 ml). The resulting cream mixture was refluxed for 6 hours and then stirred at room temperature for 17 hours. The crude white suspension was partitioned with 1M HCl (50 ml) and the organic layer separated and washed with water (2 x 50 ml), dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude yellow oil which was purified by column chromatography ($SiO_2$, $Et_2O$ : P.E. 40-60; 1 : 9) to afford the desired cyclopropane **245** as a colourless oil (4.966 g, 23.41 mmol, 75 %); $\nu_{max}$ (thin film)/$cm^{-1}$ 2982w (C-H str), 1725s (C=O str), 1638, 1445, 1370, 1319s, 1270s, 1202s, 1131s; $\delta_H$ (400 MHz; $CDCl_3$) 1.24-1.28 (6H, m, 2 x $CH_2C\underline{H}_3$), 1.54 (1H, dd, *J* 5.0 and 9.0 Hz, 3-C(H)H), 1.68 (1H, dd, *J* 5.0 and 9.0 Hz, 3-C(H)H), 2.56 (1H, m, 2-C$\underline{H}$), 4.13-4.25 (4H, m, 2 x $C\underline{H}_2CH_3$), 5.13 (1H, d, *J* 8.5 Hz, C(H)H=CH), 5.28 (1H, d, *J* 18 Hz, C(H)H=CH), 5.40 (1H, m, $CH_2$=C$\underline{H}$); $\delta_C$ (100 MHz; $CDCl_3$) 14.15, 14.27 (2 x $\underline{C}H_3$), 20.28 (3-$\underline{C}H_2$), 31.02 (2-$\underline{C}$H), 35.89 (1-$\underline{C}$), 61.38, 61.55 (2 x $\underline{C}H_2$), 118.36 ($\underline{C}H_2$=CH), 133.14 ($CH_2$=$\underline{C}$H), 167.35, 169.60 (2 x $\underline{C}$=O); *m/z* (EI) 212 ($MH^+$, 35 %), 184, 166, 139, 121, 110, 99, 94, 85, 79, 66, 57, 41, (Found 212.1050, $C_{11}H_{16}O_4$ requires 212.1049).

**2-(3,4,5-Trimethoxy-phenyl)-5-vinyl-dihydro-furan-3,3-dicarboxylic acid dibenzyl ester (246)** (1 : 1; *trans* : *cis* in DMF, yield 25%), (1 : 2: *trans* : *cis* in DMSO, yield 50%), (1 : 1 *trans* : *cis* in $CH_3CN$, yield 36 %), (1 : 3 *trans* : *cis* in DCM, yield 71 %)




To a stirred solution of cyclopropane **243** (0.336 g, 1.00 mmol) in anhydrous DCM (5 ml) was added 3,4,5-trimethoxybenzaldehyde **235** (0.196 g, 1.00 mmol) and zinc bromide (0.450 g, 2.00 mmol) at room temperature. This mixture was left to stir for 10 minutes under nitrogen before a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.115 g, 0.10 mmol) was added. The resulting mixture was heated under reflux for 17 hours. The solvent was then removed *in vacuo* and the residue dissolved in EtOAc (20 ml). The palladium catalyst was filtered through a plug of silica, and the organic layer was washed with distilled water (2 x 30 ml). The organics were dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow solid (0.560 g). This crude material was purified by column chromatography ($SiO_2$, $Et_2O$ : P.E. 40-60; 6 : 4) followed by ($SiO_2$, $Et_2O$ : P.E. 40-60; graded 0-2 : 8) to afford desired furan **246** as a white solid (0.351 g, 0.71 mmol, 66 %), m.p. 137-139°C; $\nu_{max}$ (thin film)$cm^{-1}$ 2937 (C-H str), 1729s (C=O str), 1456, 1265, 1127; $\delta_H$ (400 MHz; $CDCl_3$) 2.48 (1H, dd, *J* 6.0 and 13.5 Hz, 4-C'(H)H), 2.74 (1H, m, 4-C'(H)H), 3.63 (6H, s, PhOC'$H_3$), 3.69 (3H, m, PhOC'$H_3$), 4.41 (1H, m, 5-C'H), 5.11 (4H, s, 2 x C'$H_2$-Ph), 5.19-5.35 (2H, m, C'(H)H=C'H), 5.50 (1H, s, 2-C'H), 6.02 (1H, m, C'$H_2$=C'H), 6.55 (2H, s, Ph-H), 7.16-7.24 (10H, m, OPh'H); $\delta_C$ (100 MHz; $CDCl_3$) 40.66 (4-C'$H_2$), 55.76, 55.96, 60.78 (Ph-OC'$H_3$), 66.15 (3-C'), 67.59, 67.79 (PhO-$CH_2$), 79.16 (5-C'H), 84.21 (2-C'H), 103.60, 104.10 (Ph-C'H), 117.77 (C'$H_2$=C'H), 127.69, 128.26, 128.31, 128.38, 128.52, 128.58, 128.62 (Ph-C'H), 133.16, 134.57, 135.02, (Ph-C'), 136.42 (C'$H_2$=C'H), 152.76 (ipso-C'), 168.45, 170.54 (2 x C'=O); *m/z* (EI) 532 ($M^+$, 14 %), 370, 286, 196, 139, 91, (Found 532.2103, $C_{31}H_{32}O_8$ requires 532.2097).

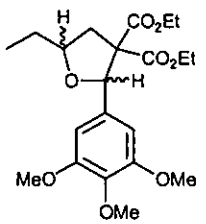
**2-(3,4,5-Trimethoxy-phenyl)-5-vinyl-dihydro-furan-3,3-dicarboxylic acid diethyl ester (247)**




To a stirred solution of 2-vinylcyclopropane-1,1-dicarboxylic acid diethyl ester **245** (0.184 g, 1.00 mmol) in anhydrous DCM (5 ml) was added 3,4,5-trimethoxybenzaldehyde **235** (0.199 g, 1.00 mmol) and zinc bromide (0.450 g, 2.00 mmol) at room temperature. This mixture was left to stir for 10 minutes under nitrogen before a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.115 g, 0.10 mmol) was added. The resulting mixture was allowed to stir at room temperature for 17 hours. The solvent was removed *in vacuo* and the residue dissolved in EtOAc (20 ml). The palladium catalyst was filtered through a plug of silica, and the organic layer was washed with distilled water (2 x 30 ml). The organics were dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow solid (0.310 g). This crude material was purified by column chromatography ($SiO_2$, gradient elution $Et_2O$ : P.E. 40-60; 0-4 : 6) to afford the desired furan **247** as a white solid (0.285 g, 0.75 mmol, 75 %), m.p. 125-128°C; $\nu_{max}$ (thin film)$cm^{-1}$ 3081, 2982, 2834 (C-H str), 1734s (C=O str); $\delta_H$ (400 MHz; $CDCl_3$) 1.15-1.23 (6H, m, 2 x $CH_2$-C$H_3$), 2.09(1H, dd, *J* 7.0 and 13.0 Hz, 4-C(H)H), 2.41 (1H, dd, *J* 6.0 and 13.0 Hz, 4-C'(H)H), 2.70 (1H, m, 4-C'(H)H), 2.95 (1H, m, 4-C(H)H), 3.73 (3H, s, PhOC'$H_3$), 3.77 (9H, s, 3 x PhOC$H_3$), 3.77 (6H, s, OC'$H_3$), 4.11-4.36 (5H, m, 5-C'H and 2 x C$H_2$-$CH_3$), 4.98 (1H, m, 5-CH), 5.09-5.36 (4H, m, $CH_2$=CH and C'$H_2$=CH), 5.53 (1H, s, 2-C'H), 5.62 (1H, s, 2-CH), 5.85 (1H, m, $CH_2$=CH), 5.64 (1H, m, C'$H_2$=C'H), 6.60 (2H, s, Ph'-H), 6.65 (2H, s, Ph-H); $\delta_C$ (100 MHz; $CDCl_3$) 13.47 ($CH_2$-$CH_3$), 13.99 (C'$H_2$-C'$H_3$), 40.45 (4-C'$H_2$), 40.67 (4-$CH_2$), 56.08 (PhO$CH_3$ and PhOC'$H_3$), 61.48 (C'$H_2$-C'$H_3$), 61.79 ($CH_2$-$CH_3$), 65.94, 66.01 (3-C and 3-C'), 79.04 (5-C'H), 79.68 (5-CH), 83.16 (2-CH), 84.11 (2-C'H), 103.59 (Ph-CH), 104.10 (Ph-C'H), 116.00 ($CH_2$=CH), 117.60 (C'$H_2$=C'H), 133.48, 133.88,

134.14 (Ph-C and Ph-C'), 136.59 (C'$H_2$=C'H), 138.21 ($CH_2$=CH), 152.71, 152.75 (ipso-C and ipso-C'), 168.60, 168.87, 169.95, 170.75 (2 x C=O and 2 x C'=O); *m/z* (EI) 408 ($M^+$, 92 %), 363, 308, 289, 220, 208, 196, 181, 166, 153, 121, 110, 77, 66, (Found 408.1783, $C_{21}H_{28}O_8$ requires 408.1784).

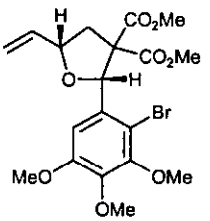
**5-Ethyl-2-(3,4,5-trimethoxy-phenyl)-dihydro-furan-3,3-dicarboxylic acid diethyl ester (248)**




A solution of the furan **247** (0.204 g, 0.50 mmol) was stirred with 10 % palladium on carbon in EtOAc (30 ml) in an atmosphere of hydrogen for 17 hours at room temperature. The catalyst was filtered off through a pad of celite and washed with EtOAc (2 x 30 ml) and DCM (30 ml). The filtrate was concentrated *in vacuo* to afford a colourless crude oil. The crude material was purified by column chromatography ($SiO_2$, $Et_2O$ : P.E. 40-60; 1 : 9) to afford the desired compound **248** as a white solid (0.200 g, 0.49 mmol, 98 %), m.p. 130-134°C; $\nu_{max}$ (thin film)$cm^{-1}$ 2976, 2937 (C-H str), 1728s (C=O str), 1592, 1462, 1262, 1236, 1128; $\delta_H$ (400 MHz; $CDCl_3$) 0.98-1.05 (6H, m, C'$H_3$ and C$H_3$), 1.23-1.42 (6H, m, $OCH_2CH_3$ and $OC'H_2C'H_3$), 1.54-2.04 (5H, m, C'$H_2$C'$H_3$ and C$H_2CH_3$ and 4-C(H)H), 2.38 (1H, dd, *J* 6.0 and 13.0 Hz, 4-C'(H)H), 2.62 (1H, m, 4-C'(H)H), 2.94 (1H, m, 4-C(H)H), 3.78, 3.79 (2 x 3H, s, PhOC'$H_3$) 3.84 (12H, s, PhOC'$H_3$ and PhOC$H_3$) 4.17-4.34 (5H, m, $OCH_2CH_3$ and $OC'H_2C'H_3$ and 5-C'H), 5.52 (1H, m, 5-CH), 5.54 (1H, s, 2-C'H), 5.62 (1H, s, 2-CH), 6.65 (2H, s, Ph'-H), 6.70 (2H, s, Ph-H); $\delta_C$ (100 MHz; $CDCl_3$) 9.98 ($CH_2$-$CH_3$), 10.17 ($CH_2$-$CH_3$), 13.44 ($OCH_2$-$CH_3$), 14.06 ($OC'H_2$-C'$H_3$), 27.25 (C'$H_2$),

28.82 (C$H_2$), 40.03 (4-C'$H_2$), 40.54 (4-C$H_2$), 56.08 (PhOC$H_3$ and PhOC'$H_3$), 61.44 (OC$H_2$), 61.63 (OC'$H_2$), 65.92, 66.14 (3C and 3C'), 79.45 (5-C'H), 80.61 (5-CH), 82.77 (2-CH), 84.12 (2-C'H), 103.79 (Ph-CH), 104.35 (Ph-C'H), 133.75, 134.30, 137.49 (Ph-C and Ph-C'), 152.70, 152.75 (ipso-C and ipso-C'), 168.96, 169.00, 169.08, 171.07 (2 x C=O and 2 x C'=O); *m/z* (EI) 410 ($M^+$, 100 %), 395, 365, 291, 214, 201, 185, 173, 139, 127, 99, 73, 57, (Found 410.1941, $C_{21}H_{30}O_8$ requires 410.1941).

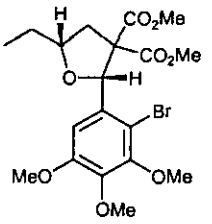
**2-(2-Bromo-3,4,5-trimethoxy-phenyl)-5-vinyl-dihydro-furan-3,3-dicarboxylic acid dimethyl ester (249)** (*cis* isomer)




To a stirred solution of 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester **107** (0.184 g, 1.00 mmol) in anhydrous MeOH (5 ml) was added bromo 3,4,5-trimethoxybenzaldehyde **233** (0.199 g, 1.00 mmol) and zinc bromide (0.450 g, 2.00 mmol) at room temperature. This mixture was left to stir for 10 minutes under nitrogen before a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.115 g, 0.10 mmol) was added. The resulting mixture was allowed to stir at room temperature for 17 hours. The solvent was removed *in vacuo* and the residue dissolved in EtOAc (20 ml). The palladium catalyst was filtered through a plug of silica, and the organic layer was washed with distilled water (2 x 30 ml). The organics were dried ($MgSO_4$) and concentrated *in vacuo* to afford a yellow solid (0.450 g). This crude material was purified by column chromatography ($SiO_2$, gradient elution $Et_2O$ : P.E. 40-60; 0-4 : 6) to afford the desired furan **249** as a white solid (0.334 g,

0.73 mmol, 73 %), m.p. 157-160°C; $\nu_{max}$ (thin film)cm$^{-1}$ 2951, 2359, 2342 (C-H str), 1733s (C=O str); $\delta_H$ (400 MHz; $CDCl_3$) 2.38 (1H, dd, *J* 4.5 and 13.0 Hz, 4-C'(H)H), 2.70 (1H, m, 4-C'(H)H), 3.15 (3H, s, OC'$H_3$), 3.81-3.86 (12H, m, OC'$H_3$ and PhOC'$H_3$), 4.41 (1H, m, 5-C'H), 5.20-5.40 (2H, m, C'$H_2$=CH), 5.93 (1H, m, C'$H_2$=C'H), 6.20 (1H, s, Ph'-H) 6.67 (1H, m, 2-C'H); $\delta_C$ (100 MHz; $CDCl_3$) 41.10 (4-C'$H_2$), 52.16, 53.20 (OC'$H_3$), 56.05 (PhOC'$H_3$), 60.97, 61.08 (PhOC'$H_3$), 65.74 (3-C'), 78.96 (5-C'H), 83.19 (2-C'H), 107.52 (Ph-C'H), 110.21 (Ph-C'Br), 117.60 (C'$H_2$=C'H), 133.60, (Ph-C'), 135.89 (C'$H_2$=C'H), 142.99 (Ph-C'), 150.35 (Ph-C'), 152.80 (ipso-C'), 170.82, 171.10 (2 x C'=O); *m/z* (EI) 458, 460 ($M^+$, 35 %, 35%), 379, 276, 259, 195, 184, 152, 124, 109, 124, 69, (Found 458.0560, $C_{19}H_{23}O_8{}^{79}Br$ requires 458.0576).

**2-(2-Bromo-3,4,5-trimethoxy-phenyl)-5-ethyl-dihydro-furan-3,3-dicaboxylic acid dimethyl ester (250)** (*cis* isomer)




A solution of the furan **249** (0.229 g, 0.50 mmol) was stirred with 10 % palladium on carbon in EtOAc (30 ml) in an atmosphere of hydrogen for 17 hours at room temperature. The catalyst was filtered off through a pad of celite and washed with EtOAc (2 x 30 ml) and DCM (30 ml). The filtrate was concentrated *in vacuo* to afford a colourless crude oil. The crude material was purified by column chromatography ($SiO_2$, $Et_2O$ : P.E. 40-60; 1 : 9) to afford the desired compound **250** as a white solid (0.230 g, 0.50 mmol, 100 %), m.p. 152-154°C; $\nu_{max}$ (thin film)cm$^{-1}$ 2950, 2878 (C-H str), 1736s (C=O str), 1483, 1396, 1273; $\delta_H$ (400 MHz; $CDCl_3$) 0.97 (3H, t, *J* 7.5 Hz, C'$H_3$), 1.68-1.78 (2H, m, C'$H_2$C'$H_3$), 2.26 (1H, dd, *J* 5.0 and 13.0 Hz, 4-C'(H)H), 2.59 (1H, m, 4-C'(H)H), 3.12 (3H, s, OC'$H_3$), 3.75-3.84 (13H, m, OC'$H_3$ and

PhOC'$\underline{H}_3$ and 5-C'$\underline{H}$), 6.17 (1H, s, Ph'-$\underline{H}$), 6.67 (1H, s, 2-C'$\underline{H}$); $\delta_C$ (100 MHz; $CDCl_3$) 10.28 ($\underline{C}'H_3$), 27.05 ($\underline{C}'H_2$), 40.82 (4-$\underline{C}'H_2$), 52.44, 53.02 (O$\underline{C}'H_3$), 56.02, 60.97, 61.18 (PhO$\underline{C}'H_3$), 65.91 (3$\underline{C}'$), 79.51 (5-$\underline{C}'H$), 82.91 (2-$\underline{C}'H$), 108.10 (Ph-$\underline{C}H$), 110.36 (Ph-$\underline{C}'Br$), 133.84, 142.94, 150.35 (Ph-*C'*), 152.35, (ipso-$\underline{C}'$), 168.91, 171.11 (2 x $\underline{C}'$=O); *m/z* (EI) 460, 462 ($M^+$, 22 %, 20 %), 381, 274, 186, 173, 145, 132, 122, 113, 94, 77, (Found 460.0736, $C_{19}H_{25}O_8{}^{79}Br$ requires 460.0733).

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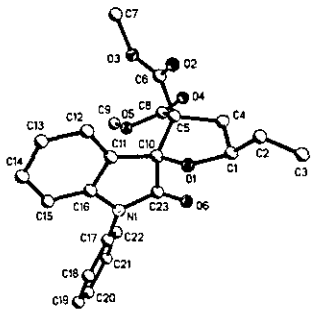
# Appendix

## 6.1 Crystal Structure Determination Details for 2.3




Data were collected at 150(2) K on a Bruker SMART 1000 diffractometer. The structure was solved by direct methods and refined by full-matrix least-squares on $F^2$ using the SHELXTL suite of programs[1]. All the non-hydrogen atoms were refined with anisotropic atomic displacement parameters and hydrogen atoms were inserted at calculated positions using a riding model. Details of the data collection and structure refinement are given in Table 1.

1. Sheldrick G.M. (1998). SHELXTL version 5.1, Bruker AXS, Madison, Wisconsin, USA.

**Table 1. Crystal data and structure refinement for gp1.**

| | | |
|---|---|---|
| Identification code | gp1 | |
| Empirical formula | C23 H21 N O6 | |
| Formula weight | 407.41 | |
| Temperature | 150(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | P2(1)/n | |
| Unit cell dimensions | a = 11.6979(7) Å | α= 90°. |
| | b = 13.6072(8) Å | β= 94.4470(10)°. |
| | c = 12.7017(8) Å | γ = 90°. |
| Volume | 2015.7(2) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.342 $Mg/m^3$ | |
| Absorption coefficient | 0.098 $mm^{-1}$ | |
| F(000) | 856 | |
| Crystal size | 0.34 x 0.23 x 0.09 $mm^3$ | |
| Crystal description | Colourless flake from large block | |
| Theta range for data collection | 2.20 to 28.79°. | |
| Index ranges | -15<=h<=14, -17<=k<=18, -16<=l<=17 | |
| Reflections collected | 16896 | |
| Independent reflections | 4737 [R(int) = 0.0182] | |
| Completeness to theta = 25.00° | 100.0 % | |
| Absorption correction | Multiscan | |
| Max. and min. transmission | 1.000000 and 0.965668 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 4737 / 0 / 271 | |
| Goodness-of-fit on $F^2$ | 1.031 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0376, wR2 = 0.0931 | |
| R indices (all data) | R1 = 0.0505, wR2 = 0.1012 | |
| Largest diff. peak and hole | 0.275 and -0.185 $e.Å^{-3}$ | |

**Table 2. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for gp1. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.**

| | x | y | z | U(eq) |
|---|---|---|---|---|
| O(1) | 6566(1) | 2007(1) | 11856(1) | 28(1) |
| C(1) | 5575(1) | 2111(1) | 11100(1) | 30(1) |
| C(2) | 4525(1) | 1906(1) | 11657(1) | 47(1) |
| C(3) | 3662(2) | 2531(2) | 11662(2) | 79(1) |
| C(4) | 5770(1) | 1394(1) | 10197(1) | 29(1) |
| C(5) | 6952(1) | 915(1) | 10484(1) | 23(1) |
| C(6) | 6780(1) | -79(1) | 11014(1) | 25(1) |
| O(2) | 6104(1) | -212(1) | 11661(1) | 37(1) |
| O(3) | 7462(1) | -766(1) | 10667(1) | 37(1) |
| C(7) | 7357(2) | -1737(1) | 11130(2) | 56(1) |
| C(8) | 7616(1) | 767(1) | 9511(1) | 26(1) |
| O(4) | 7171(1) | 590(1) | 8653(1) | 46(1) |
| O(5) | 8746(1) | 843(1) | 9740(1) | 28(1) |
| C(9) | 9448(1) | 655(1) | 8866(1) | 38(1) |
| C(10) | 7508(1) | 1646(1) | 11327(1) | 23(1) |
| C(11) | 8454(1) | 1309(1) | 12123(1) | 22(1) |
| C(12) | 8478(1) | 579(1) | 12882(1) | 28(1) |
| C(13) | 9478(1) | 449(1) | 13544(1) | 32(1) |
| C(14) | 10422(1) | 1048(1) | 13450(1) | 31(1) |
| C(15) | 10401(1) | 1795(1) | 12694(1) | 27(1) |
| C(16) | 9409(1) | 1913(1) | 12040(1) | 23(1) |
| N(1) | 9178(1) | 2622(1) | 11234(1) | 24(1) |
| C(17) | 10007(1) | 3292(1) | 10862(1) | 24(1) |
| C(18) | 10604(1) | 3923(1) | 11562(1) | 26(1) |
| C(19) | 11409(1) | 4559(1) | 11185(1) | 29(1) |
| C(20) | 11592(1) | 4573(1) | 10122(1) | 30(1) |
| C(21) | 10982(1) | 3945(1) | 9426(1) | 31(1) |
| C(22) | 10189(1) | 3297(1) | 9792(1) | 28(1) |
| C(23) | 8091(1) | 2506(1) | 10766(1) | 25(1) |
| O(6) | 7634(1) | 2991(1) | 10047(1) | 34(1) |

**Table 3. Bond lengths [Å] and angles [°] for gp1.**

| | | | |
|---|---|---|---|
| O(1)-C(10) | 1.4225(14) | C(11)-C(12) | 1.3835(17) |
| O(1)-C(1) | 1.4539(15) | C(11)-C(16) | 1.3968(17) |
| C(1)-C(2) | 1.490(2) | C(12)-C(13) | 1.3986(18) |
| C(1)-C(4) | 1.5375(18) | C(13)-C(14) | 1.3851(19) |
| C(2)-C(3) | 1.320(3) | C(14)-C(15) | 1.3968(18) |
| C(4)-C(5) | 1.5460(16) | C(15)-C(16) | 1.3843(17) |
| C(5)-C(8) | 1.5226(17) | C(16)-N(1) | 1.4164(15) |
| C(5)-C(6) | 1.5310(17) | N(1)-C(23) | 1.3708(15) |
| C(5)-C(10) | 1.5660(16) | N(1)-C(17) | 1.4372(15) |
| C(6)-O(2) | 1.1975(15) | C(17)-C(18) | 1.3859(17) |
| C(6)-O(3) | 1.3262(16) | C(17)-C(22) | 1.3911(17) |
| O(3)-C(7) | 1.4549(17) | C(18)-C(19) | 1.3903(18) |
| C(8)-O(4) | 1.1946(15) | C(19)-C(20) | 1.3841(19) |
| C(8)-O(5) | 1.3360(15) | C(20)-C(21) | 1.3871(19) |
| O(5)-C(9) | 1.4541(15) | C(21)-C(22) | 1.3861(18) |
| C(10)-C(11) | 1.5111(16) | C(23)-O(6) | 1.2166(15) |
| C(10)-C(23) | 1.5541(17) | | |

| | | | |
|---|---|---|---|
| C(10)-O(1)-C(1) | 109.21(9) | O(5)-C(8)-C(5) | 111.82(10) |
| O(1)-C(1)-C(2) | 108.24(11) | C(8)-O(5)-C(9) | 115.37(10) |
| O(1)-C(1)-C(4) | 105.90(10) | O(1)-C(10)-C(11) | 110.01(9) |
| C(2)-C(1)-C(4) | 114.23(12) | O(1)-C(10)-C(23) | 109.92(10) |
| C(3)-C(2)-C(1) | 122.7(2) | C(11)-C(10)-C(23) | 102.18(9) |
| C(1)-C(4)-C(5) | 105.86(10) | O(1)-C(10)-C(5) | 104.24(9) |
| C(8)-C(5)-C(6) | 109.40(10) | C(11)-C(10)-C(5) | 120.59(10) |
| C(8)-C(5)-C(4) | 111.57(10) | C(23)-C(10)-C(5) | 109.79(9) |
| C(6)-C(5)-C(4) | 109.32(10) | C(12)-C(11)-C(16) | 120.16(11) |
| C(8)-C(5)-C(10) | 115.33(10) | C(12)-C(11)-C(10) | 131.18(11) |
| C(6)-C(5)-C(10) | 108.77(9) | C(16)-C(11)-C(10) | 108.59(10) |
| C(4)-C(5)-C(10) | 102.15(9) | C(11)-C(12)-C(13) | 118.74(12) |
| O(2)-C(6)-O(3) | 124.52(12) | C(14)-C(13)-C(12) | 120.57(12) |
| O(2)-C(6)-C(5) | 123.50(12) | C(13)-C(14)-C(15) | 121.09(12) |
| O(3)-C(6)-C(5) | 111.97(10) | C(16)-C(15)-C(14) | 117.81(12) |
| C(6)-O(3)-C(7) | 115.73(11) | C(15)-C(16)-C(11) | 121.61(11) |
| O(4)-C(8)-O(5) | 124.57(12) | C(15)-C(16)-N(1) | 128.09(11) |
| O(4)-C(8)-C(5) | 123.60(12) | C(11)-C(16)-N(1) | 110.29(10) |

| | | | |
|---|---|---|---|
| C(23)-N(1)-C(16) | 110.69(10) | C(20)-C(19)-C(18) | 120.28(12) |
| C(23)-N(1)-C(17) | 123.85(10) | C(19)-C(20)-C(21) | 120.19(12) |
| C(16)-N(1)-C(17) | 125.03(10) | C(22)-C(21)-C(20) | 120.15(12) |
| C(18)-C(17)-C(22) | 121.03(11) | C(21)-C(22)-C(17) | 119.24(12) |
| C(18)-C(17)-N(1) | 120.09(11) | O(6)-C(23)-N(1) | 127.04(12) |
| C(22)-C(17)-N(1) | 118.88(11) | O(6)-C(23)-C(10) | 124.73(11) |
| C(17)-C(18)-C(19) | 119.09(12) | N(1)-C(23)-C(10) | 108.22(10) |

**Table 4. Anisotropic displacement parameters ($Å^2 x 10^3$) for gp1. The anisotropic displacement factor exponent takes the form: $-2\pi^2[ h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12} ]$**

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| O(1) | 19(1) | 35(1) | 29(1) | -8(1) | 1(1) | 1(1) |
| C(1) | 21(1) | 32(1) | 37(1) | -5(1) | -4(1) | 3(1) |
| C(2) | 25(1) | 68(1) | 49(1) | -14(1) | 3(1) | -2(1) |
| C(3) | 30(1) | 114(2) | 92(2) | -36(1) | 8(1) | 14(1) |
| C(4) | 23(1) | 31(1) | 33(1) | -4(1) | -7(1) | 3(1) |
| C(5) | 20(1) | 26(1) | 21(1) | -1(1) | -3(1) | 0(1) |
| C(6) | 22(1) | 29(1) | 24(1) | -1(1) | -5(1) | -4(1) |
| O(2) | 36(1) | 38(1) | 38(1) | 0(1) | 11(1) | -12(1) |
| O(3) | 37(1) | 27(1) | 48(1) | 11(1) | 11(1) | 7(1) |
| C(7) | 53(1) | 33(1) | 81(1) | 26(1) | 13(1) | 10(1) |
| C(8) | 30(1) | 26(1) | 22(1) | 3(1) | -1(1) | 3(1) |
| O(4) | 44(1) | 71(1) | 22(1) | -7(1) | -4(1) | 4(1) |
| O(5) | 27(1) | 34(1) | 24(1) | -1(1) | 6(1) | 2(1) |
| C(9) | 41(1) | 43(1) | 33(1) | 2(1) | 16(1) | 7(1) |
| C(10) | 20(1) | 26(1) | 22(1) | -2(1) | 0(1) | 0(1) |
| C(11) | 20(1) | 29(1) | 19(1) | -3(1) | 0(1) | 0(1) |
| C(12) | 26(1) | 35(1) | 21(1) | 1(1) | 1(1) | -4(1) |
| C(13) | 33(1) | 40(1) | 22(1) | 6(1) | -2(1) | -2(1) |
| C(14) | 25(1) | 42(1) | 25(1) | 0(1) | -5(1) | 1(1) |
| C(15) | 20(1) | 35(1) | 27(1) | -3(1) | 0(1) | -2(1) |
| C(16) | 22(1) | 26(1) | 21(1) | -2(1) | 3(1) | 0(1) |
| N(1) | 20(1) | 26(1) | 25(1) | 1(1) | -1(1) | -2(1) |
| C(17) | 20(1) | 23(1) | 27(1) | 0(1) | 2(1) | -1(1) |
| C(18) | 25(1) | 29(1) | 25(1) | -3(1) | 3(1) | -1(1) |
| C(19) | 27(1) | 27(1) | 34(1) | -5(1) | 2(1) | -5(1) |
| C(20) | 26(1) | 27(1) | 36(1) | 2(1) | 7(1) | -3(1) |
| C(21) | 35(1) | 32(1) | 26(1) | 0(1) | 7(1) | 0(1) |
| C(22) | 31(1) | 27(1) | 26(1) | -3(1) | 1(1) | -2(1) |
| C(23) | 23(1) | 24(1) | 28(1) | -2(1) | -1(1) | -1(1) |
| O(6) | 29(1) | 33(1) | 40(1) | 11(1) | -8(1) | -2(1) |

**Table 5. Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2$x $10^3$) for gp1.**

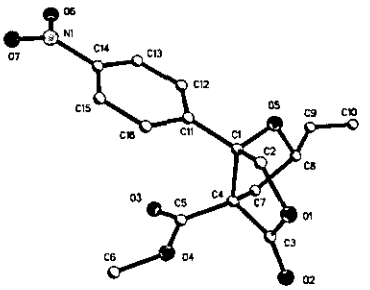
| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(1) | 5542 | 2799 | 10821 | 36 |
| H(2) | 4474 | 1300 | 12022 | 57 |
| H(3A) | 3696 | 3141 | 11302 | 94 |
| H(3B) | 3008 | 2371 | 12027 | 94 |
| H(4A) | 5770 | 1749 | 9516 | 35 |
| H(4B) | 5160 | 888 | 10136 | 35 |
| H(7A) | 7893 | -2189 | 10825 | 83 |
| H(7B) | 6571 | -1978 | 10982 | 83 |
| H(7C) | 7535 | -1697 | 11896 | 83 |
| H(9A) | 10260 | 729 | 9108 | 58 |
| H(9B) | 9249 | 1124 | 8296 | 58 |
| H(9C) | 9310 | -16 | 8606 | 58 |
| H(12) | 7827 | 174 | 12952 | 33 |
| H(13) | 9511 | -56 | 14063 | 38 |
| H(14) | 11094 | 950 | 13908 | 37 |
| H(15) | 11047 | 2208 | 12631 | 33 |
| H(18) | 10466 | 3921 | 12289 | 32 |
| H(19) | 11834 | 4986 | 11660 | 35 |
| H(20) | 12137 | 5014 | 9868 | 35 |
| H(21) | 11107 | 3960 | 8696 | 37 |
| H(22) | 9776 | 2861 | 9319 | 34 |

**Table 6. Torsion angles [°] for gp1.**

| | | | |
|---|---|---|---|
| C(10)-O(1)-C(1)-C(2) | 147.22(12) | C(4)-C(5)-C(10)-C(23) | -84.97(11) |
| C(10)-O(1)-C(1)-C(4) | 24.32(13) | O(1)-C(10)-C(11)-C(12) | 61.92(17) |
| O(1)-C(1)-C(2)-C(3) | 125.22(17) | C(23)-C(10)-C(11)-C(12) | 178.63(13) |
| C(4)-C(1)-C(2)-C(3) | -117.09(19) | C(5)-C(10)-C(11)-C(12) | -59.37(18) |
| O(1)-C(1)-C(4)-C(5) | -1.99(14) | O(1)-C(10)-C(11)-C(16) | -115.05(11) |
| C(2)-C(1)-C(4)-C(5) | -121.00(13) | C(23)-C(10)-C(11)-C(16) | 1.66(12) |
| C(1)-C(4)-C(5)-C(8) | -141.92(11) | C(5)-C(10)-C(11)-C(16) | 123.66(12) |
| C(1)-C(4)-C(5)-C(6) | 96.95(12) | C(16)-C(11)-C(12)-C(13) | -1.21(18) |
| C(1)-C(4)-C(5)-C(10) | -18.16(13) | C(10)-C(11)-C(12)-C(13) | -177.89(12) |
| C(8)-C(5)-C(6)-O(2) | -164.65(11) | C(11)-C(12)-C(13)-C(14) | 0.8(2) |
| C(4)-C(5)-C(6)-O(2) | -42.21(15) | C(12)-C(13)-C(14)-C(15) | -0.1(2) |
| C(10)-C(5)-C(6)-O(2) | 68.57(15) | C(13)-C(14)-C(15)-C(16) | -0.21(19) |
| C(8)-C(5)-C(6)-O(3) | 14.96(14) | C(14)-C(15)-C(16)-C(11) | -0.16(18) |
| C(4)-C(5)-C(6)-O(3) | 137.40(11) | C(14)-C(15)-C(16)-N(1) | 178.84(12) |
| C(10)-C(5)-C(6)-O(3) | -111.82(11) | C(12)-C(11)-C(16)-C(15) | 0.88(18) |
| O(2)-C(6)-O(3)-C(7) | -0.4(2) | C(10)-C(11)-C(16)-C(15) | 178.25(11) |
| C(5)-C(6)-O(3)-C(7) | 179.97(13) | C(12)-C(11)-C(16)-N(1) | -178.28(11) |
| C(6)-C(5)-C(8)-O(4) | 88.36(15) | C(10)-C(11)-C(16)-N(1) | -0.91(13) |
| C(4)-C(5)-C(8)-O(4) | -32.72(18) | C(15)-C(16)-N(1)-C(23) | -179.47(12) |
| C(10)-C(5)-C(8)-O(4) | -148.67(13) | C(11)-C(16)-N(1)-C(23) | -0.38(14) |
| C(6)-C(5)-C(8)-O(5) | -90.71(12) | C(15)-C(16)-N(1)-C(17) | 7.80(19) |
| C(4)-C(5)-C(8)-O(5) | 148.20(10) | C(11)-C(16)-N(1)-C(17) | -173.11(11) |
| C(10)-C(5)-C(8)-O(5) | 32.25(14) | C(23)-N(1)-C(17)-C(18) | 131.39(13) |
| O(4)-C(8)-O(5)-C(9) | -2.47(19) | C(16)-N(1)-C(17)-C(18) | -56.80(17) |
| C(5)-C(8)-O(5)-C(9) | 176.60(10) | C(23)-N(1)-C(17)-C(22) | -48.23(17) |
| C(1)-O(1)-C(10)-C(11) | -166.85(10) | C(16)-N(1)-C(17)-C(22) | 123.58(13) |
| C(1)-O(1)-C(10)-C(23) | 81.39(11) | C(22)-C(17)-C(18)-C(19) | -0.90(19) |
| C(1)-O(1)-C(10)-C(5) | -36.22(12) | N(1)-C(17)-C(18)-C(19) | 179.49(11) |
| C(8)-C(5)-C(10)-O(1) | 153.93(10) | C(17)-C(18)-C(19)-C(20) | 1.24(19) |
| C(6)-C(5)-C(10)-O(1) | -82.78(11) | C(18)-C(19)-C(20)-C(21) | -0.6(2) |
| C(4)-C(5)-C(10)-O(1) | 32.73(11) | C(19)-C(20)-C(21)-C(22) | -0.3(2) |
| C(8)-C(5)-C(10)-C(11) | -82.00(13) | C(20)-C(21)-C(22)-C(17) | 0.7(2) |
| C(6)-C(5)-C(10)-C(11) | 41.29(14) | C(18)-C(17)-C(22)-C(21) | -0.05(19) |
| C(4)-C(5)-C(10)-C(11) | 156.80(11) | N(1)-C(17)-C(22)-C(21) | 179.57(11) |
| C(8)-C(5)-C(10)-C(23) | 36.23(13) | C(16)-N(1)-C(23)-O(6) | -179.60(12) |
| C(6)-C(5)-C(10)-C(23) | 159.53(10) | C(17)-N(1)-C(23)-O(6) | -6.8(2) |

| | |
|---|---|
| C(16)-N(1)-C(23)-C(10) | 1.47(13) |
| C(17)-N(1)-C(23)-C(10) | 174.30(10) |
| O(1)-C(10)-C(23)-O(6) | -64.07(15) |
| C(11)-C(10)-C(23)-O(6) | 179.15(12) |
| C(5)-C(10)-C(23)-O(6) | 50.03(16) |
| O(1)-C(10)-C(23)-N(1) | 114.89(11) |
| C(11)-C(10)-C(23)-N(1) | -1.89(12) |
| C(5)-C(10)-C(23)-N(1) | -131.01(10) |

## 6.2 Crystal Structure Determination Details for 2.4




Data were collected at 150(2) K on a Bruker SMART 1000 diffractometer. The structure was solved by direct methods and refined by full-matrix least-squares on $F^2$ using the SHELXTL suite of programs[1]. All the non-hydrogen atoms were refined with anisotropic atomic displacement parameters and hydrogen atoms were inserted at calculated positions using a riding model. Details of the data collection and structure refinement are given in Table 1.

1. Sheldrick G.M. (1998). SHELXTL version 5.1, Bruker AXS, Madison, Wisconsin, USA.

**Table 1. Crystal data and structure refinement for gp2.**

| | | |
|---|---|---|
| Identification code | gp2 | |
| Empirical formula | C16 H15 N O7 | |
| Formula weight | 333.29 | |
| Temperature | 150(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Tetragonal | |
| Space group | P4(3)2(1)2 | |
| Unit cell dimensions | a = 7.6903(6) Å | α= 90°. |
| | b = 7.6903(6) Å | β= 90°. |
| | c = 51.979(6) Å | γ = 90°. |
| Volume | 3074.1(5) $Å^3$ | |
| Z | 8 | |
| Density (calculated) | 1.440 $Mg/m^3$ | |
| Absorption coefficient | 0.115 $mm^{-1}$ | |
| F(000) | 1392 | |
| Crystal size | 0.39 x 0.22 x 0.14 $mm^3$ | |
| Crystal description | Colourless rod | |
| Theta range for data collection | 1.57 to 25.00°. | |
| Index ranges | -9<=h<=9, -8<=k<=9, -61<=l<=58 | |
| Reflections collected | 14596 | |
| Independent reflections | 2704 [R(int) = 0.0674] | |
| Completeness to theta = 25.00° | 100.0 % | |
| Absorption correction | Semi-empirical from equivalents | |
| Max. and min. transmission | 1.000000 and 0.914425 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 2704 / 0 / 217 | |
| Goodness-of-fit on $F^2$ | 1.049 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0455, wR2 = 0.0918 | |
| R indices (all data) | R1 = 0.0676, wR2 = 0.1013 | |
| Absolute structure parameter | -1.3(17) | |
| Largest diff. peak and hole | 0.170 and -0.177 $e.Å^{-3}$ | |

**Table 2. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for gp2. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.**

| | x | y | z | U(eq) |
|---|---|---|---|---|
| C(1) | 6180(3) | 7452(3) | 676(1) | 22(1) |
| C(2) | 4581(4) | 8255(4) | 803(1) | 26(1) |
| O(1) | 5182(2) | 9123(2) | 1033(1) | 28(1) |
| C(3) | 6772(4) | 8533(3) | 1106(1) | 24(1) |
| O(2) | 7474(3) | 9061(3) | 1294(1) | 32(1) |
| C(4) | 7500(3) | 7262(3) | 904(1) | 21(1) |
| C(5) | 7687(4) | 5424(4) | 1003(1) | 23(1) |
| O(3) | 8660(3) | 4363(3) | 915(1) | 31(1) |
| O(4) | 6564(2) | 5115(2) | 1196(1) | 28(1) |
| C(6) | 6563(5) | 3347(4) | 1296(1) | 40(1) |
| C(7) | 9194(4) | 7999(4) | 795(1) | 26(1) |
| C(8) | 8530(4) | 9457(4) | 622(1) | 28(1) |
| C(9) | 9691(4) | 10037(4) | 412(1) | 31(1) |
| C(10) | 10123(4) | 11672(4) | 376(1) | 34(1) |
| O(5) | 6965(2) | 8705(2) | 509(1) | 27(1) |
| C(11) | 5833(4) | 5788(4) | 527(1) | 22(1) |
| C(12) | 6777(4) | 5427(4) | 307(1) | 28(1) |
| C(13) | 6553(4) | 3861(4) | 176(1) | 30(1) |
| C(14) | 5364(4) | 2689(4) | 269(1) | 28(1) |
| N(1) | 5085(4) | 1057(3) | 127(1) | 35(1) |
| O(6) | 6015(3) | 765(3) | -60(1) | 55(1) |
| O(7) | 3951(3) | 66(3) | 203(1) | 40(1) |
| C(15) | 4395(4) | 3008(4) | 487(1) | 29(1) |
| C(16) | 4637(4) | 4544(4) | 619(1) | 28(1) |

**Table 3. Bond lengths [Å] and angles [°] for gp2.**

| | | | |
|---|---|---|---|
| C(1)-O(5) | 1.430(3) | C(7)-C(8) | 1.525(4) |
| C(1)-C(11) | 1.517(4) | C(8)-O(5) | 1.459(3) |
| C(1)-C(2) | 1.526(4) | C(8)-C(9) | 1.480(4) |
| C(1)-C(4) | 1.571(4) | C(9)-C(10) | 1.313(4) |
| C(2)-O(1) | 1.447(3) | C(11)-C(12) | 1.386(4) |
| O(1)-C(3) | 1.358(3) | C(11)-C(16) | 1.409(4) |
| C(3)-O(2) | 1.190(3) | C(12)-C(13) | 1.392(4) |
| C(3)-C(4) | 1.538(4) | C(13)-C(14) | 1.372(4) |
| C(4)-C(5) | 1.510(4) | C(14)-C(15) | 1.376(4) |
| C(4)-C(7) | 1.530(4) | C(14)-N(1) | 1.471(4) |
| C(5)-O(3) | 1.198(3) | N(1)-O(7) | 1.224(3) |
| C(5)-O(4) | 1.344(3) | N(1)-O(6) | 1.230(3) |
| O(4)-C(6) | 1.456(3) | C(15)-C(16) | 1.379(4) |
| | | | |
| O(5)-C(1)-C(11) | 109.6(2) | C(5)-O(4)-C(6) | 115.6(2) |
| O(5)-C(1)-C(2) | 109.3(2) | C(8)-C(7)-C(4) | 102.0(2) |
| C(11)-C(1)-C(2) | 114.8(2) | O(5)-C(8)-C(9) | 108.6(2) |
| O(5)-C(1)-C(4) | 104.4(2) | O(5)-C(8)-C(7) | 102.9(2) |
| C(11)-C(1)-C(4) | 114.8(2) | C(9)-C(8)-C(7) | 117.1(3) |
| C(2)-C(1)-C(4) | 103.3(2) | C(10)-C(9)-C(8) | 123.1(3) |
| O(1)-C(2)-C(1) | 106.7(2) | C(1)-O(5)-C(8) | 111.75(19) |
| C(3)-O(1)-C(2) | 111.4(2) | C(12)-C(11)-C(16) | 119.0(3) |
| O(2)-C(3)-O(1) | 121.6(3) | C(12)-C(11)-C(1) | 119.8(2) |
| O(2)-C(3)-C(4) | 127.7(3) | C(16)-C(11)-C(1) | 121.1(2) |
| O(1)-C(3)-C(4) | 110.5(2) | C(11)-C(12)-C(13) | 120.8(3) |
| C(5)-C(4)-C(7) | 113.1(2) | C(14)-C(13)-C(12) | 118.7(3) |
| C(5)-C(4)-C(3) | 113.5(2) | C(13)-C(14)-C(15) | 122.2(3) |
| C(7)-C(4)-C(3) | 109.1(2) | C(13)-C(14)-N(1) | 118.8(3) |
| C(5)-C(4)-C(1) | 113.9(2) | C(15)-C(14)-N(1) | 119.0(3) |
| C(7)-C(4)-C(1) | 103.5(2) | O(7)-N(1)-O(6) | 123.8(3) |
| C(3)-C(4)-C(1) | 102.8(2) | O(7)-N(1)-C(14) | 118.3(3) |
| O(3)-C(5)-O(4) | 124.5(3) | O(6)-N(1)-C(14) | 117.9(3) |
| O(3)-C(5)-C(4) | 124.5(3) | C(14)-C(15)-C(16) | 119.2(3) |
| O(4)-C(5)-C(4) | 110.9(2) | C(15)-C(16)-C(11) | 120.2(3) |

**Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for gp2. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$**

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| C(1) | 21(2) | 21(2) | 23(1) | 6(1) | 1(1) | 0(1) |
| C(2) | 22(2) | 29(2) | 28(2) | -4(1) | 2(1) | 2(1) |
| O(1) | 26(1) | 26(1) | 31(1) | -6(1) | 0(1) | 5(1) |
| C(3) | 30(2) | 18(2) | 24(2) | 3(1) | 0(1) | -4(1) |
| O(2) | 38(1) | 26(1) | 31(1) | -4(1) | -4(1) | 1(1) |
| C(4) | 22(2) | 19(2) | 21(1) | -2(1) | -2(1) | 1(1) |
| C(5) | 23(2) | 24(2) | 21(2) | -2(1) | -6(1) | 0(1) |
| O(3) | 36(1) | 26(1) | 31(1) | 0(1) | 1(1) | 9(1) |
| O(4) | 28(1) | 22(1) | 36(1) | 3(1) | 8(1) | 0(1) |
| C(6) | 49(2) | 23(2) | 47(2) | 7(2) | 9(2) | -4(2) |
| C(7) | 20(2) | 29(2) | 28(2) | 2(1) | 0(1) | -1(1) |
| C(8) | 27(2) | 24(2) | 32(2) | 2(1) | 2(1) | -2(1) |
| C(9) | 30(2) | 33(2) | 29(2) | 0(1) | 6(1) | 0(2) |
| C(10) | 29(2) | 36(2) | 39(2) | 7(2) | 3(2) | 0(2) |
| O(5) | 24(1) | 29(1) | 26(1) | 6(1) | -1(1) | -5(1) |
| C(11) | 20(2) | 27(2) | 20(1) | 1(1) | -3(1) | 3(1) |
| C(12) | 24(2) | 35(2) | 25(2) | 0(1) | 3(1) | -1(1) |
| C(13) | 28(2) | 40(2) | 22(2) | -7(1) | 1(1) | 6(2) |
| C(14) | 25(2) | 30(2) | 30(2) | -9(1) | -4(1) | 4(1) |
| N(1) | 33(2) | 35(2) | 36(2) | -13(1) | -7(1) | 8(1) |
| O(6) | 61(2) | 56(2) | 49(2) | -28(1) | 15(1) | -4(1) |
| O(7) | 33(1) | 36(1) | 50(1) | -11(1) | -9(1) | -5(1) |
| C(15) | 25(2) | 29(2) | 33(2) | -5(1) | -1(1) | -7(1) |
| C(16) | 27(2) | 30(2) | 28(2) | -5(1) | 5(1) | -3(1) |

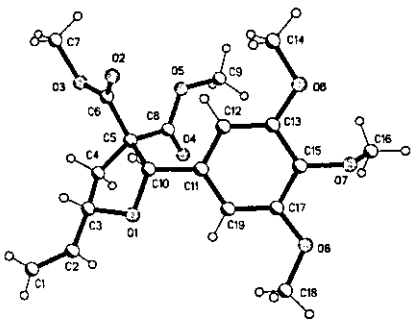
**Table 5. Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2$x $10^3$) for gp2.**

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(2A) | 4021 | 9098 | 685 | 31 |
| H(2B) | 3725 | 7340 | 847 | 31 |
| H(6A) | 5691 | 3246 | 1432 | 60 |
| H(6B) | 7715 | 3072 | 1365 | 60 |
| H(6C) | 6283 | 2533 | 1157 | 60 |
| H(7A) | 9954 | 8455 | 933 | 31 |
| H(7B) | 9836 | 7111 | 695 | 31 |
| H(8) | 8202 | 10480 | 730 | 33 |
| H(9) | 10146 | 9187 | 297 | 37 |
| H(10A) | 9685 | 12545 | 488 | 41 |
| H(10B) | 10873 | 11981 | 238 | 41 |
| H(12) | 7586 | 6257 | 243 | 34 |
| H(13) | 7211 | 3610 | 26 | 36 |
| H(15) | 3569 | 2178 | 545 | 35 |
| H(16) | 3996 | 4764 | 771 | 34 |

**Table 6. Torsion angles [°] for gp2.**

| | | | |
|---|---|---|---|
| O(5)-C(1)-C(2)-O(1) | -87.6(2) | O(5)-C(8)-C(9)-C(10) | 116.6(3) |
| C(11)-C(1)-C(2)-O(1) | 148.9(2) | C(7)-C(8)-C(9)-C(10) | -127.5(3) |
| C(4)-C(1)-C(2)-O(1) | 23.2(3) | C(11)-C(1)-O(5)-C(8) | -129.8(2) |
| C(1)-C(2)-O(1)-C(3) | -18.7(3) | C(2)-C(1)-O(5)-C(8) | 103.7(2) |
| C(2)-O(1)-C(3)-O(2) | -178.4(2) | C(4)-C(1)-O(5)-C(8) | -6.3(3) |
| C(2)-O(1)-C(3)-C(4) | 5.6(3) | C(9)-C(8)-O(5)-C(1) | 153.4(2) |
| O(2)-C(3)-C(4)-C(5) | 70.1(4) | C(7)-C(8)-O(5)-C(1) | 28.7(3) |
| O(1)-C(3)-C(4)-C(5) | -114.2(2) | O(5)-C(1)-C(11)-C(12) | 22.6(3) |
| O(2)-C(3)-C(4)-C(7) | -57.0(4) | C(2)-C(1)-C(11)-C(12) | 146.0(3) |
| O(1)-C(3)-C(4)-C(7) | 118.7(2) | C(4)-C(1)-C(11)-C(12) | -94.5(3) |
| O(2)-C(3)-C(4)-C(1) | -166.4(3) | O(5)-C(1)-C(11)-C(16) | -161.3(2) |
| O(1)-C(3)-C(4)-C(1) | 9.2(3) | C(2)-C(1)-C(11)-C(16) | -37.9(4) |
| O(5)-C(1)-C(4)-C(5) | -141.7(2) | C(4)-C(1)-C(11)-C(16) | 81.6(3) |
| C(11)-C(1)-C(4)-C(5) | -21.7(3) | C(16)-C(11)-C(12)-C(13) | -0.1(4) |
| C(2)-C(1)-C(4)-C(5) | 104.0(3) | C(1)-C(11)-C(12)-C(13) | 176.1(2) |
| O(5)-C(1)-C(4)-C(7) | -18.5(3) | C(11)-C(12)-C(13)-C(14) | 0.8(4) |
| C(11)-C(1)-C(4)-C(7) | 101.5(3) | C(12)-C(13)-C(14)-C(15) | -0.3(4) |
| C(2)-C(1)-C(4)-C(7) | -132.8(2) | C(12)-C(13)-C(14)-N(1) | 178.1(2) |
| O(5)-C(1)-C(4)-C(3) | 95.0(2) | C(13)-C(14)-N(1)-O(7) | -175.9(3) |
| C(11)-C(1)-C(4)-C(3) | -144.9(2) | C(15)-C(14)-N(1)-O(7) | 2.6(4) |
| C(2)-C(1)-C(4)-C(3) | -19.2(3) | C(13)-C(14)-N(1)-O(6) | 4.5(4) |
| C(7)-C(4)-C(5)-O(3) | -31.8(4) | C(15)-C(14)-N(1)-O(6) | -177.0(3) |
| C(3)-C(4)-C(5)-O(3) | -156.8(3) | C(13)-C(14)-C(15)-C(16) | -0.8(4) |
| C(1)-C(4)-C(5)-O(3) | 86.0(3) | N(1)-C(14)-C(15)-C(16) | -179.3(3) |
| C(7)-C(4)-C(5)-O(4) | 150.8(2) | C(14)-C(15)-C(16)-C(11) | 1.6(4) |
| C(3)-C(4)-C(5)-O(4) | 25.8(3) | C(12)-C(11)-C(16)-C(15) | -1.1(4) |
| C(1)-C(4)-C(5)-O(4) | -91.4(3) | C(1)-C(11)-C(16)-C(15) | -177.3(3) |
| O(3)-C(5)-O(4)-C(6) | -0.7(4) | | |
| C(4)-C(5)-O(4)-C(6) | 176.7(2) | | |
| C(5)-C(4)-C(7)-C(8) | 158.7(2) | | |
| C(3)-C(4)-C(7)-C(8) | -74.0(3) | | |
| C(1)-C(4)-C(7)-C(8) | 35.0(3) | | |
| C(4)-C(7)-C(8)-O(5) | -38.7(3) | | |
| C(4)-C(7)-C(8)-C(9) | -157.6(2) | | |

## 6.3 Crystal Structure Determination Details for 2.6




Data were collected at 150(2) K on a Bruker SMART 1000 diffractometer. The structure was solved by direct methods and refined by full-matrix least-squares on $F^2$ using the SHELXTL suite of programs[1]. All the non-hydrogen atoms were refined with anisotropic atomic displacement parameters, and the hydrogen atoms were inserted at calculated positions using a riding model. Details of the data collection and structure refinement are given in Table 1.

1. Sheldrick G.M. (2001). SHELXTL version 6.12, Bruker AXS, Madison, Wisconsin, USA.

**Table 1. Crystal data and structure refinement for gp4.**

| | | |
|---|---|---|
| Identification code | gp4 | |
| Empirical formula | C19 H24 O8 | |
| Formula weight | 380.38 | |
| Temperature | 150(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | P2(1)/n | |
| Unit cell dimensions | a = 14.7881(11) Å | α= 90°. |
| | b = 8.2006(6) Å | β= 97.6760(10)°. |
| | c = 15.2339(11) Å | γ = 90°. |
| Volume | 1830.9(2) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.380 $Mg/m^3$ | |
| Absorption coefficient | 0.108 $mm^{-1}$ | |
| F(000) | 808 | |
| Crystal size | 0.39 x 0.35 x 0.10 $mm^3$ | |
| Crystal description | colourless hexagonal plate | |
| Theta range for data collection | 1.80 to 25.00°. | |
| Index ranges | -17<=h<=17, -9<=k<=9, -18<=l<=17 | |
| Reflections collected | 12665 | |
| Independent reflections | 3232 [R(int) = 0.0219] | |
| Completeness to theta = 25.00° | 99.9 % | |
| Absorption correction | Semi-empirical from equivalents | |
| Max. and min. transmission | 1.000000 and 0.924426 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 3232 / 0 / 244 | |
| Goodness-of-fit on $F^2$ | 1.049 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0385, wR2 = 0.0995 | |
| R indices (all data) | R1 = 0.0498, wR2 = 0.1069 | |
| Largest diff. peak and hole | 0.360 and -0.227 $e.Å^{-3}$ | |

**Table 2. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for gp4. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.**

| | x | y | z | U(eq) |
|---|---|---|---|---|
| C(1) | 7913(1) | 11058(3) | -2690(1) | 34(1) |
| C(2) | 7884(1) | 11402(2) | -1854(1) | 30(1) |
| C(3) | 8127(1) | 10226(2) | -1119(1) | 24(1) |
| O(1) | 8784(1) | 10907(2) | -437(1) | 25(1) |
| C(4) | 7327(1) | 9840(2) | -613(1) | 23(1) |
| C(5) | 7793(1) | 9192(2) | 287(1) | 20(1) |
| C(6) | 7763(1) | 7334(2) | 361(1) | 22(1) |
| O(2) | 8397(1) | 6495(2) | 658(1) | 39(1) |
| O(3) | 6940(1) | 6755(2) | 63(1) | 31(1) |
| C(7) | 6824(2) | 4995(2) | 111(1) | 38(1) |
| C(8) | 7377(1) | 9961(2) | 1055(1) | 21(1) |
| O(4) | 7112(1) | 11345(2) | 1057(1) | 30(1) |
| O(5) | 7370(1) | 8926(2) | 1727(1) | 24(1) |
| C(9) | 7099(1) | 9608(2) | 2536(1) | 30(1) |
| C(10) | 8819(1) | 9809(2) | 289(1) | 21(1) |
| C(11) | 9283(1) | 10594(2) | 1128(1) | 21(1) |
| C(12) | 9457(1) | 9625(2) | 1886(1) | 23(1) |
| C(13) | 9885(1) | 10307(2) | 2667(1) | 23(1) |
| O(6) | 10094(1) | 9475(2) | 3448(1) | 28(1) |
| C(14) | 9943(1) | 7755(2) | 3427(1) | 33(1) |
| C(15) | 10155(1) | 11942(2) | 2695(1) | 23(1) |
| O(7) | 10631(1) | 12573(2) | 3463(1) | 27(1) |
| C(16) | 10056(1) | 13183(3) | 4064(1) | 37(1) |
| C(17) | 10000(1) | 12887(2) | 1931(1) | 24(1) |
| O(8) | 10297(1) | 14464(2) | 2017(1) | 32(1) |
| C(18) | 10465(1) | 15284(2) | 1227(1) | 30(1) |
| C(19) | 9553(1) | 12216(2) | 1145(1) | 23(1) |

Table 3. Bond lengths [Å] and angles [°] for gp4.

| | | | |
|---|---|---|---|
| C(1)-C(2) | 1.312(3) | O(5)-C(9) | 1.457(2) |
| C(2)-C(3) | 1.485(3) | C(10)-C(11) | 1.512(2) |
| C(3)-O(1) | 1.438(2) | C(11)-C(19) | 1.388(3) |
| C(3)-C(4) | 1.528(2) | C(11)-C(12) | 1.397(2) |
| O(1)-C(10) | 1.420(2) | C(12)-C(13) | 1.388(2) |
| C(4)-C(5) | 1.544(2) | C(13)-O(6) | 1.371(2) |
| C(5)-C(6) | 1.529(2) | C(13)-C(15) | 1.398(3) |
| C(5)-C(8) | 1.530(2) | O(6)-C(14) | 1.428(2) |
| C(5)-C(10) | 1.599(2) | C(15)-O(7) | 1.383(2) |
| C(6)-O(2) | 1.202(2) | C(15)-C(17) | 1.392(3) |
| C(6)-O(3) | 1.329(2) | O(7)-C(16) | 1.421(2) |
| O(3)-C(7) | 1.457(2) | C(17)-O(8) | 1.367(2) |
| C(8)-O(4) | 1.201(2) | C(17)-C(19) | 1.401(2) |
| C(8)-O(5) | 1.331(2) | O(8)-C(18) | 1.430(2) |
| | | | |
| C(1)-C(2)-C(3) | 123.85(19) | O(1)-C(10)-C(11) | 110.71(14) |
| O(1)-C(3)-C(2) | 111.42(15) | O(1)-C(10)-C(5) | 105.28(13) |
| O(1)-C(3)-C(4) | 102.15(13) | C(11)-C(10)-C(5) | 117.34(13) |
| C(2)-C(3)-C(4) | 112.89(15) | C(19)-C(11)-C(12) | 120.60(16) |
| C(10)-O(1)-C(3) | 105.47(13) | C(19)-C(11)-C(10) | 121.34(16) |
| C(3)-C(4)-C(5) | 103.61(14) | C(12)-C(11)-C(10) | 118.04(16) |
| C(6)-C(5)-C(8) | 109.57(14) | C(13)-C(12)-C(11) | 119.46(17) |
| C(6)-C(5)-C(4) | 113.25(14) | O(6)-C(13)-C(12) | 124.57(16) |
| C(8)-C(5)-C(4) | 111.10(14) | O(6)-C(13)-C(15) | 114.85(15) |
| C(6)-C(5)-C(10) | 110.66(14) | C(12)-C(13)-C(15) | 120.56(16) |
| C(8)-C(5)-C(10) | 110.31(13) | C(13)-O(6)-C(14) | 117.12(14) |
| C(4)-C(5)-C(10) | 101.73(13) | O(7)-C(15)-C(17) | 120.49(16) |
| O(2)-C(6)-O(3) | 123.85(17) | O(7)-C(15)-C(13) | 119.75(16) |
| O(2)-C(6)-C(5) | 124.72(16) | C(17)-C(15)-C(13) | 119.59(16) |
| O(3)-C(6)-C(5) | 111.43(15) | C(15)-O(7)-C(16) | 113.27(13) |
| C(6)-O(3)-C(7) | 116.48(15) | O(8)-C(17)-C(15) | 115.59(15) |
| O(4)-C(8)-O(5) | 124.40(16) | O(8)-C(17)-C(19) | 124.24(16) |
| O(4)-C(8)-C(5) | 123.79(16) | C(15)-C(17)-C(19) | 120.16(16) |
| O(5)-C(8)-C(5) | 111.78(14) | C(17)-O(8)-C(18) | 117.01(14) |
| C(8)-O(5)-C(9) | 115.92(14) | C(11)-C(19)-C(17) | 119.60(16) |

**Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for gp4. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$**

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| C(1) | 34(1) | 43(1) | 25(1) | 9(1) | 0(1) | -3(1) |
| C(2) | 29(1) | 30(1) | 30(1) | 3(1) | 2(1) | -4(1) |
| C(3) | 26(1) | 25(1) | 20(1) | -2(1) | 0(1) | -2(1) |
| O(1) | 27(1) | 30(1) | 19(1) | 2(1) | 1(1) | -8(1) |
| C(4) | 24(1) | 24(1) | 20(1) | 1(1) | 0(1) | 0(1) |
| C(5) | 18(1) | 23(1) | 20(1) | -1(1) | 2(1) | 0(1) |
| C(6) | 23(1) | 25(1) | 18(1) | -2(1) | 4(1) | 0(1) |
| O(2) | 29(1) | 26(1) | 61(1) | 4(1) | -1(1) | 4(1) |
| O(3) | 30(1) | 23(1) | 35(1) | 2(1) | -6(1) | -6(1) |
| C(7) | 49(1) | 24(1) | 37(1) | 0(1) | -7(1) | -12(1) |
| C(8) | 18(1) | 22(1) | 22(1) | 0(1) | 2(1) | -3(1) |
| O(4) | 39(1) | 23(1) | 32(1) | 1(1) | 12(1) | 6(1) |
| O(5) | 29(1) | 24(1) | 19(1) | 0(1) | 6(1) | 1(1) |
| C(9) | 39(1) | 34(1) | 19(1) | -2(1) | 9(1) | 1(1) |
| C(10) | 20(1) | 24(1) | 19(1) | 0(1) | 4(1) | -1(1) |
| C(11) | 17(1) | 26(1) | 21(1) | -3(1) | 4(1) | 1(1) |
| C(12) | 20(1) | 23(1) | 24(1) | -1(1) | 2(1) | -3(1) |
| C(13) | 20(1) | 30(1) | 19(1) | 1(1) | 2(1) | 1(1) |
| O(6) | 34(1) | 30(1) | 20(1) | 2(1) | -3(1) | -4(1) |
| C(14) | 40(1) | 31(1) | 26(1) | 6(1) | 0(1) | -6(1) |
| C(15) | 18(1) | 29(1) | 21(1) | -5(1) | 1(1) | -2(1) |
| O(7) | 24(1) | 35(1) | 21(1) | -7(1) | 0(1) | -5(1) |
| C(16) | 34(1) | 52(1) | 26(1) | -14(1) | 5(1) | -5(1) |
| C(17) | 22(1) | 24(1) | 26(1) | -3(1) | 6(1) | -2(1) |
| O(8) | 43(1) | 25(1) | 27(1) | -3(1) | 4(1) | -10(1) |
| C(18) | 30(1) | 28(1) | 33(1) | 1(1) | 7(1) | -5(1) |
| C(19) | 22(1) | 26(1) | 20(1) | 1(1) | 3(1) | 1(1) |

**Table 5. Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2$x $10^3$) for gp4.**

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(1A) | 8099 | 10005 | -2855 | 41 |
| H(1B) | 7749 | 11862 | -3132 | 41 |
| H(2) | 7695 | 12465 | -1710 | 36 |
| H(3) | 8370 | 9198 | -1351 | 29 |
| H(4A) | 6923 | 9003 | -926 | 28 |
| H(4B) | 6965 | 10831 | -534 | 28 |
| H(7A) | 6196 | 4706 | -128 | 57 |
| H(7B) | 6949 | 4641 | 730 | 57 |
| H(7C) | 7248 | 4453 | -237 | 57 |
| H(9A) | 7113 | 8750 | 2986 | 45 |
| H(9B) | 6480 | 10050 | 2412 | 45 |
| H(9C) | 7522 | 10481 | 2756 | 45 |
| H(10) | 9196 | 8850 | 155 | 25 |
| H(12) | 9282 | 8509 | 1868 | 27 |
| H(14A) | 10116 | 7301 | 4021 | 49 |
| H(14B) | 10313 | 7250 | 3014 | 49 |
| H(14C) | 9296 | 7533 | 3233 | 49 |
| H(16A) | 10431 | 13609 | 4593 | 56 |
| H(16B) | 9667 | 12301 | 4234 | 56 |
| H(16C) | 9673 | 14059 | 3779 | 56 |
| H(18A) | 10672 | 16399 | 1372 | 45 |
| H(18B) | 9902 | 15318 | 807 | 45 |
| H(18C) | 10937 | 14697 | 959 | 45 |
| H(19) | 9434 | 12867 | 627 | 27 |

**Table 6. Torsion angles [°] for gp4.**

| | | | |
|---|---|---|---|
| C(1)-C(2)-C(3)-O(1) | 127.9(2) | C(5)-C(10)-C(11)-C(12) | 65.5(2) |
| C(1)-C(2)-C(3)-C(4) | -117.8(2) | C(19)-C(11)-C(12)-C(13) | 1.4(3) |
| C(2)-C(3)-O(1)-C(10) | 168.88(15) | C(10)-C(11)-C(12)-C(13) | 179.73(15) |
| C(4)-C(3)-O(1)-C(10) | 48.09(16) | C(11)-C(12)-C(13)-O(6) | -179.63(16) |
| O(1)-C(3)-C(4)-C(5) | -39.22(17) | C(11)-C(12)-C(13)-C(15) | -0.9(3) |
| C(2)-C(3)-C(4)-C(5) | -158.98(15) | C(12)-C(13)-O(6)-C(14) | 6.8(2) |
| C(3)-C(4)-C(5)-C(6) | -101.87(16) | C(15)-C(13)-O(6)-C(14) | -171.98(16) |
| C(3)-C(4)-C(5)-C(8) | 134.31(15) | O(6)-C(13)-C(15)-O(7) | 2.8(2) |
| C(3)-C(4)-C(5)-C(10) | 16.91(17) | C(12)-C(13)-C(15)-O(7) | -175.97(15) |
| C(8)-C(5)-C(6)-O(2) | -99.8(2) | O(6)-C(13)-C(15)-C(17) | 178.16(15) |
| C(4)-C(5)-C(6)-O(2) | 135.52(18) | C(12)-C(13)-C(15)-C(17) | -0.7(3) |
| C(10)-C(5)-C(6)-O(2) | 22.0(2) | C(17)-C(15)-O(7)-C(16) | 97.0(2) |
| C(8)-C(5)-C(6)-O(3) | 79.70(17) | C(13)-C(15)-O(7)-C(16) | -87.7(2) |
| C(4)-C(5)-C(6)-O(3) | -44.96(19) | O(7)-C(15)-C(17)-O(8) | -3.9(2) |
| C(10)-C(5)-C(6)-O(3) | -158.44(14) | C(13)-C(15)-C(17)-O(8) | -179.17(15) |
| O(2)-C(6)-O(3)-C(7) | 0.3(3) | O(7)-C(15)-C(17)-C(19) | 177.12(15) |
| C(5)-C(6)-O(3)-C(7) | -179.22(15) | C(13)-C(15)-C(17)-C(19) | 1.8(3) |
| C(6)-C(5)-C(8)-O(4) | -161.51(16) | C(15)-C(17)-O(8)-C(18) | 157.49(16) |
| C(4)-C(5)-C(8)-O(4) | -35.6(2) | C(19)-C(17)-O(8)-C(18) | -23.6(2) |
| C(10)-C(5)-C(8)-O(4) | 76.4(2) | C(12)-C(11)-C(19)-C(17) | -0.2(3) |
| C(6)-C(5)-C(8)-O(5) | 20.36(19) | C(10)-C(11)-C(19)-C(17) | -178.49(15) |
| C(4)-C(5)-C(8)-O(5) | 146.26(14) | O(8)-C(17)-C(19)-C(11) | 179.67(16) |
| C(10)-C(5)-C(8)-O(5) | -101.71(16) | C(15)-C(17)-C(19)-C(11) | -1.4(3) |
| O(4)-C(8)-O(5)-C(9) | -6.0(2) | | |
| C(5)-C(8)-O(5)-C(9) | 172.14(14) | | |
| C(3)-O(1)-C(10)-C(11) | -164.55(13) | | |
| C(3)-O(1)-C(10)-C(5) | -36.80(16) | | |
| C(6)-C(5)-C(10)-O(1) | 131.48(14) | | |
| C(8)-C(5)-C(10)-O(1) | -107.10(15) | | |
| C(4)-C(5)-C(10)-O(1) | 10.87(17) | | |
| C(6)-C(5)-C(10)-C(11) | -104.89(17) | | |
| C(8)-C(5)-C(10)-C(11) | 16.5(2) | | |
| C(4)-C(5)-C(10)-C(11) | 134.50(15) | | |
| O(1)-C(10)-C(11)-C(19) | 4.7(2) | | |
| C(5)-C(10)-C(11)-C(19) | -116.17(18) | | |
| O(1)-C(10)-C(11)-C(12) | -173.68(14) | | |