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# NEW ROUTES TO HIGHLY FUNCTIONALISED HETEROCYCLIC COMPOUNDS FROM CYCLOPROPANES

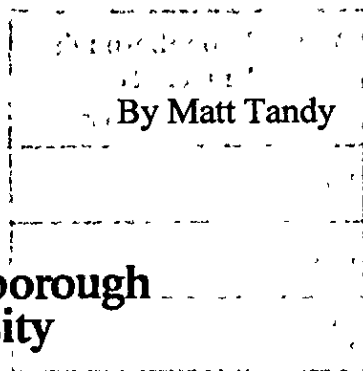
A thesis submitted to the department of chemistry

in partial fulfilment of the requirements

for the degree of

Doctor of Philosophy

at Loughborough University





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For all those who believed  
I could achieve this even  
when I doubted it myself.

## ABSTRACT

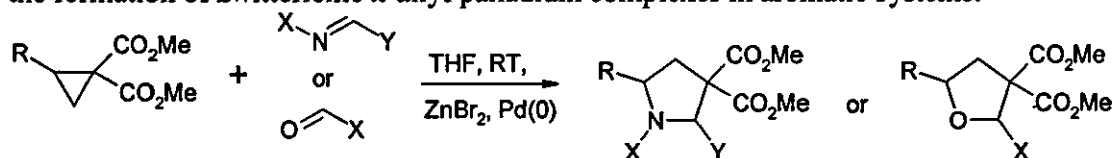
Matthew D. Tandy  
Loughborough University

D. Phil  
2005

### New Routes to Highly Functionalized Heterocyclic Compounds from Cyclopropanes

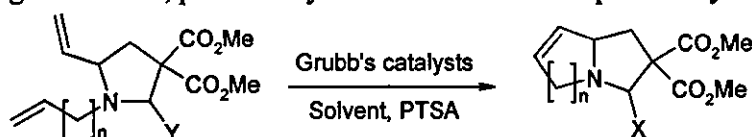
Heterocyclic compounds are of great importance in the pharmaceutical industry as well as academic research so key methodology, which generates a highly functionalized medium ring in the minimum number of steps, is of great interest. This project addresses this challenge by looking at the formation of pyrrolidines and furans from cyclopropanes via a [2+3] cycloaddition reaction in a highly atom efficient approach.

Prior to our work in this field, Tsuji and others have shown the formation of a zwitterionic  $\pi$ -allyl palladium complex derived from vinylcyclopropanes and naphthalenes is possible. During the project, we have improved the understanding of the formation of zwitterionic  $\pi$ -allyl palladium complexes in aromatic systems.

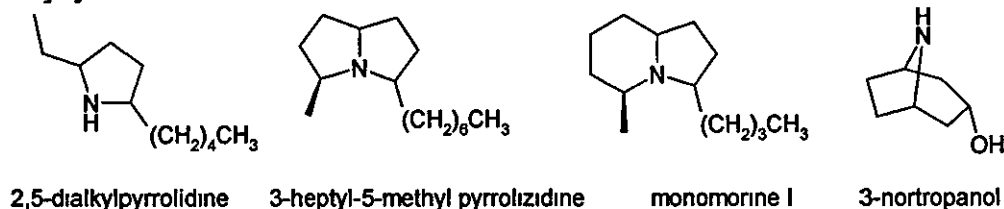


R = vinyl or aromatic

Ring closing metathesis reactions using Grubb's catalysis are some of the most important modern reactions. It was felt that the application of ring closing metathesis reactions to the substrates which are formed via the [2+3] cycloaddition would be of great benefit, particularly in the field of natural product synthesis.



The final major aspect of the work conducted in this project is the application of the core [2+3] cycloaddition to the formation of a number of natural products. It is thought that 2,5-dialkylpyrrolidine, 3-heptyl-5-methyl pyrrolizidine, monomorine I and 3-nortropanol are viable targets because of their pyrrolidine / fused pyrrolidine cores. However much work is needed to form the desired natural products via the [2+3] cycloaddition intermediate.



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## Abbreviations

%	percent
( <i>RR</i> )-DPPBA	2-diphenylphosphinobenzoic acid <i>trans</i> -cyclohexane-1,2-diamine
$[\alpha]^{20}_D$	specific rotation (deg ml / g dm)
Å	Angstrom
Ac	acetyl
acac	acetylacetonate
aq.	aqueous
Ar	aromatic
atm	atmosphere
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
b.p.	boiling point
BPPF	bis(diphenylphosphino)ferrocenylethylamine
Br	bromide
BSA	<i>N,O</i> -bis(trimethylsilyl)acetamide
Bu	butyl
$^{13}\text{C}$	carbon NMR
CA	chiral auxiliary
CAN	ceric ammonium nitrate
cat.	catalytic
$\text{CDCl}_3$	deuterated chloroform
$\text{CHCl}_3$	chloroform
Cl	chlorine
cm	centimetre
$\text{cm}^{-1}$	wave number
CN	nitrile
$\text{CO}_2$	carbon dioxide
COD	1,5-cyclooctadiene

Cu	copper
Cu(acac) <sub>2</sub>	copper acetylacetonate
CuCl <sub>2</sub>	copper chloride
d	days
d.e.	diastereomeric excess
DEPT	distortionless enhancement by polarisation transfer
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
dec	decomposition
DIAD	diisopropyl azodicarboxylate
DMF	<i>N,N'</i> -dimethyl formamide
DMSO	dimethyl sulfoxide
dppe	bis(diphenylphosphino)ethane
e.e.	enantiomeric excess
EI	electron impact
eq	equivalent(s)
ESI	electronspray ionization
Et	ethyl
<i>et. al.</i>	<i>et alia</i>
Et <sub>2</sub> O / ether	diethyl ether
EtCN	propionitrile
Et <sub>4</sub> NCl	tetraethylammonium chloride monohydrate
EtOAc	ethyl acetate
EWG / E	electron withdrawing group
F	fluorine
FAB	fast atom bombardment
Fig	figure
FT-IR	Fourier transform infrared
FVT	flash-vacuum thermolysis
g	grams
GHz	gigahertz

Grubb's I	benzylidene-bis(tricyclohexylphosphine)dichlororuthenium
Grubb's II	[(1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene) dichloro(phenylmethylene)-(tricyclohexylphosphine)ruthenium]
h	hours
$^1\text{H}$	proton NMR
H / H <sub>2</sub>	hydrogen
H <sub>2</sub> O	water
HCl	hydrochloric acid
HCO <sub>2</sub> NH <sub>4</sub>	ammonium formate
HIV	human immunodeficiency virus
HOSO <sub>2</sub> Cl	chlorosulphonic acid
I	iodine
K <sub>2</sub> CO <sub>3</sub>	potassium carbonate
KF-Al <sub>2</sub> O <sub>3</sub>	potassium fluoride on alumina
KI	potassium iodine
KOAc	potassium acetate
KOH	potassium hydroxide
kV	kilovolt
lit.	literature value
Ln / L	ligand
m	metre
M	mol dm <sup>-3</sup>
m/z	mass to charge ratio
Me	methyl
Me <sub>2</sub> S	dimethylsulphide
MeCN	acetonitrile
MeOH	methanol
Me <sub>3</sub> SnOAc	trimethyltinacetate
mg	milligram
MgSO <sub>4</sub>	magnesium sulphate
MHz	megahertz

min	minute
mL	millilitre
mm	millimetre
mmol	millimole
MnO <sub>2</sub>	manganese(IV) dioxide
mol sieves	molecular sieves
mol%	mole percent
MW	microwave
N	nitrogen
N <sub>2</sub>	nitrogen gas
NaCl	sodium chloride
NaHCO <sub>3</sub>	sodium hydrogen carbonate
NaIO <sub>4</sub>	sodium periodate
NaO <i>t</i> Bu	sodium <i>tert</i> -butoxide
NaOH	sodium hydroxide
NaOMe	Sodium methoxide
Ni	nickel
Ni(COD)	nickel 1,5-cyclooctadiene
NMR	nuclear magnetic resonance
NO <sub>2</sub>	nitro
NOE	nuclear overhauser effect
[O]	oxidation
O <sub>2</sub>	oxygen gas
O <sub>3</sub>	ozone
OAc	acetyl
°C	degrees Celsius
<sup>-</sup> OEt	ethoxide
OH	hydroxide
OMe	methoxide
P	phosphorous
P(O)Bu <sub>3</sub>	tri- <i>n</i> -butyl phosphine oxide

P(O <sup><i>i</i></sup> Pr) <sub>3</sub>	tri- <i>i</i> -propyl phosphine oxide
P.E.	petrol ether 60:40
PBr <sub>3</sub>	phosphorous tri-bromide
PBu <sub>3</sub>	phosphorous tri- <i>n</i> -butyl
PCy <sub>3</sub>	phosphorous tri-cyclohexane
Pd	palladium
Pd(OAc) <sub>2</sub>	palladium acetate
Pd(PPh <sub>3</sub> ) <sub>4</sub>	palladium tetrakis(triphenylphosphine)
Pd/C	palladium on carbon (10 mol%)
Pd <sub>2</sub> (dba) <sub>3</sub>	palladium tris(dibenzylideneacetone)
PdCl <sub>2</sub>	palladium chloride
Ph	phenyl
Ph(O)I	iodosobenzene
<sup><i>p</i></sup> -PMB	<i>p</i> -methoxybenzyl
PPFA	<i>N,N</i> -dimethyl-1,2-(diphenylphosphino)ferrocenylethylamine
PPh <sub>3</sub>	triphenylphosphine
psi	pounds per square inch
PTSA	<i>p</i> -toluenesulphonic acid monohydrate
RADAR	radio direction finding
RBF	round bottomed flask
RCM	ring closing metathesis
R <sub>f</sub>	retention factor
Rh	rhodium
Rh <sub>2</sub> (OAc) <sub>4</sub>	rhodium acetate
ROMP	ring opening metathesis polymerization
RT	room temperature
Ru	ruthenium
SiO <sub>2</sub>	silica gel
<i>t</i> -	tertiary-
<i>t</i> -BuOK	potassium tert-butoxide
TFA	trifluoroacetic acid

THF	tetrahydrofuran
TLC	thin layer chromatography
TMM	trimethylenemethane
TMS	trimethylsilyl
Ts	<i>p</i> -toluenesulfonyl
w	watt
ZnBr <sub>2</sub>	zinc bromide
μL	microlitre

#### IR data

w	weak
m	medium
s	strong
br	broad

#### NMR data

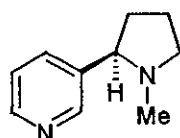
s	singlet
d	doublet
dd	doublet of doublets
t	triplet
q	quartet
m	multiplet
ppm	parts per million
<i>J</i>	coupling constant

## **Chapter 1 – Introduction**

### **Section 1.1 – General Introduction to Pyrrolidines and Palladium Catalysts**

#### **1.1.1 – The Importance of Pyrrolidines as a Pharmacophore in Pharmaceuticals**

Pyrrolidine is a nitrogen heterocycle which occurs widely in nature as a component of many alkaloids, for example the pyrrolizidine, indolizidine and quinolizidine alkaloids.<sup>1</sup> The pyrrolidine core is also present in a number of antibiotics, antibacterial, antifungal and compounds which are known to have a cytotoxic effect.<sup>1</sup> Since they offer opportunities to develop novel pharmacologically active agents, routes to the pyrrolidines are an important goal for modern synthesis. An example of a common natural product which contains a pyrrolidine in it, is nicotine **1** (Fig 1), which affects the central nervous system by acting as a neurotransmitter.<sup>2</sup> It could therefore be possible to change or add functional groups to the parent molecule in order to develop a range of novel, non-natural neurotransmitters.<sup>2</sup>

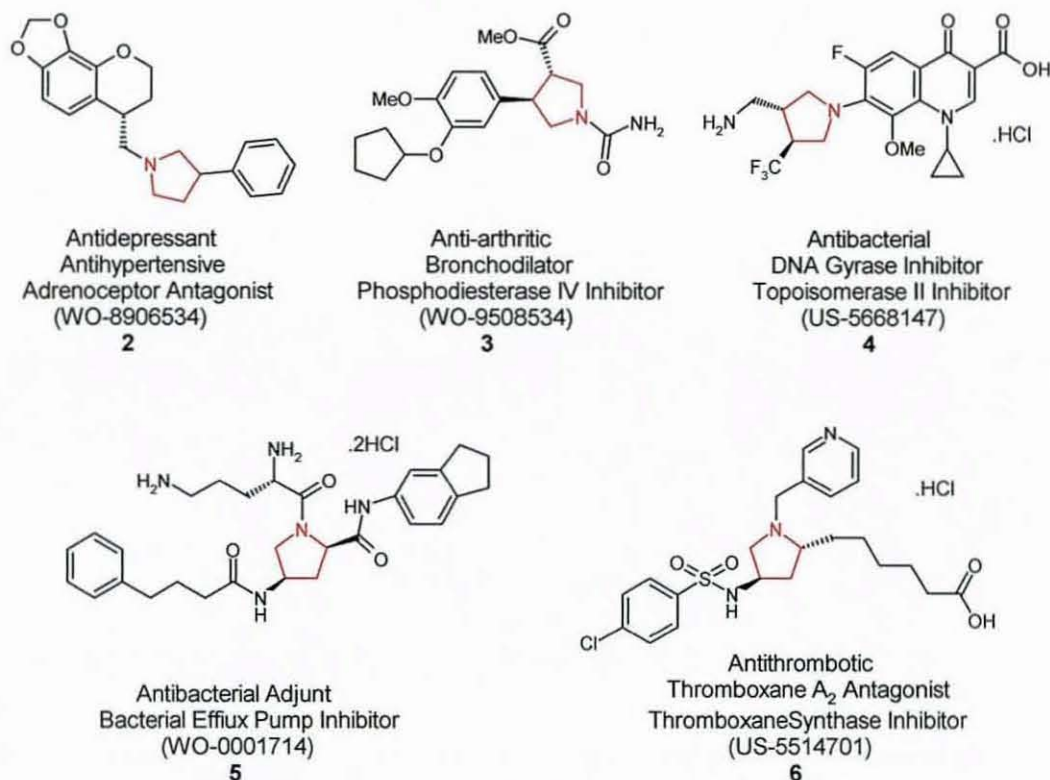


(S)-nicotine **1**

**Fig 1- Nicotine**

The importance of heterocyclic rings in drugs cannot be underestimated. Heterocyclic compounds show a wide range of bio-activity,<sup>2</sup> and drugs containing pyrrolidines have been shown to have properties varying from antidepressants,

antihypertensive, anti-arthritic, anti-HIV activity to antibacterial properties 2-6 (Fig 2) as well as many other pharmacological effects.<sup>3</sup>



**Fig 2** – Drugs containing pyrrolidine rings.

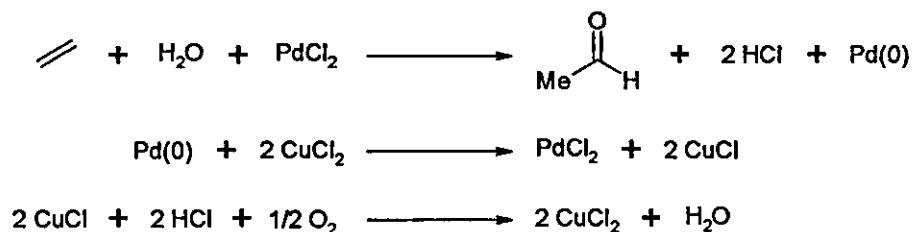
The development of new methodologies which generates novel highly functionalized heterocyclic compounds in a minimum number of steps is highly desirable, due to the demand for short and easy routes to small molecules for biological testing and also in the synthesis of natural products containing heterocyclic components.

### 1.1.2 – General Introduction to Common Palladium Catalyst

Palladium is a rare and expensive metal in group 10 of the Periodic Table, and is one of the most important metals used as a catalyst in organic synthesis. A number of compounds such as Pd(PPh<sub>3</sub>)<sub>4</sub>, Pd<sub>2</sub>(dba)<sub>3</sub>, PdCl<sub>2</sub> and Pd(OAc)<sub>2</sub> (which are

the most commonly used forms of palladium in organic synthesis) are commercially available. Palladium catalysts exhibit a wide range of reactivity and can be used for a number of reactions such as transmetalation, oxidative additions and carbopalladations as well as [2+3]-cycloadditions.<sup>4</sup>

Palladium chemistry became popular in the 1960's when the Wacker process was developed using a palladium (II) catalyst. This reaction is the formation of acetaldehyde from ethylene which is catalysed using  $\text{PdCl}_2$ .<sup>4</sup> In this reaction, ethylene and oxygen is bubbled through acidified water in the presence of  $\text{PdCl}_2\text{-CuCl}_2$ . During the reaction palladium forms a complex with ethylene, is reduced to  $\text{Pd}(0)$ , and is then re-oxidized by  $\text{Cu(II)}$ . The process is run in one vessel at 50-130 °C and at pressures of 3-10 atm.



**Scheme 1 – Wacker process<sup>4</sup>**

Researchers soon realised the importance palladium reactions and in particular their reactivity with aryl halides. Since the 1960s, the use of palladium as a catalyst has risen dramatically, it is now common place to have palladium catalyst in many reaction processes and an understanding of the mechanism in some palladium mediated processes is now well known. The reason for much of the success of palladium catalysts is the diversity of reactions that can be carried out,<sup>4</sup> and with every new application of this catalyst which is discovered more chemists will use this remarkable metal.

### 1.1.3 – Introduction to [2+3]-Cycloaddition Reactions

The [2+3]-cycloaddition reaction is one of the most versatile methods for the construction of five membered rings, mainly heterocycles and to a lesser extent cyclopentanes. A cycloaddition approach can be carried out using many synthetic methods; either intra-molecularly or inter-molecularly, and proceeds with the formation of two bonds in a single reaction.

Metal catalysis are playing an increasingly important role in [2+3]-cycloaddition reactions and often allow several stereo-centers to be selectively created and integrated in the target molecule.<sup>4-9</sup>

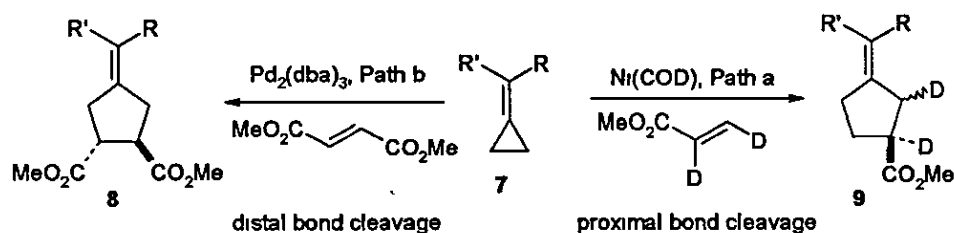
## Section 1.2 – [2+3]-Cycloadditions Reactions

### 1.2.1 – Methylene Cyclopropanes and Their Analogues in [2+3]-Cycloadditions

Transition-metal-catalyzed [2+3]-cycloaddition reactions are one of the most effective methods for constructing five-membered carbo- and heterocycles. Methylene cyclopropanes are particularly useful 'three carbon components' for [2+3]-cycloaddition reactions, and the synthesis of carbo- and hetero-cycles via the intermolecular [2+3]-cycloaddition reaction of methylene cyclopropanes with a carbon-carbon multiple bond has been reported by several groups, as have the heterocyclic variants of these reactions.<sup>10-18</sup>

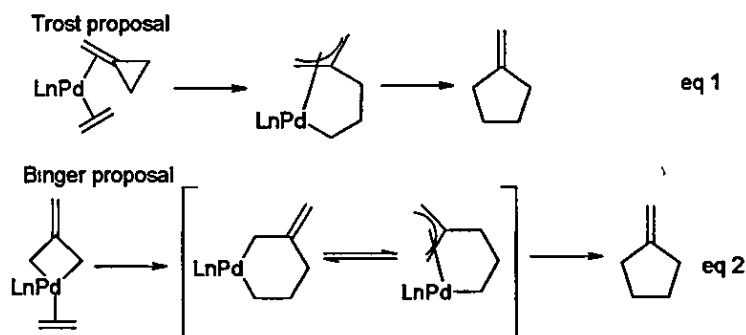
Methylene cyclopropanes **7**, were first looked at by Trost *et al.* and were found to undergo [2+3]-cycloaddition with alkenes in the presence of some transition metal catalysts.<sup>19</sup> Among these metals, nickel and palladium complexes are the best documented and can react with methylene cyclopropanes and olefins to generate five membered rings, although there are some differences in the chemoselectivity and stereoselectivity of these reactions.<sup>8, 10-12, 20</sup>

Binger *et al.*, the same time as Trost, was one of the first to look into this [2+3]-cycloaddition, made a number of interesting and important discoveries.<sup>21</sup> Palladium or nickel catalysts can facilitate this cycloaddition process, although the regio-chemical outcome of the reactions is highly dependent on the nature of the metal and its associated ligands. Binger showed that nickel catalysts, particularly in the presence of ligands (COD in this example), favours formation of products from cleavage of the proximal bond of the cyclopropane **9** (Scheme 5, path a),<sup>21</sup> whereas a palladium catalysts gives products from distal bond cleavage **8** (Scheme 5, path b).<sup>21</sup> Also geometrically defined alkene acceptors often generate products in which the initial alkene geometry has been preserved. The ability to control both the regio and stereochemical outcome of this process suggests that it might provide a powerful method for cyclopentanoid synthesis.



**Scheme 2** – Palladium and nickel reactions with cyclopropanes<sup>20</sup>

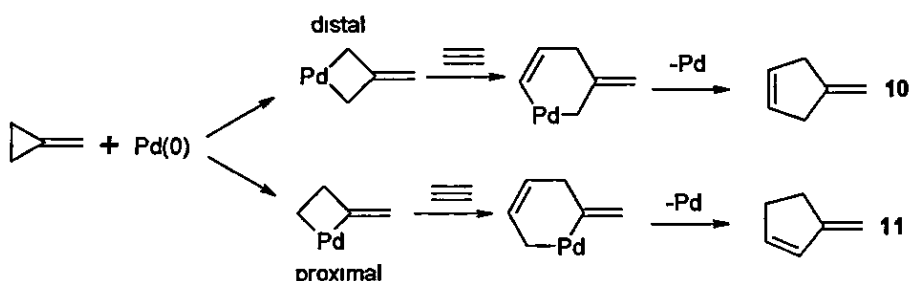
In the [2+3]-cycloaddition, a methylene cyclopropane complex is suggested to be formed initially as a reaction intermediate, in which the cyclopropane coordinates to the metal center to form a metallacycle. There may be two metallacyclic forms, depending on whether the metal species attacks the distal bond or a proximal bond of the cyclopropane. There have been two mechanistic proposals postulated to explain the [2+3]-cycloaddition of methylene cyclopropanes which take into account the initial reaction intermediates. The mechanism proposed by Trost proceeds via a  $\eta^2$ -alkene substituted cyclopropane intermediate (Scheme 3, eq 1),<sup>10</sup> whereas Binger proposed a mechanism which goes via a metallacyclobutane intermediate (Scheme 3, eq 2)<sup>10</sup>



**Scheme 3** – Proposals for mechanisms for [2+3] cycloaddition

In the mechanism originally proposed by Trost, the distal bond of the methylene cyclopropane coordinates to the metal and attacks the double bond of the olefin trapping agent to generate a  $\pi$ -allyl intermediate. This can then ring close to give the cyclopentane (Scheme 3, eq 1). This is a logical proposal because the cleavage of the distal bond of the cyclopropane ring has been shown to be more favorable than that of a proximal bond.<sup>10</sup> However there is evidence from Noyori *et*

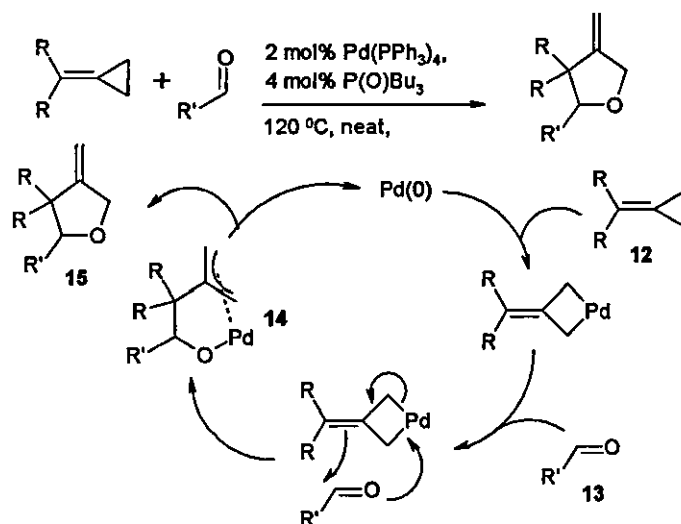
*al.*<sup>10</sup> that the cycloaddition when using palladium between methylene cyclopropane 7 and alkene Scheme 2 occurs via the Binger mechanism which involves the proximal bond opening. These coupling reactions investigated by Noyori, Binger and Trost have shown some differences in the chemo- and stereoselectivity. As during the opening of the proximal bond would lead to coordination of the alkene trapping agent and subsequent rearrangement to the metalacyclohexane species, which could then ring contract with the loss of palladium to give the cyclopentene 11 (Scheme 4).



**Scheme 4** – Binger mechanism opening both distal and proximal bonds<sup>22</sup>

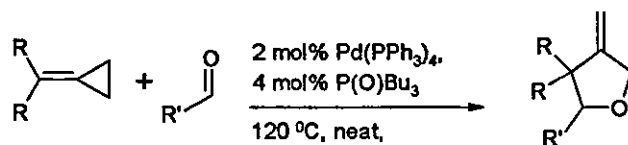
The synthesis of cyclic ethers by [2+3]-cycloadditions falls into two categories, in where either vinylic oxiranes are used as a "two carbon and one-oxygen component" in the palladium-catalyzed cycloaddition, or in the reaction of TMM precursors, which are thought to be "three-carbon components," with carbonyl compounds.

This second type of chemistry has been used by Yamamoto *et al.*<sup>22</sup> in the formation of tetrahydrofurans 15 by the reaction of methylene cyclopropanes 12 and aldehydes 13 (Scheme 5) in the presence of palladium(0). This is a particularly interesting example as the reaction is carried out neat using a low catalytic loading of palladium (2 mol%). Here it is suggested that the insertion of palladium occurs into the distal bond of the methylene cyclopropane, leading to the palladacyclobutane complex. The pallada-ene type reaction of the metallacyclobutene with the aldehyde 13 may proceed to give the  $\pi$ -allylpalladium complex 14. Reductive elimination of palladium(0) then gives the [2+3]-cycloadduct 15.



**Scheme 5** – Tetrahydrofuran formation using the Binger proposal

Yamamoto<sup>22</sup> has synthesized various types of exo-methylene tetrahydrofuran derivatives through this palladium-catalyzed [2+3]-cycloaddition between methylene cyclopropanes and aldehydes. This atom-economical reaction may be potentially useful for constructing biologically important tetrahydrofuran skeletons

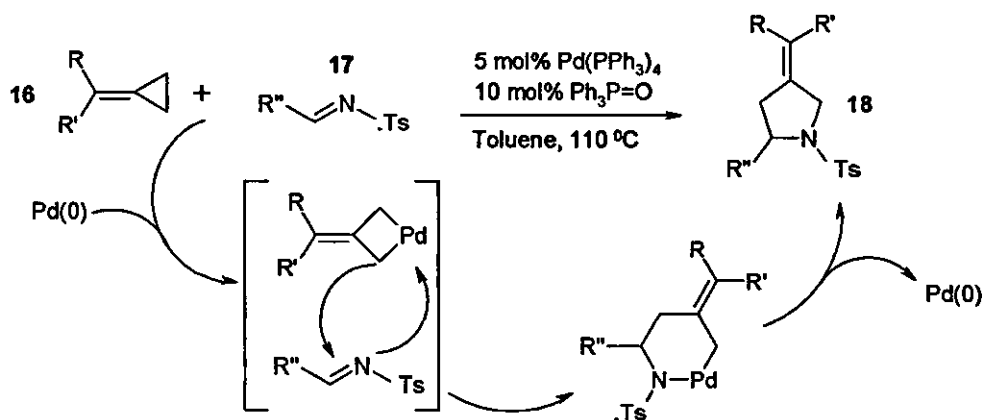


	<i>Cyclopropane</i>	<i>Aldehyde</i>	<i>Time (h)</i>	<i>Yield (%)</i>
1			5	75
2			11	71
3			16	86
4			20	77
5			12	51

6			19	64
7			19	3

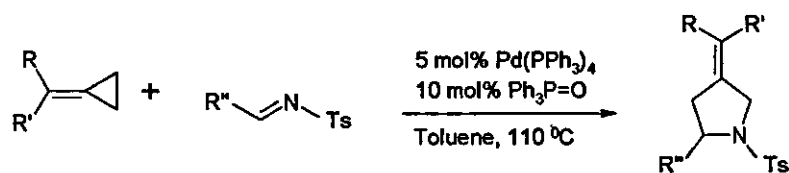
**Table 1** – Reactions between exo-methylene cyclopropanes and aldehydes

A further example of this chemistry also carried out by Yamamoto *et. al*<sup>8</sup> showed that an *N*-tosyl imine **17** reacted with methylene cyclopropane to give pyrrolidines **18** (Scheme 6). This reaction underwent the same [2+3]-cycloaddition which was seen in Scheme 5. Yamamoto *et. al.* then used this reaction to generate a range of pyrrolidines. A plausible mechanism is that the oxidative addition of palladium(0) to a distal bond of the alkylidene cyclopropane leads to the palladacyclobutane complex which reacts with the imine to give the  $\pi$ -allylpalladium complex. Reductive elimination of palladium(0) gives the [2+3]-cycloadduct. Using this process, Yamamoto has developed a novel and efficient route to pyrrolidine derivatives through the palladium catalyzed [2+3]-cycloaddition between methylene cyclopropanes and imines.



**Scheme 6** – Formation of pyrrolidine using [2+3]-cycloaddition

The reaction conditions for these palladium-catalyzed [2+3]-cycloaddition of methylene cyclopropanes with *N*-tosyl imines **17** is the presence of 5 mol% of  $\text{Pd}(\text{PPh}_3)_4$  and 10 mol% of triphenylphosphine oxide at 120 °C which gives the corresponding pyrrolidine [2+3]-cycloadducts in good to excellent yields (Table 2).



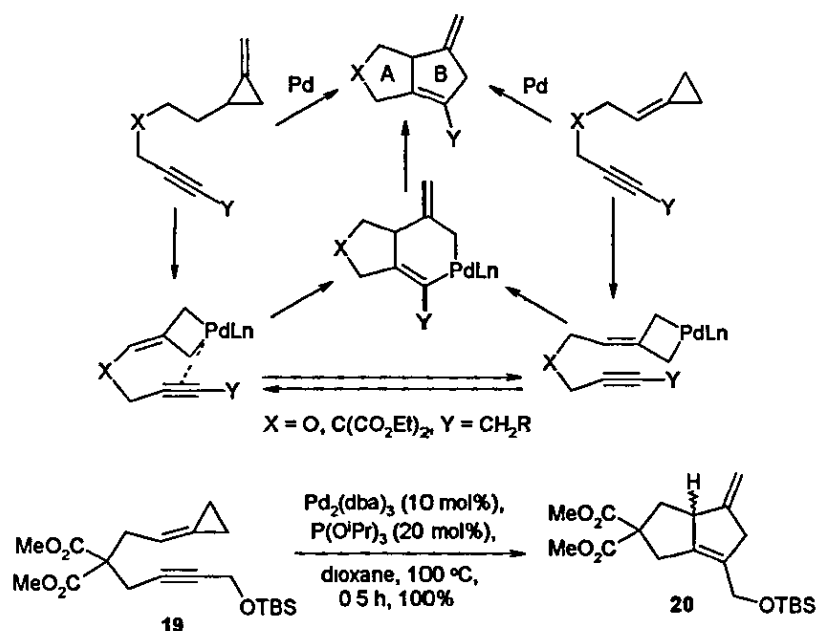
	<i>Cyclopropane</i>	<i>Imine</i>	<i>Time (h)</i>	<i>Yield (%)</i>
1			16	89
2			18	88
3			13	91
4			20	71
5			17	91
6			16	93

**Table 2** – Reactions between exo-methylene cyclopropanes and imines

#### *Tethered methylene cyclopropane [2+3]-cycloaddition chemistry*

As well as the transition metal catalyzed [2+3]-cycloaddition of methylene cyclopropanes with olefins to generate five membered heterocyclic compounds, this reaction can be carried out in an intramolecular fashion, as shown by the Mascareñas<sup>15</sup> and Motherwell<sup>16-18, 21, 24</sup> groups. This intramolecular method should offer some considerable advantages over the intermolecular approach, as it should provide an enhanced level of regio-control and stereo-control during the palladium catalyzed [2+3]-cycloaddition reaction. This is because compounds such as these are known to readily undergo regio-specific distal cleavage of the cyclopropane ring in the presence of palladium catalysts allowing for a more controlled [2+3]-cycloaddition.

The reaction mechanism for this process is thought to be the same as the palladium catalyzed [2+3]-cycloaddition onto a methylene cyclopropane (Scheme 5) i.e. with palladium insertion into the cyclopropane to generate a metallacyclobutene intermediate. This cyclic intermediate could then coordinate to the tethered alkyne/alkene bond. Ring closure of this intermediary species would leave, in this case, the 5,6-bicycle metallacyclic product. The final step in the reaction would be the loss of palladium leaving the 5,5-bicycle. It would even be possible to alter the size of the 'A' and 'B' ring by adjusting the length of the tether (Scheme 7). The reaction shown below was performed by Mascareñas *et. al.*<sup>15</sup> and shows how different substrates can be reacted to generate the same bicyclic system

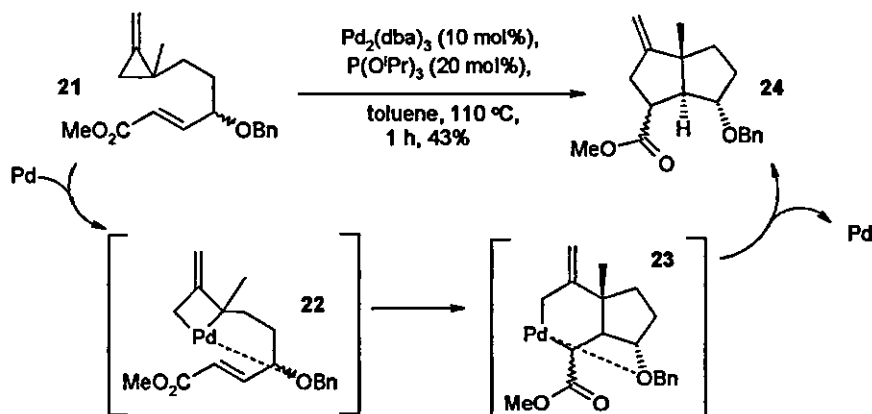


**Scheme 7 – Tethered methylenecyclopropane**

The major cycloadduct **20** consisted of two isomers in a 5:1 ratio. However no attempts were made to ascertain the absolute configuration at the proton indicated in Scheme 7. The reaction is highly dependant not only on the nature of the ancillary ligands around palladium, but also on the exact nature of the substrate. Motherwell proposed that the mechanism proceeds through ring opening of the cyclopropane to generate a charged intermediate. However due to steric hindrance in the transition state and interactions between the palladium and substrates there was

scrambling of the regio-chemistry of the ester during the ring closure step. Although this type of reaction is interesting it does have its drawbacks as it is limited due to its relatively low reactivity of the substrates.

A further example by Motherwell *et al.*<sup>18</sup> of this type of chemistry has an electron donating group which is used in the [2+3]-cycloaddition reaction in an attempt to improve the stereochemical outcome of the reaction. During this highly selective reaction there is an oxidative addition of the palladium into the distal bond of the methylene cyclopropane **21** which results in formation of a transition state **22** where the oxygen atoms on the protected alcohol adopt a pseudo-axial orientation, enabling it to complex and stabilize the cationic  $\pi$ -allyl palladium intermediate. Subsequent ring closure would lead to the formation of the desired bi-cyclic product **24** (Scheme 8).<sup>18</sup>



**Scheme 8** – Trost tethered methylenecyclopropane mechanism

Catalysts for these reactions were prepared *in situ* from di-palladium tris(dibenzylideneacetone) by addition of four equivalents of triisopropylphosphite. The cyclisations were performed by simply refluxing the substrate in toluene in the presence of 5-20 mol% of this catalyst mixture. These results were further supported by NOE measurements which confirmed the location of the exocyclic double bond

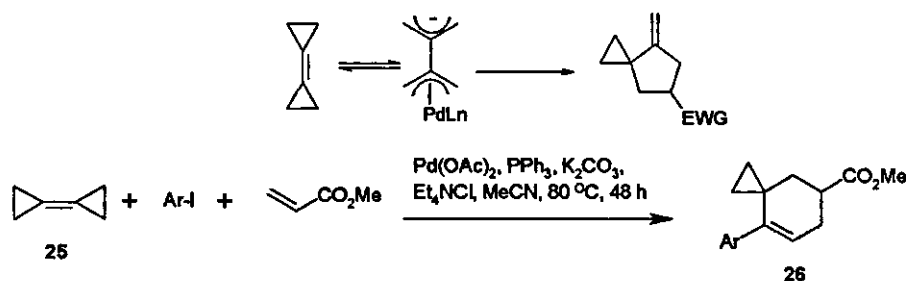
The examples clearly highlight that the intramolecular variant of the palladium catalyzed [2+3]-cycloaddition is a useful for controlling regioselectivity and minimizing unwanted dimerisation reactions. It is also evident that changes

particularly in the nature of the tethering chain may have a profound effect on these cyclisations.

### Bicyclopropylidene

An example of bicyclopropylidene **25** looks at the use of aryl halides which can be efficiently cross-coupled to it. This reaction has been widely explored and shown to have reasonably high combinatorial potential since not only can different aryl halides and different dienophiles, but even differently substituted bicyclopropylidenes, be employed.

As well as being a highly interesting substrate the products generated from this reaction are extremely noteworthy in themselves. When the palladium inserts into the cyclopropane there is a zwitterionic intermediate formed. This zwitterionic intermediate can then either ring open the second cyclopropane or remain cleaved, where the anionic charge is stabilized by the cyclopropane ring. In this example by Meijere *et. al.*,<sup>13</sup> the overall reaction, after initial carbopalladation of the highly strained double bond in **25**, again involves a cyclopropylcarbonyl to homo-allyl rearrangement leading to the corresponding homo-allyl palladium species. This can finally undergo a hydride elimination to give the aryl-substituted diene **26**. This intermediate is then immediately trapped by any dienophile present in the mixture of the one-pot operation to give the tetraenes **26** (Scheme 9)



Scheme 9 – Bicyclopropylidene [2+3]-cycloaddition

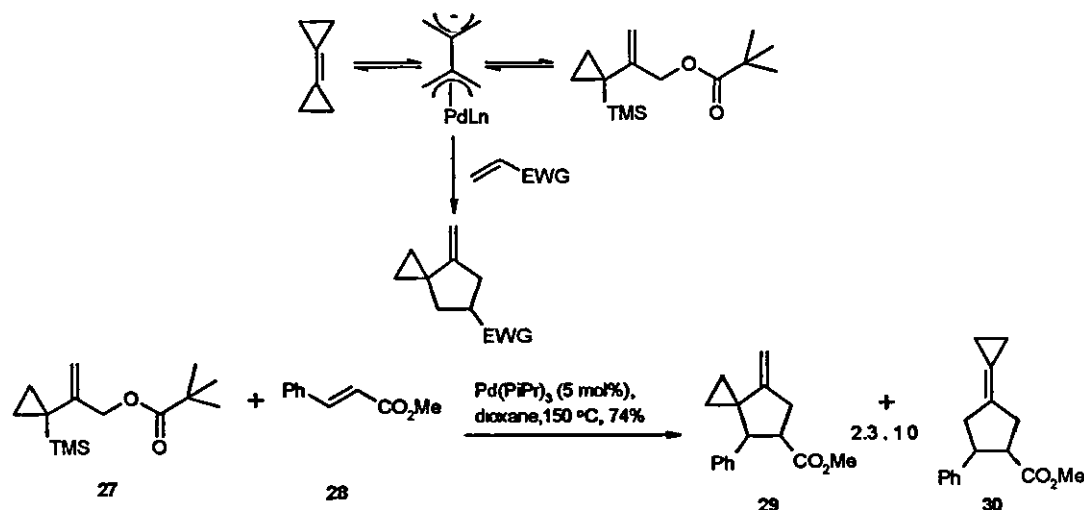
The use of bicyclopropylidene **25** in multi-component reactions is greatly enhanced by the presence of tris-(2-furyl)phosphine as a ligand instead of triphenylphosphine which generates an  $\sigma$ -allyl- /  $\pi$ -allylpalladium complex. The

formal rearrangement of the homoallyl- to the  $\pi$ -allylpalladium intermediate most probably proceeds by  $\beta$ -hydride elimination and immediately ensuing hydrido-palladation. When the reaction is performed in acetonitrile at 80 °C, the tetraenes **26** can be isolated.

	<i>Ar</i>	<i>Yield (%)</i>	<i>Cis:Trans</i>
1	Ph-I	100	-
2	2-Me-C <sub>6</sub> H <sub>4</sub> -I	99	2:1
3	4-Me-C <sub>6</sub> H <sub>4</sub> -I	91	-
4	2,4-Me-C <sub>6</sub> H <sub>3</sub> -I	98	2.5:1
5	2-Bn-C <sub>6</sub> H <sub>4</sub> -I	85	2:1
6	3-Pyr-I	67	-

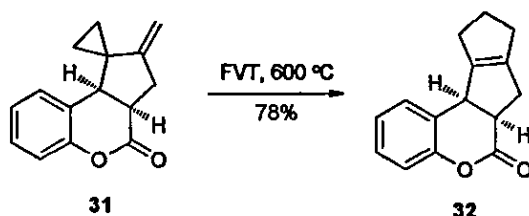
**Table 3** – Bicyclopopylidene [2+3]-cycloaddition<sup>13</sup> as shown in Scheme 9

As well as the use of the bicyclopopylidene **25** it is also possible to generate the same zwitterionic intermediate species through loss of a leaving group **27** (Scheme 10). The zwitterion can then be trapped using an activated alkene **28** to give the products **29-30**.<sup>12</sup> The products from this reaction still retain the spirocyclic structures as observed in Scheme 9.



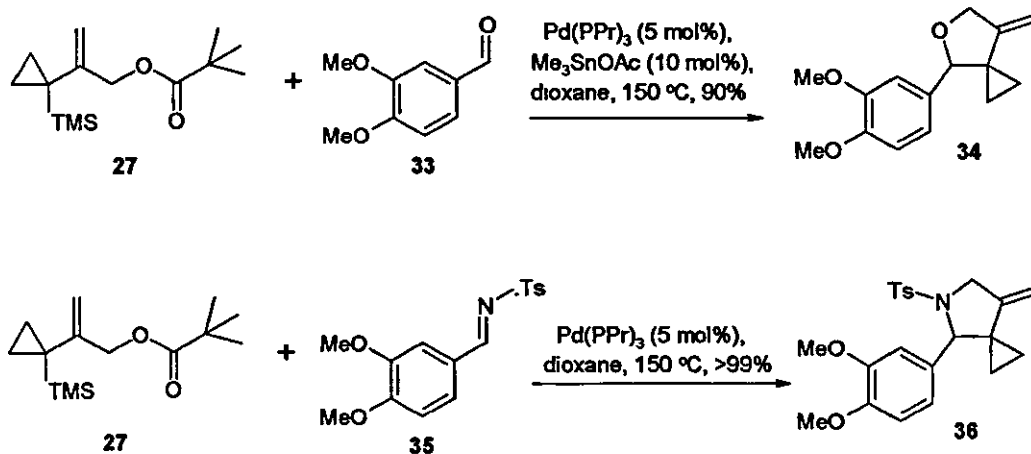
**Scheme 10** – Bis-methylenecyclopropane

The precursor **27** was synthesized in 18% overall yield from 1-bromovinyl-trimethylsilane. 2-Spirocyclopropylenethylene cyclopentanes and / or cyclopropylidene cyclopropanes are obtained depending upon the substrate, ligand, and solvent.<sup>12</sup> The reaction proceeded with 5 mol% palladium acetate and 50 mol% triisopropyl phosphite in dioxane at 150 °C. The bicyclopropylidenes have proven useful in further palladium catalyzed [2+3]-cycloadditions. The vinylcyclopropanes can then undergo smooth thermal rearrangement as illustrated in the isomerization of **31** to **32** in Scheme 11. Palladium catalyzed cycloadditions showed no reactivity when electron deficient alkenes are used as acceptors



**Scheme 11 – Isomerization of product**

With heteroatom - like aldehydes and aldimides, 2-spirocyclopropyl methylene tetrahydrofurans **34** and pyrrolidines **36** can be formed. Examples of heteroatom reactions with bicyclopropylidene **25** have been performed by Trost *et al*,<sup>13</sup> who showed that heteroatom acceptors showed a high selectivity for the formation of the vinyl cyclopropane. However in reactions using aldehydes as a trapping agent a two component catalyst was needed (5 mol% palladium tris(triisopropylphosphate) and 10 mol% trimethyl tin acetate) to generate the corresponding aldehyde **34**. However in the case of imines only palladium was needed as a catalyst to generate pyrrolidine **36** (Scheme 12)



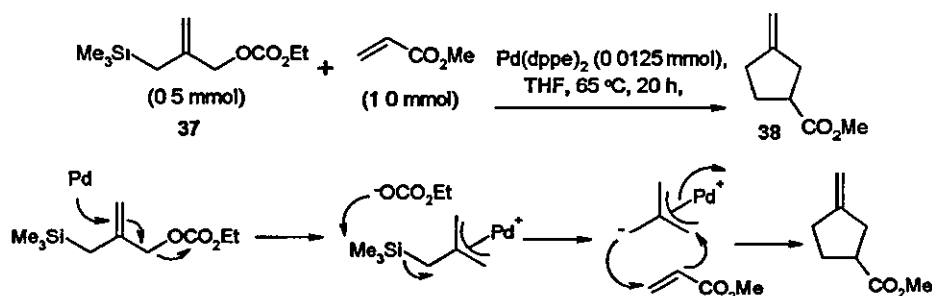
**Scheme 12** – Heteroatom reactions with bicyclopropylidene<sup>13</sup>

### 1.2.2 – Generating Zwitterionic Species in [2+3]-Cycloadditions From Isobutylene Derivatives.

For a palladium catalyzed [2+3]-cycloaddition reaction to occur a zwitterion needs to be formed from a substrate before it can react with a trapping agent such as alkene, alkyne, imine or aldehyde. Several groups have looked at the formation of such a zwitterionic reactive intermediates.<sup>25-31</sup> One way which has been commonly used is to have a leaving group generate the 1,3-dipole, i.e. when palladium reacts with the substrate elimination occurs to give the zwitterion which is then free to react with a trapping agent to form the cyclic product.

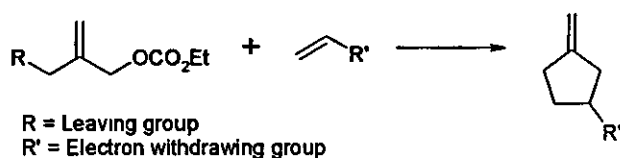
Although 1,3-dipolar cycloaddition reactions have been successfully employed in the synthesis of heterocyclic five-membered rings for some time, the application of cycloaddition reactions to the construction of carbo-cyclic equivalents has only recently received attention. However the usefulness of methods in organic synthesis depends upon accessibility of starting material with various functional groups.

In an example of this reaction type, which was performed by Tsuji,<sup>25</sup> there is a palladium-catalyzed [2+3]-cycloaddition using 2-(trimethylsilylmethyl) allyl carbonates **37** and a trapping agent to form methylene cyclopentanes **38**. In reactions such as these the zwitterionic  $\pi$ -allyl complexes are thought to form. It is generated by the loss of both the leaving groups (Scheme 13)<sup>25</sup>



Scheme 13 – Isobutylene derivative general reaction

Reaction of the carbonates **37** (0.5 mmol) and ethyl acrylate (1.0 mmol) in the presence of  $\text{Pd}_2(\text{dba})_3$  (0.0125 mmol) in THF (5 mL) at 65 °C for 20 h gave methylenecyclopentanes after purification by column chromatography on  $\text{SiO}_2$ . Various five membered cyclic compounds were obtained in good yields. This reaction proceeds through loss of the TMS and  $\text{OCO}_2\text{Et}$  groups via coordination of palladium to generate a zwitterionic intermediate. Reaction of this zwitterionic intermediate with an activated olefin leads to the formation of a cyclopentane product. A variety of cyclopentane derivatives can be easily derived from the cycloaddition adduct by standard chemistry with the exomethylene and the ester groups.



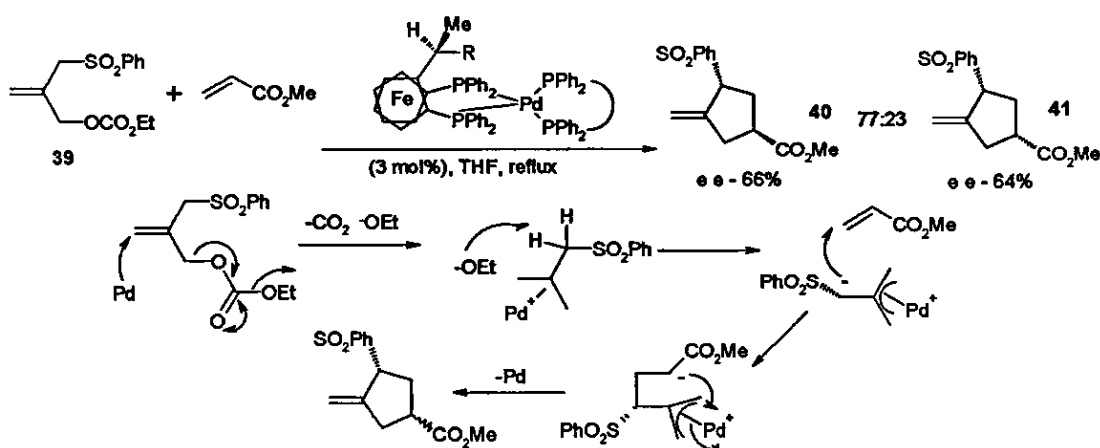
Scheme 14 – Products formed from [2+3]-cycloaddition

	Carbonate	Olefin	Product	Time (h)	Yield (%)
1				20	77
2				2	66
3				10	65
4				1	89
5				1	51
6				24	61
7				18	73

Table 4 – Isobutylene derivatives [2+3]-cycloadditions

A further example described by Hayashi *et al.*<sup>26</sup> uses 2-(phenylsulfonyl)-propenyl carbonate 39 which forms a zwitterionic intermediate through loss of a leaving group, in this case carbon dioxide and <sup>-</sup>OEt, which also acts as a base to deprotonate next to the phenylsulfonyl group. After the deprotonation has occurred it was possible to trap the zwitterion using an alkene. The resulting product from the

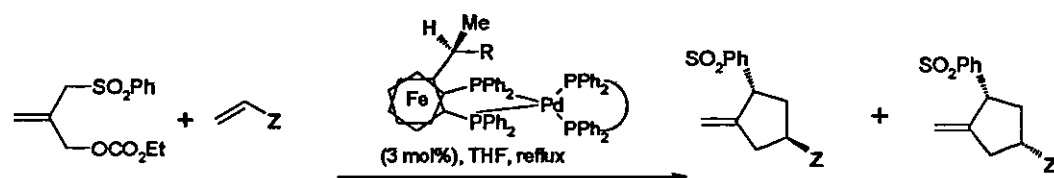
trapping step can then undergo a ring closure to generate the phenylsulfonyl substituted cyclopentane **40-41** product (Scheme 15).<sup>26</sup> It is interesting to note that this reaction was the first efficient palladium [2+3]-cycloaddition reaction to be performed using a ferrocenylphosphine ligand (BPPF) to give enantiomerically enriched products.



Scheme 15 – Propyl carbonate mechanism

Reaction of carbonate **39** with methyl acrylate in the presence of 3 mol% of a palladium catalyst ( $R = -NMeCH(CH_2OH)_2$ ) gave 76% yield of methyl-1-benzene sulfonyl-5-methylene cyclopentane-3-carboxylate which consists of *cis* and *trans* isomers in a ratio of 23 to 77. The key intermediates are zwitterionic  $\pi$ -allylpalladium complexes which are diastereomeric isomers formed by oxidative addition of **39** to palladium(0) followed by deprotonation with the generated alkoxide anion. The subsequent cyclisation step where the resulting enolate attacks the  $\pi$ -allyl carbon is not important for the enantioselection in the present cyclisation.

Higher stereoselectivity was observed in the reaction with the ferrocenylphosphine containing *N*-methyl-*N*-bis(hydroxymethyl)methyl amino group (Table 5, entries 1 and 5). Other types of chiral phosphine ligands such as (*S,S*)-chiraphos and (+)-BINAP were not as stereoselective (entries 3 and 4).



	<i>R</i> in catalyst	$CH_2=CHZ$	Time (h)	Yield (%)	<i>Cis/Trans</i> (e e)
1	-NMeCH(CH <sub>2</sub> OH) <sub>2</sub>	CO <sub>2</sub> Me	40	58	18 (73) / 82 (58)
2	-NMe <sub>2</sub>	CO <sub>2</sub> Me	47	76	23 (66) / 77 (64)
3	( <i>S,S</i> )-chiraphos	CO <sub>2</sub> Me	42	51	27 (46) / 73 (21)
4	(+)-BINAP	CO <sub>2</sub> Me	46	63	22 (19) / 78 (4)
5	-NMeCH(CH <sub>2</sub> OH) <sub>2</sub>	COMe	64	77	34 (75) / 66 (78)
6	-NMe <sub>2</sub>	COMe	38	86	28 (54) / 72 (61)

**Table 5** – Ligands used on chiral ferrocene in the reaction in **Scheme 15**

The products formed from this chemistry are useful precursors for further reactions. In the example shown below which was performed by Tsuji *et al.*,<sup>25</sup> it can be seen that the isobutylene derivative substrate **42** can be reacted in a number of different ways to generate different cyclopentane **43** / cyclopentene **44** products depending on the conditions which are used in the reaction (**Scheme 16**)<sup>25</sup> It can be seen that the products **43** and **44** are then capable of undergoing further reactions by standard transformations to form a further range of products **44–49**.

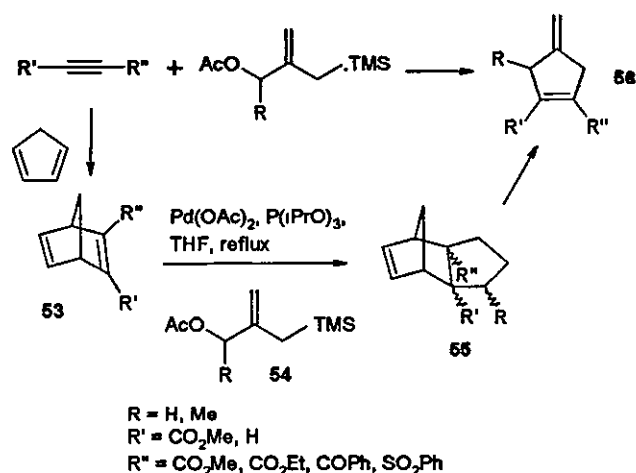


As summarized in **Table 6**, a range of TMM precursors were examined for this procedure; all reacted well and gave complete control of regioselectivity and excellent stereoselectivity. The solvent effect on the selectivity in this case is also interesting as higher diastereoselectivity was found in toluene than THF. The utility of the chiral aldehyde equivalent **49** in the [2+3]-cycloaddition opens up the possibility to generate a wide range of cyclopentane-containing natural products.

	<i>R</i>	<i>Conditions</i>	<i>Yield (%)</i>	<i>e e</i>
1	H	Toluene, 100 °C, 12 h	93	>98/2
2	H	THF, 60 °C, 24 h	93	>98/2
3	CN	THF, 60 °C, 12 h	94	5.5/1
4	CN	Toluene, 100 °C, 6 h	91	94/2
5	Me	Toluene, 100 °C, 48 h	60	>98/2
6	Ph	Toluene, 100 °C, 24 h	79	>98/2

**Table 6** – Conditions used in the optimization of step in the synthesis of Brefeldin A

Trost *et al.*<sup>30</sup> also looked into the regioselective cycloaddition of this complex to olefins possessing an electron withdrawing group (**Scheme 18**) Cycloaddition to the readily available norbornadienes proceeds well in most cases using an *in situ* method for generating the catalyst by mixing palladium acetate with triisopropylphosphite in which the latter serves as both reducing agent of Pd(II) and ligand for Pd(0) Reactions carried out in refluxing THF 1-7 mol% palladium acetate and 7-8 eq of triisopropylphosphate.

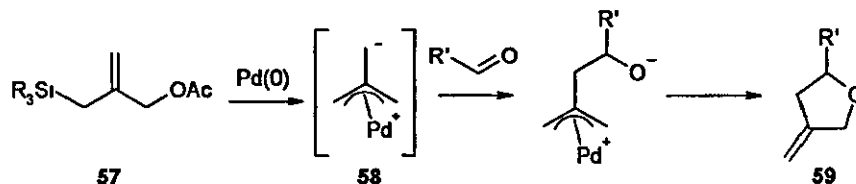


**Scheme 18** – Cyclopentane formation by Trost

	Compound (56)	Exo : Endo (R)	Yield (%)
1	$\text{R} = \text{H}, \text{R}' = \text{CO}_2\text{Me}, \text{R}'' = \text{CO}_2\text{Me}$	3.5 : 1	84
2	$\text{R} = \text{Me}, \text{R}' = \text{CO}_2\text{Me}, \text{R}'' = \text{CO}_2\text{Me}$	5 : 1	71
3	$\text{R} = \text{H}, \text{R}' = \text{H}, \text{R}'' = \text{CO}_2\text{Me}$	4.5 : 1	85
4	$\text{R} = \text{H}, \text{R}' = \text{H}, \text{R}'' = \text{CO}_2\text{Et}$	4.6 : 1	87
5	$\text{R} = \text{H}, \text{R}' = \text{H}, \text{R}'' = \text{COPh}$	-	29
6	$\text{R} = \text{H}, \text{R}' = \text{H}, \text{R}'' = \text{SO}_2\text{Ph}$	-	7

**Table 7** – Cyclopentenenes formed (product 56 Scheme 18)

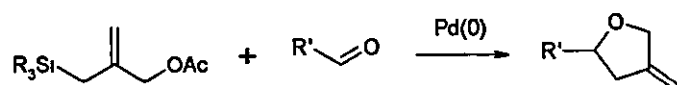
Trost<sup>30</sup> has also performed these reactions using 2-trimethylsilylmethylallyl acetate **57** which effectively adds to electron deficient olefins to form methylene tetrahydrofurans, but which failed to add effectively to carbonyl groups.

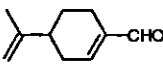
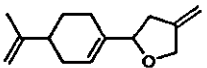
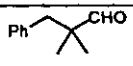
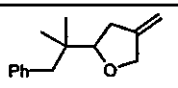
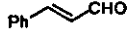
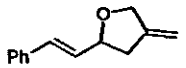

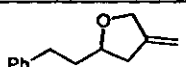
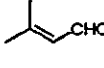
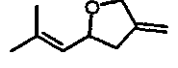
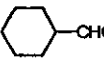
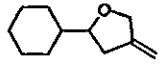
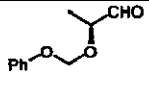
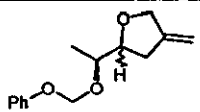


**Scheme 19** – Cycloaddition with aldehydes

In this reaction a mixture of 5 mol% of palladium acetate, 20 mol% of tri-*n*-butyl tin acetate, and 25 mol% of triphenylphosphine is heated at reflux in THF until a clear yellow solution forms. The aldehyde (1 eq) and 2-trimethylsilylmethylallyl acetate (1.2 eq) are added (concentration 0.5 M) and reflux continued until TLC indicates reaction is complete (15 min to 5 h). The reaction is diluted with hexane and filtered through a plug of silica gel. Evaporation and chromatography of the residue provides the pure methylene tetrahydrofuran.

The zwitterion formed upon reaction of the TMM complex with the aldehyde, may be intercepted by the silicon or tin acetate by-product of the formation of **58**, faster than it cyclises to the methylene tetrahydrofuran. It is interesting to note that unsaturated aldehydes only give carbonyl addition and no double bond addition, and ketones do not give cycloadducts.



	<i>Aldehyde</i>	<i>Product</i>	<i>Yield (%)</i>
1			71
2			75
3			89
4			71
5			80
6			88
7			74

**Table 8** – Tetrahydrofuran derivatives formed from palladium [2+3]-cycloaddition

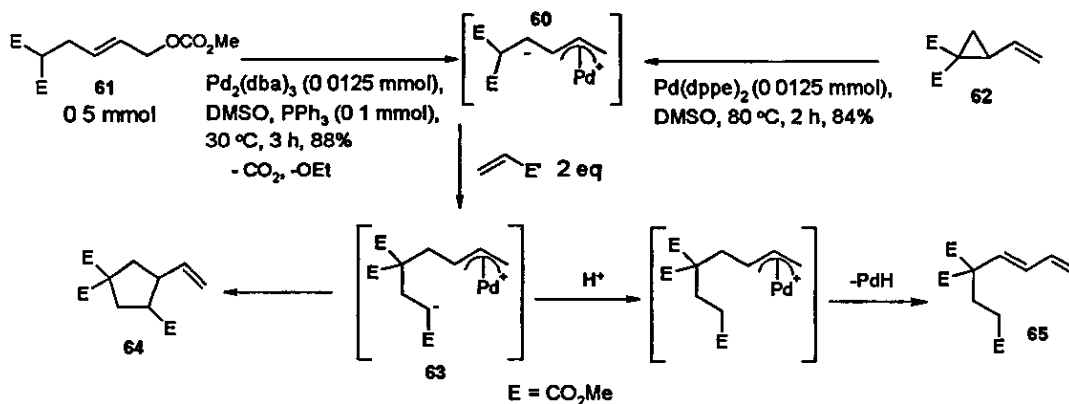
### 1.2.3 – $\pi$ -Allyl Complexes in Palladium Catalyzed [2+3]-Cycloaddition Reactions

The synthesis of five-membered heterocyclic rings by nucleophilic ring-opening of three-membered heterocycles has been extensively studied, because of the potential biological activity of some of the products. A drawback of this system is that the reactions generally require relatively high temperatures (50-120 °C depending on substrates) to proceed to completion.

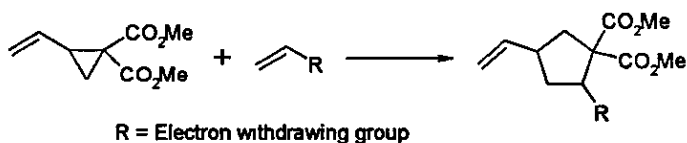
The final example of the creation of zwitterionic species through palladium chemistry is through coordination of a vinyl bond next to a three-membered ring. This chemistry is of particular interest as it is possible to use heterocyclic rings to generate a 1,3-dipole, because many three-membered heterocyclic rings are easily formed (epoxides, aziridines and thiiranes) as well as cyclopropanes.

When looking at this chemistry, it is impossible to ignore the work of Tsuji,<sup>32-33</sup> who is one of the pioneers in the field of palladium catalyzed reactions. He showed that when using a palladium(0) catalyst, a zwitterionic 1,3-dipole could be formed, through ring opening of the activated vinyl cyclopropane (Scheme 3). This occurs when the palladium coordinates to the vinyl bond. The ring-opened cyclopropane then gives a zwitterionic intermediate in which the negative charge is stabilized using two esters which are  $\beta$  to the vinyl group, and the charge positive is coordinated to the  $\pi$ -allyl complex. This charged intermediate can then be trapped using either an activated alkene or a cumulated trapping agent to create the substituted vinyl cyclopentane **64** (Scheme 20). In this example there was also a minor product seen in the reaction, the product **65** is thought to be formed when the intermediate **63** is generated in the presence of an acid. This caused the loss of palladium hydride and the generation of the diene product in low yield.

The vinylcyclopropane (0.5 mmol) underwent smooth [2+3]-cycloaddition reaction with methyl acrylate (1 mmol) in the presence of  $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$  (0.0125 mmol) and dppe (0.05 mmol) in DMSO (3 mL) at 30-80 °C for 1-3 h to give the vinyl cyclopentane in good yields.



Scheme 20 – Tsuji's vinyl cyclopentane formation

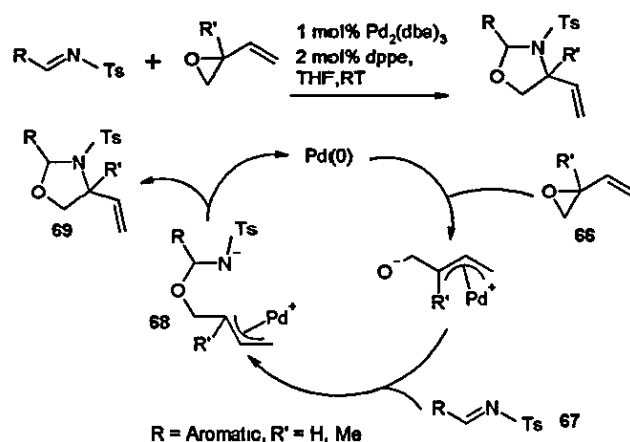


	Vinylcyclopropane	Olefin	Ligand	Temp (°C)	Time (h)	Yield (%)
1			dppe	80	2	84
2			$\text{P}^n\text{Bu}_3$	30	1	87
3			$\text{P}^n\text{Bu}_3$	30	1	66
4			$\text{P}^n\text{Bu}_3$	30	3	89
5			dppe	80	3	78
6			$\text{P}^n\text{Bu}_3$	30	3	77
7			dppe	80	2	23

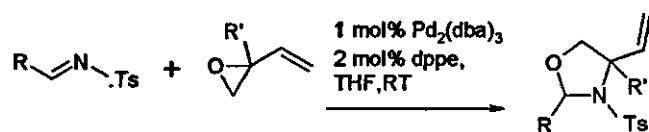
Table 9 – [2+3]-Cycloadditions using vinyl cyclopropane (Scheme 20)

The palladium-catalyzed [2+3]-cycloaddition reaction of vinyl oxiranes with heterocumulenes has also been reported by Yamamoto *et. al.*<sup>34</sup> This particular substrate has been considered a versatile tool in the construction of certain heterocycles in organic synthesis. A reaction between the vinyl oxirane and a carbon-carbon multiple bond would lead to the formation of tetrahydrofurans or dihydrofurans depending on the trapping agent used. In this example, however, Yamamoto looked at the synthesis of 1,3-oxazolidines via the [2+3]-cycloaddition. Previously the most popular method of constructing 1,3-oxazolidines was by the condensation of 1,2-amino alcohols with carbonyl compounds in the presence of acid catalysts.

Yamamoto expected that an imine incorporated in a [2+3]-cycloaddition with vinyl epoxides would produce 1,3-oxazolidines. The key step of the [2+3]-cycloaddition is thought to be the nucleophilic addition of an oxygen anion, which is generated by the reaction of vinylic oxirane **66** with palladium, to an imine **67**. Ring closure from the intermediate **68** formed from this reaction would lead to the 1,3-oxazolidines **69**. The reaction conditions which Yamamoto used in these reactions were 1 mol% of  $\text{Pd}_2(\text{dba})_3$ , 2 mol% dppe in THF at room temperature under an inert atmosphere (Scheme 21)



**Scheme 21 – Regioselective 1,3-oxazolidine formation**

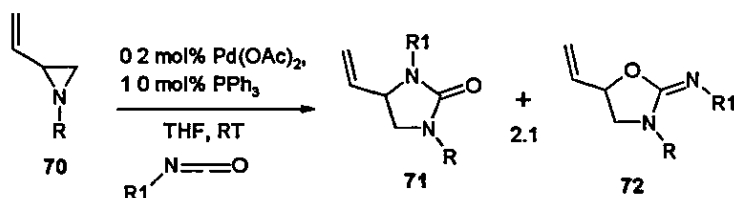


	Imine	Vinylic oxirane	Time (h)	Yield (%)	Cis:Trans
1			2	97	73:27
2			2	96	88:12
3			4	>99	70:30
4			3	>99	60:40
5			3	93	62:38
6			1	78	57:43
7			1	74	50:50

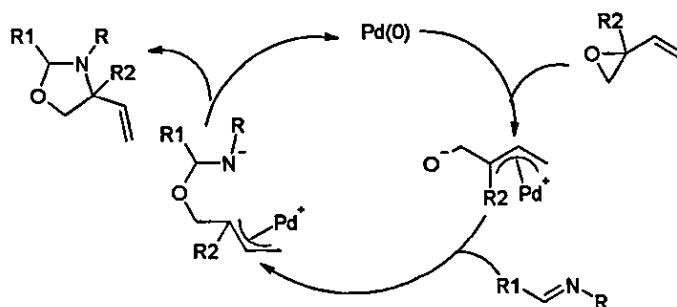
Table 10 – [2+3]-Cycloadditions using vinyl epoxides

As well as reactions with vinyl cyclopropanes (Scheme 20) and vinyl epoxides (Scheme 21), other work has been performed in the area of [2+3]-cycloaddition chemistry. This work includes using a number of different vinyl heterocyclic compounds which could be used to generate the three atom component of the reaction system.<sup>23</sup> For example, Alper *et. al*<sup>35</sup> have used vinyl arizidines **70** which are an example of a 3-component system which is capable of undergoing a palladium [2+3]-cycloaddition, such as has been seen in the work outlined by Tsuji (Scheme 20). The palladium causes a ring opening of the vinyl arizidines **70** to generate a  $\pi$ -allyl zwitterionic species. The resulting intermediate should react readily with the electrophilic heterocumulene carbon atom giving rise to a further intermediate, cyclisation of which affords the two possible five-membered hetero-

cyclic rings and regenerates the original palladium(0) complex. In this example, the reaction is between an isocyanate ( $\text{N}=\text{C}=\text{O}$ ) which, when reacted with a vinyl aziridine, forms a substituted heterocyclic products **71** and **72** (Scheme 22).<sup>35</sup>

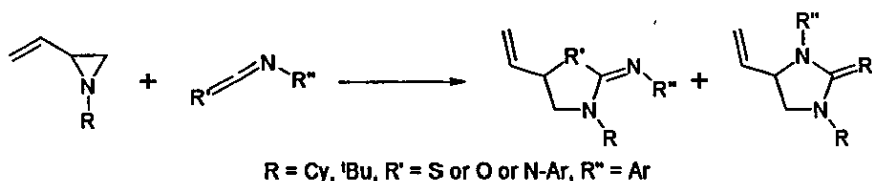


**Scheme 22** – Heterocycles from vinyl aziridine


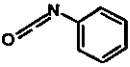

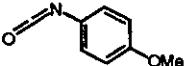

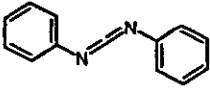

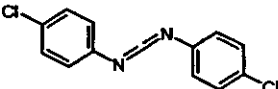

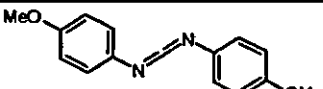

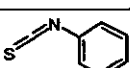

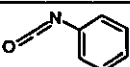

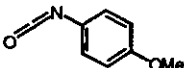

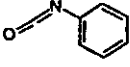


**Scheme 23** – Zwitterion formation in palladium reactions

Isocyanates, isothiocyanates, and carbodiimides have been used by Alper as heterocumulenes to give imidazolidinones, imidazolidinethiones, and imidazolidine imines as products. For isocyanates, the reaction was complete after stirring for only 2 h however, for carbodiimides and isothiocyanates, 20 h was usually required for completion. The difference in reactivity of the latter may be explained by the relatively reduced nucleophilic character at nitrogen and sulfur, respectively, in these substrates. It is noteworthy that isocyanate reactivity is apparently unaffected by the electronic influence of the aromatic substituent. The products were isolated as an approximately 2:1 mixture of *cis* and *trans* isomers



**Scheme 24** – Products formed from [2+3]-cycloaddition

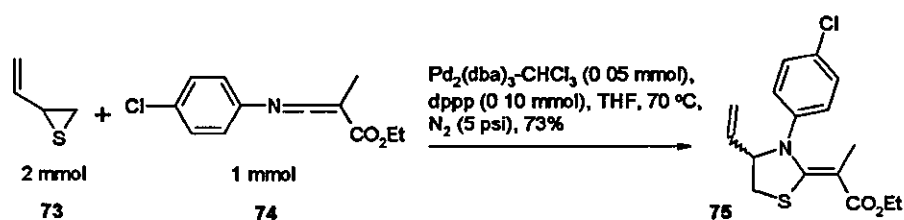
	Aziridine	Heterocumulene	Time (h)	Combined Yield (%)
1			2	89
2			2	88
3			2	60
4			20	61
5			20	36
6			20	96
7			2	67
8			2	61
9			2	74

**Table 11** – [2+3]-Cycloadditions using vinyl aziridine (see Scheme 24 for products)

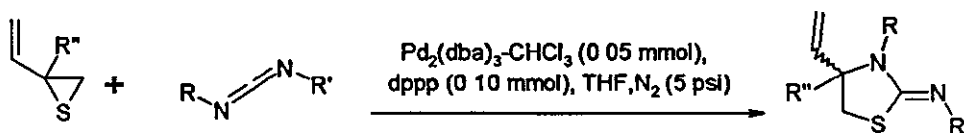
Sulfur containing heterocycles are of particular interest, especially the thiazolidine and the oxathiolane moieties that are found in a wide range of products possessing biological activity. It is also possible to use vinyl thiiranes **73** to undergo this type of [2+3]-cycloaddition reaction as Alper *et. al.*<sup>35</sup> showed. Here the vinyl thiirane undergoes palladium catalyzed [2+3]-cycloaddition via the same route as the aziridine. The mechanism for this reaction is thought to proceed via the ring opening of the vinyl thiiranes from palladium insertion into the vinyl bond to create the

zwitterionic species. The dipole intermediate can then react with the imine bond in **74** to form the desired product **75** (Scheme 25) in good yields (73%).<sup>35</sup>

It is easy to prepare thiazolidine, oxathiolane, and dithiolane derivatives by the regioselective reaction of 2-vinylthiiranes with heterocumulenes in the presence of 5 mol%  $\text{Pd}_2(\text{dba})_3$  and 10 mol% dppp. The reaction proceeds in excellent yield when carbodiimides containing electron withdrawing substituents on the aromatic ring were used for the reaction with the vinyl thiiranes.



**Scheme 25 – Reaction with vinyl thiiranes**

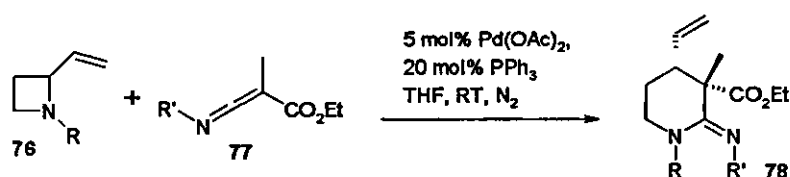


	<i>Vinyl thiiranes</i>	<i>Carbodiimides / Isocyanates</i>	<i>Reaction conditions</i>	<i>Yield (%)</i>
1			50 °C, 24 h	97
2			70 °C, 24 h	98
3			80 °C, 24 h	95
4			80 °C, 24 h	85
5			60 °C, 24 h	60
6			60 °C, 24 h	43

7			80 °C, 24 h	80
8			50 °C, 24 h	47

**Table 12** – [2+3]-Cycloadditions using vinyl thiranes

As well as the [2+3]-cycloadditions which have been examined, it is also possible to perform [2+4]-cycloadditions. Alper *et al.* has reported<sup>36</sup> such reactions in the synthesis of tetrahydropyrimidinone, tetrahydropyrimidinime and thiazinanimine analogs by mild palladium catalyzed cyclisation of 2-vinylazetidines **76** with aryl and alkylisocyanates, diarylcarbodiimides and arylisothiocyanates. The six-membered ring products are obtained in good to high yields and with excellent regioselectivity. Using ketenimines **77**, palladium-catalyzed ring expansion enables the synthesis of only one regioisomer of tetrahydropiperidine **78** derivate compounds. The cycloaddition is totally stereoselective, as NOE experiments show the carboethoxy and vinyl groups in *cis* position.



**Scheme 26** – [2+4]-cycloaddition

The tetrahydropiperidin-2-ylidenes were prepared regioselectivity in moderate to good yields, under mild conditions, by palladium(0) catalyzed cycloaddition reactions of *N*-alkylated 2-vinylazetidines with ketenimines and ketene. The best results are obtained when ketene is used with a heterocumulene (Table 13)

	<i>Vinyl azetidine</i>	<i>Ketenimine</i>	<i>Time (h)</i>	<i>Yield (%)</i>
1			48	61
2			48	57
3			22	65
4			24	51
5			24	52
6			24	55
7			2	66
8			24	69

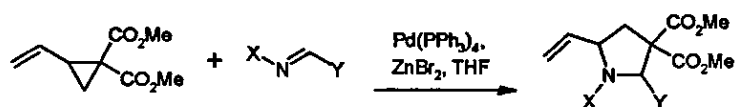
Table 13 – Palladium catalyzed [2+4]-cycloadditions (see Scheme 26)

### 1.2.4 – Conclusion

As can be seen from the previous examples, the palladium-catalyzed reactions of methylene cyclopropanes and vinyl substituted three membered rings have been studied by a number groups. The research by these groups has proven that palladium-catalyzed reactions are a synthetically useful route to both cyclopentanes and heterocycles.

Of the methods which have been examined so far it is the palladium catalyzed [2+3]-cycloaddition using vinyl cyclopropane in conjunction with an olefin trapping agent, developed by Tsuji (Scheme 20), which is the most applicable to the work which we have been doing over the last three years. The aim for this

project was to develop new methods for the synthesis of pyrrolidines using vinyl cyclopropanes and palladium chemistry, in which we planned to use imines in this same reaction to generate a highly functionalized pyrrolidine (Scheme 27)



**Scheme 27** – Development of Tsuji’s work employing imines

### *Section 1.3 – Aims*

The work covered in this thesis has covered six main areas :

Chapter 2.1 – To develop the synthesis of pyrrolidines via a palladium-catalysed [2+3]-cycloaddition.

Chapter 2.2 – Use the palladium catalyst [2+3]-cycloaddition on a range of ethyl ester imines to generate pyrrolidines, with an ethyl ester in the  $\alpha$  position of the pyrrolidine ring (proline analogues)

Chapter 2.3 – To determine if it is possible to perform [2+3]-cycloaddition chemistry under microwave irradiation, as there is a great deal of precedent for the use of microwave irradiation in palladium chemistry.

Chapter 2.4 – To develop the chemistry towards the synthesis of natural products using ring closing metathesis.

Chapter 2.5 – To extend the substrate scope to include a range of aromatic cyclopropanes.

Chapter 2.6 – To apply the methodology developed to the synthesis of naturally occurring alkaloid products.

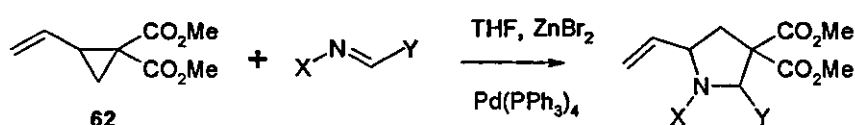
## Chapter 2 – Results and Discussion

### Section 2.1 – General Pyrrolidines

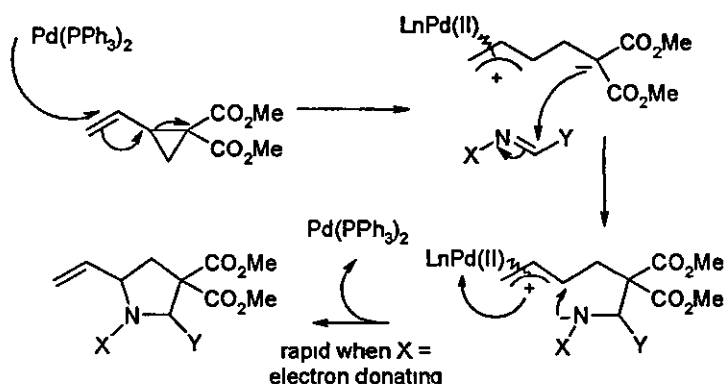
#### 2.1.1 – Introduction

##### *[2+3]-Cycloaddition reaction*

The formation of highly functionalized pyrrolidine compounds from vinyl cyclopropanes and imines has been the main focus of this project and was initially looked at by Dr Lam Tang at Oxford University during his PhD<sup>37</sup> and continued by Dr Chester Chu during a postdoctoral position at Loughborough University. This [2+3]-cycloaddition is achieved through coordination of the palladium(0) catalyst to the vinyl group of the cyclopropane, which causes ring opening of the cyclopropane to generate a 1,3-dipole. This zwitterionic species can then be reacted with an imine to form the desired pyrrolidine product. Tang and Chu showed that the pyrrolidine products from this type of palladium [2+3]-cycloaddition reaction can be prepared in good yields under relatively mild reaction conditions (Scheme 28). It was our goal to further develop this chemistry and explore the diversity of this reaction, as well as to examine how our chemistry can be adapted towards the synthesis of natural products and additionally to find ways to improve the stereoselectivity of this process



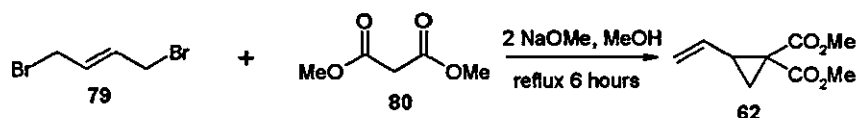
Scheme 28 – General [2+3]-cycloaddition reaction



**Scheme 29** – Mechanism of pyrrolidine synthesis

### *Vinyl cyclopropane synthesis*

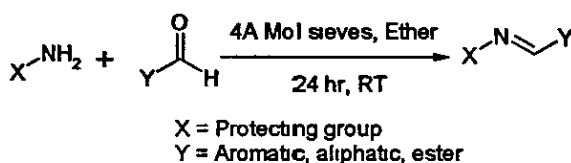
The preparation of the required vinyl cyclopropane was developed by G. S. Skinner *et al*<sup>38</sup> in the 1940's (Scheme 30). The vinyl cyclopropane is easily prepared from dimethyl malonate and 1,4-dibromobutene which are refluxed together in the presence of sodium methoxide to generate the desired product in 65-70% yield. Our preparation of vinyl cyclopropane is usually performed on a 5-10 gram scale and the product stored at <4 °C until required.



**Scheme 30** – Vinyl cyclopropane formation

### *Imine synthesis*

A range of imines were required to explore this chemistry. These imines would allow an in-depth examination of the different reactivities of the various functional groups in the imines. The groups which were attached to nitrogen groups such as PMB, tosyl and benzyl which are easily removed under standard conditions or groups on which further chemistry could be carried out. A typical imine synthesis is to combine an amine and an aldehyde in the presence of molecular sieves using diethyl ether as a solvent. The molecular sieves in this reaction are used to remove water from the reaction and therefore drive the reaction to completion (Scheme 31).

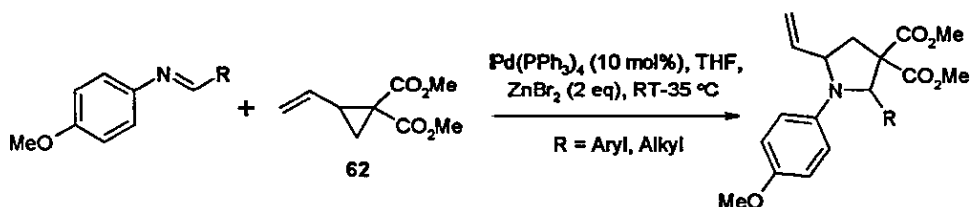


**Scheme 31 – General imine formation**

### 2.1.2 – Results for Palladium Catalyzed [2+3]-Cycloaddition Reactions

#### *Reactions with N-(4-methoxy-phenyl) imines*

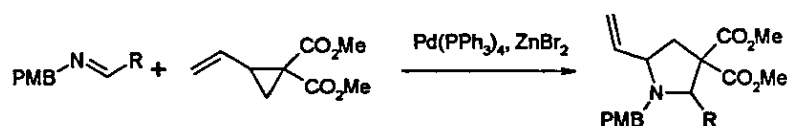
The first of the cyclisation reactions performed were carried out on *N*-(4-methoxy-phenyl) imines. This type of imine was used in the limited number of reactions by Tang,<sup>37</sup> and we wished to start the project by expanding the range of this type of imine in a hope to develop a greater insight into the chemistry of the [2+3]-cycloadditions (**Scheme 32**, **Tables 14-19**) This type of imine is important to examine as PMB is one of the most popular electron donating protecting groups used in organic synthesis due to the ease of removal using CAN, and it was our intention to explore this chemistry during the early part of the project.



**Scheme 32 – General *N*-(4-methoxy-phenyl) imine cyclisation**

The *cis:trans* ratios of the product mixtures were determined by chemical shifts of the CH<sub>2</sub> on the pyrrolidine ring. Although NOE's were performed they proved to be inconclusive, due to the pyrrolidine ring being able to adopt several conformations. However the *cis:trans* ratios could be determined by <sup>1</sup>H NMR analysis, and this combined with information from X-ray crystal structures of a *cis* and *trans* product which were isolated as single diastereoisomers (see **page 60**) allowed us to assign the the NMR data for all the products formed.

This project began using the same imine (PMB phenyl) which was used by Tang. The initial experiment (entry 1, Table 14) was a direct repeat of Tang's work, which was performed in order to determine the reproducibility of the reaction. When the reaction was carried out using the conditions outlined by Tang (10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, 2 eq ZnBr<sub>2</sub>, THF, RT for 72 h), and the results obtained were comparable in yield and diastereoselectivity to those Tang achieved. It was also decided to try this experiment in a different non protic solvent (DMF) (entry 2), however the results for this experiment were less encouraging as it failed to yield any product.



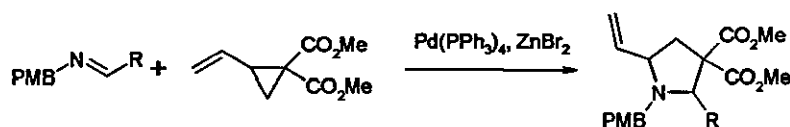
	Imine	Solvent	Temp (°C)	Time (h)	Yield (%)	Cis:Trans
1		THF	RT	72	60 (81)	4:1 5
2		DMF	RT	72	0 (81)	-

1 mmol scale and had 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, 2 eq. ZnBr<sub>2</sub>.

Table 14– *N*-PMB imine [2+3]-cycloaddition with VCP

After the initial success of repeating the *N*-PMB imine reaction under the conditions developed by Tang, it was decided to attempt a range of substituted aromatic groups on the carbon of the imine. The first example chosen was the 4-nitro-phenyl, which being a powerful electron withdrawing group should show some electronic differences from a simple phenyl ring. However this reaction was much slower and proceeded in a significantly lower yield. Entry 1 was carried out at RT for 96 hours and gave 29% yield (4:1 *cis:trans*), however when the temperature was increased to 40 °C (entry 2) and reflux (entry 3), both for 72 hours, there was no product seen. In an attempt to decrease the reaction time the reaction was performed

at reflux (Table 15, entry 3); however this proved to be unsuccessful and caused decomposition of the starting materials. 4-Cyano-phenyl (Table 15, entry 4) was also attempted under these conditions and gave a yield of 22% with 6.1 in favour of the *cis* product.

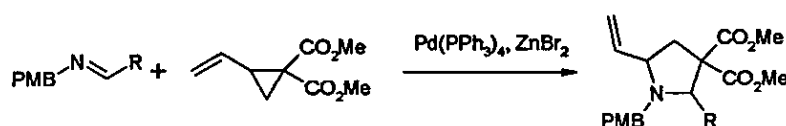


	Imine	Solvent	Temp (°C)	Time (h)	Yield (%)	Cis:Trans
1		THF	RT	96	29 (82)	4:1 5
2		THF	40	72	0 (82)	-
3		THF	Reflux	72	0 (dec) (82)	-
4		THF	RT	72	22 (83)	6:1

1 mmol scale and had 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, 2 eq ZnBr<sub>2</sub>.

**Table 15 – N-PMB imine [2+3]-cycloaddition with VCP**

An aromatic electron donating was next examined, both 4-methyl (entries 1-2, Table 16) and 4-methoxy-phenyl (entry 3, Table 16) were attempted and both of these proved to be more reactive than electron withdrawing groups. The 4-methyl gave 42% yield and 8:1 in favor of the *cis* isomer and the 4-methoxy-phenyl gave a 59% yield, however there was complete control of diastereoselectivity with giving only the *cis* product formed. When the reaction was carried out at reflux, however, there was decomposition of the starting materials (entry 1).

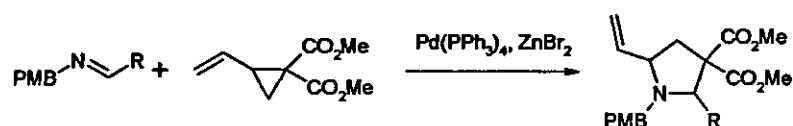


	<i>Imine</i>	<i>Solvent</i>	<i>Temp</i> (°C)	<i>Time</i> (h)	<i>Yield</i> (%)	<i>Cis.Trans</i>
1		THF	Reflux	24	0 (dec) (84)	-
2		THF	40	72	42 (84)	8:1
3		THF	35	48	59 (85)	1 0

1 mmol scale and had 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, 2 eq. ZnBr<sub>2</sub>

**Table 16** – *N*-PMB imine [2+3]-cycloaddition with VCP

One of the most important experiments was done using 4-bromo-phenyl (entry 1-2, Table 17) as this substrate could have reacted via an insertion of palladium into the carbon-bromine bond. The sole product observed from the reaction at RT (entry 1, Table 17) was the desired [2+3]-cycloaddition product, in low yields but good stereoselectivity, however the reaction failed at reflux. Another of the halogens used was 4-fluoro-phenyl (entry 3, Table 17) and it is interesting to note that the 4-fluoro-phenyl gave a very similar yield (55%) to the [2+3]-cycloaddition using the *N*-PMB phenyl imine (entry 1, Table 14), however the stereoselectivity for this imine was very poor.

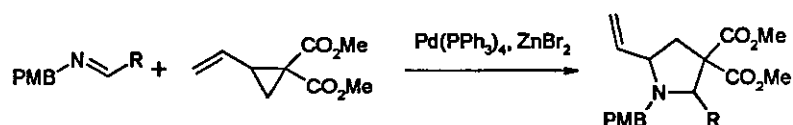


	Imine	Solvent	Temp (°C)	Time (h)	Yield (%)	Cis:Trans
1		THF	RT	72	24 (86)	8:1
2		THF	Reflux	24	0 (dec) (86)	-
3		THF	35	48	55 (87)	1:1

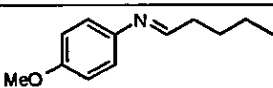
1 mmol scale and had 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, 2 eq. ZnBr<sub>2</sub>

**Table 17** – *N*-PMB imine [2+3]-cycloaddition with VCP

The final two *N*-PMB imines used in the palladium-catalyzed [2+3]-cycloaddition were a hetero-aromatic thienyl, (entry 1, Table 18) which was reacted at RT for 72 hours however this failed to generate the pyrrolidine product. The *N*-PMB butane imine (entry 2) was more successful and gave a yield of 34% after reacting for 48 hours at 35 °C.



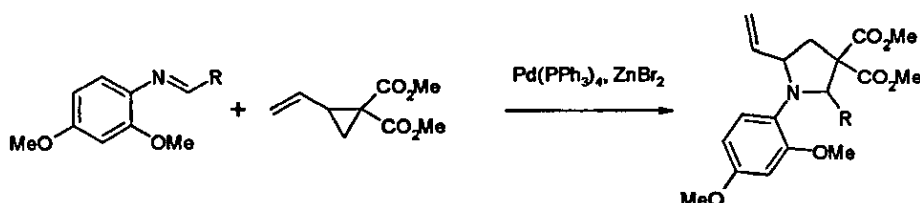
	Imine	Solvent	Temp (°C)	Time (h)	Yield (%)	Cis Trans
1		THF	RT	72	0 (88)	-

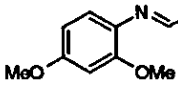
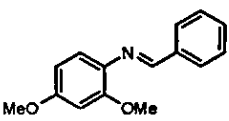
2		THF	35	48	34 (89)	1 0
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1 mmol scale and had 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, 2 eq. ZnBr<sub>2</sub>.

**Table 18 – *N*-PMB imine [2+3]-cycloaddition with VCP**

After the success of generating pyrrolidine via a [2+3]-cycloaddition between a vinyl cyclopropane and an *N*-PMB substituted imine it was decided to attempt a second electron rich group on the nitrogen of the imine, 2,4-methoxyphenyl. The [2+3]-cycloaddition was attempted on two substrates, *N*-2,4-dimethoxyphenyl ethyl imine (**entry 1, table 19**) which was reacted for 48 hours at RT, however this failed to yield any results. The second imine was substituted with a phenyl group (**entry 2, table 19**). The cycloaddition using the *N*-2,4-dimethoxyphenyl phenyl imine proved to be a much more successful generating a yield of 72% after reacting for 48 hours at 35 °C. However the diastereoselectivity was very poor for this substrate.



	Imine	Solvent	Temp (°C)	Time (h)	Yield (%)	Cis:Trans
1		THF	RT	48	0 (90)	-
2		THF	RT	48	72 (91)	1:1

1 mmol scale and had 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, 2 eq. ZnBr<sub>2</sub>.

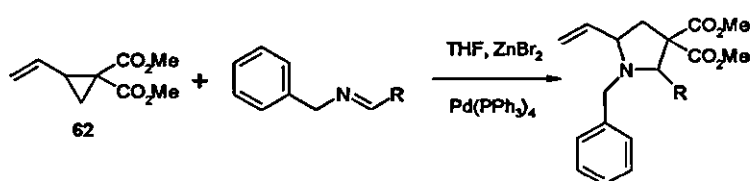
**Table 19 – *N*-PMB imine [2+3]-cycloaddition with VCP**

The results clearly indicate simple aromatics or electron donating groups (OMe, Me, F) on the aromatic ring give the best yields, which is most likely because

coordination between the imine and one equivalent of the zinc bromide is enhanced, with greater electron density at the imine bond. Alkyl chains and electron withdrawing groups (CN, NO<sub>2</sub>) gave significantly lower yields.

#### Reactions with *N*-benzyl imines

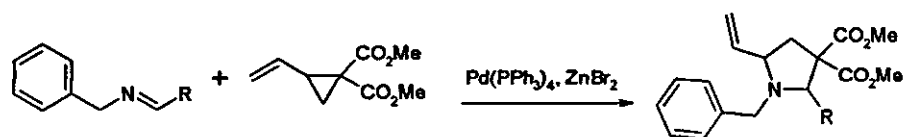
After examining the [2+3]-cycloaddition reactions of a range of PMB imines, it was decided to attempt the formation of pyrrolidines from *N*-benzyl imines. The advantage of this group is that the aromatic ring is spaced away from the nitrogen. The benzyl group also can be easily removed under hydrogenolysis and other reducing reactions.



Scheme 33 – General [2+3]-cycloaddition using *N*-Benzyl imine imines

The initial work with the *N*-benzyl imines was carried out using a phenyl group on the carbon (**entries 1-2, Table 20**); this was done so a direct comparison could be drawn between the work with the *N*-PMB and the *N*-benzyl groups. The reaction was run in THF for 24 hours at 35 °C and in DMF for 96 hours at the same temperature in order to compare solvent systems (**Table 20**). The results for this clearly show a dramatic reduction in reaction times and improved yields over the *N*-PMB group, however DMF still proved to be an undesirable solvent (**entry 2**).

The variation of substitution of a methyl substituted aromatic rings (**entries 3-5, Table 20**) was then examined. It can be seen from **Table 20** that when the substitution was in the *para* or *ortho* position of the phenyl ring, the [2+3]-cycloaddition gave the desired product in reasonable yield, but however substitution in the *meta* position of the aromatic ring failed to yield any product.

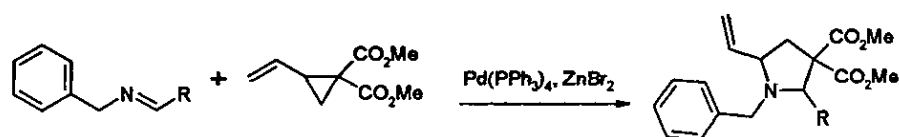


	<i>Imine</i>	<i>Solvent</i>	<i>Temp (°C)</i>	<i>Time (h)</i>	<i>Yield (%)</i>	<i>Cis. Trans</i>
1		THF	35	24	93 (92)	10:1
2		DMF	35	96	41 (92)	4:1
3		THF	35	48	58 (93)	24:1
4		THF	35	48	0 (94)	-
5		THF	35	24	59 (95)	1:0

1 mmol scale and had 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, 2 eq. ZnBr<sub>2</sub>

**Table 20** -*N*-Benzyl imine [2+3]-cycloaddition with VCP

The next substrates examined were a range of hetero-aromatics. The results for pyridines (**Table 21**) are remarkably similar to those seen in **Table 20** with good yields for substitution in the *para* position and trace amounts in the *ortho* position, and no reaction when the aromatic ring is *meta* substituted. Both the thiophene (**entries 6-7**) and tetrahydrofuran (**entries 4-5**) ring systems were also tested in this [2+3]-cycloaddition chemistry and it has been observed that the more reactive substrate is the 3-position as these gave roughly twice the yield of the 2-substituted aromatics.

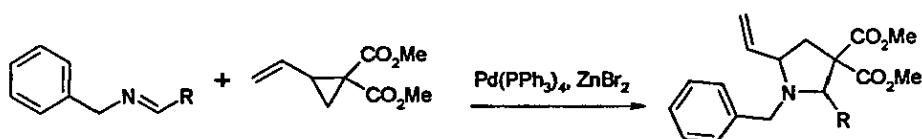


	Imine	Solvent	Temp (°C)	Time (h)	Yield (%)	Cis:Trans
1		THF	35	48	57 (96)	7:1
2		THF	35	48	0 (97)	-
3		THF	35	72	Trace (98)	-
4		THF	35	24	69 (99)	1:0
5		THF	35	48	30 (100)	5:1
6		THF	35	48	62 (101)	4:1
7		THF	35	48	34 (102)	6:1

1 mmol scale and had 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, 2 eq. ZnBr<sub>2</sub>

**Table 21** – *N*-Benzyl imine [2+3]-cycloaddition with VCP

Both 4-bromo-phenyl (Table 22, entry 1) and the 4-methoxy-phenyl (Table 22, entry 2) were also examined. The yields of these products were much higher than the reactions performed using *N*-PMB protection, and the diastereoselectivity for these substrates is also significantly better than for the PMB cyclisations, with a single diastereoisomer (*cis*) being formed in both the reactions.

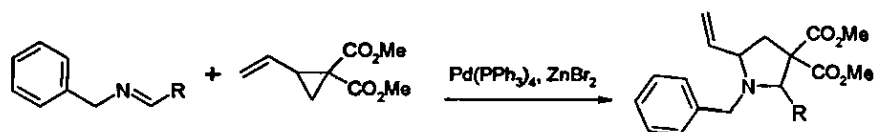


	<i>Imine</i>	<i>Solvent</i>	<i>Temp (°C)</i>	<i>Time (h)</i>	<i>Yield (%)</i>	<i>Cis:Trans</i>
1		THF	35	24	68 (103)	1.0
2		THF	35	48	79 (104)	1.0

1 mmol scale and had 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, 2 eq. ZnBr<sub>2</sub>

**Table 22** – *N*-Benzyl imine [2+3]-cycloaddition with VCP

The next target was a range of aliphatic *N*-benzyl imines (Table 23). The effects of adding spacer units between the imine bond and an aromatic ring were first examined. The results for these reactions show a drop in reactivity when a single CH<sub>2</sub> is placed between the imine bond and the aromatic ring (entry 1). However when two CH<sub>2</sub> are placed between the imine and the aromatic ring, the results are approximately the same (entry 2) as the results for the single CH<sub>2</sub> spacer unit. However when the aromatic chain group is replaced by a simple aliphatic chain as can be seen in there is a slight increase in yields of the pyrrolidines as the chain length increases (entries 3-5). The imine derived from trimethylacetaldehyde was interesting as this showed that when a very bulky group is directly attached to the imine there is no product seen from the [2+3]-cycloaddition. Knowledge of this limitation allowed us to plan future reactions more carefully.

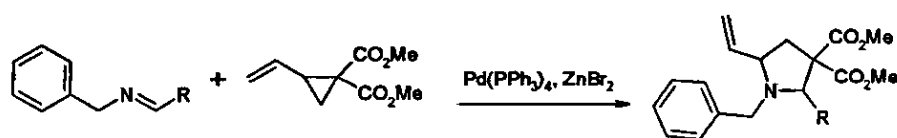


	<i>Imine</i>	<i>Solvent</i>	<i>Temp (°C)</i>	<i>Time (h)</i>	<i>Yield (%)</i>	<i>Cis:Trans</i>
1		THF	35	48	69 (105)	1:0
2		THF	35	48	62 (106)	2:1
3		THF	35	48	53 (107)	4:1
4		THF	35	48	68 (108)	8:1
5		THF	35	48	76 (109)	8:1
6		THF	35	48	0 (110)	-

1 mmol scale and had 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, 2 eq ZnBr<sub>2</sub>

**Table 23** – *N*-Benzyl imine [2+3]-cycloaddition with VCP

Our interest was next focused on imines which were suitable for further manipulation. The entries on **Table 24** were performed to examine more specialized areas of the [2+3]-cycloaddition chemistry. Product **111** is a natural product precursor for 3-nortropanol.<sup>1</sup> The final entry used a substrate derived from *D*-glyceraldehyde acetonide, and it was hoped that the chirality in the initial substrate would allow for the formation of an optically pure pyrrolidine. However the pyrrolidine when purified was found to be racemic from  $[\alpha]^{20}_D$  studies of the resulting pyrrolidine.



	Imine	Solvent	Temp (°C)	Time (h)	Yield (%)	Cis:Trans
1		THF	35	48	Trace (111)	-
2		THF	35	48	42 (112)	1:1

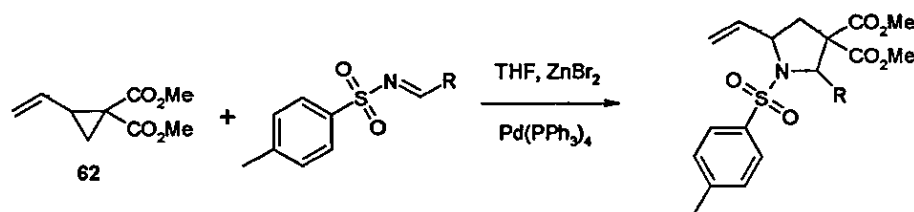
1 mmol scale and had 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, 2 eq. ZnBr<sub>2</sub>.

**Table 24** – *N*-Benzyl imine [2+3]-cycloaddition with VCP

A large number of *N*-benzyl derivatives were synthesized ranging from the simple phenyl compounds and alkyl pyrrolidine to more complex derivatives. Overall the highest yields were those of relatively simple groups such as phenyl or pentane.

#### Reactions with *N*-tosyl imines

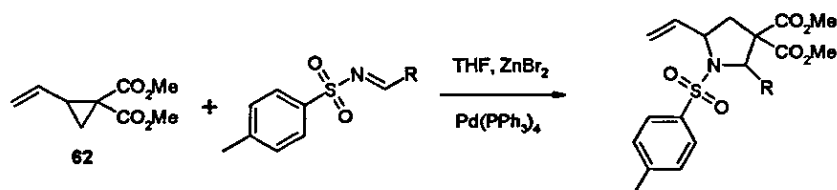
The next imines to be explored were *N*-tosyl imines. The powerfully electron withdrawing group on the nitrogen is important as we have already looked into an electron donating groups, and wished to determine the effect of electronics on the reaction



**Scheme 34** – *N*-Tosyl imine pyrrolidine formation

The reactions carried out with the *N*-tosyl imines have shown a clear difference to the electron donating PMB and the electron neutral benzyl protection groups. The major difference in the reactions carried out on the *N*-tosyl groups (Table 25), is the time over which the reactions are performed, as these substrates

have a much slower reaction rate. The yield of the pyrrolidines are however slightly higher than the corresponding PMB pyrrolidine but still are not as high as those achieved with the benzyl group.



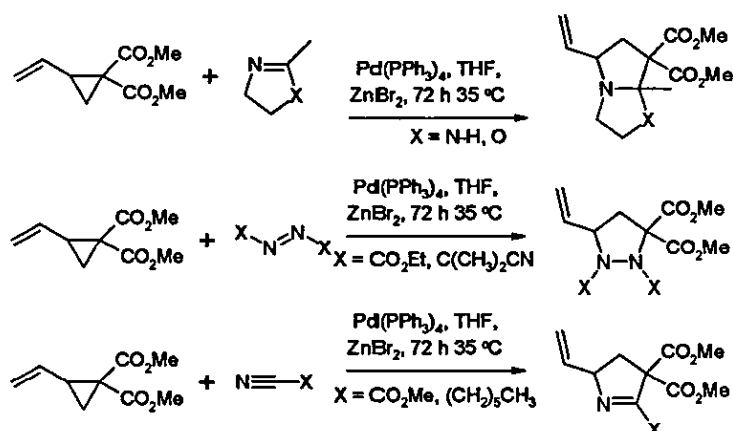
	Imine	Solvent	Temp (°C)	Time (h)	Yield (%)	Cis:Trans
1		THF	RT	96	64 (113)	1:1
2		THF	RT	96	0 (114)	-
3		THF	RT	96	75 (115)	8:1

1 mmol scale and had 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, 2 eq. ZnBr<sub>2</sub>.

Table 25 – *N*-Tosyl imine [2+3]-cycloaddition with VCP

### 2.1.3 – Dihydro-oxazole, dihydro-imidazole, Azo and Nitriles as Trapping Agents

With the success of the imine chemistry, it was decided to examine other types of X=C and X=Y bonds, as this would diversify the range of heterocycles systems which we could produce. Trapping agents included an oxazole and imidazole which are cyclic imine analogues, azo compounds and nitriles (Table 26) (Scheme 35)

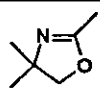

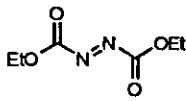
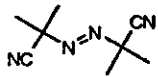
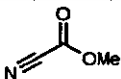
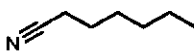


**Scheme 35** – Possible products formed from [2+3]-cycloaddition with various trapping agents

There have been many reasons to expand the range of trapping agents used, for instance, **entries 1-2** in **Table 26** are 2,4,4-trimethyl-2-oxazoline and 2-methyl-2-imidazoline, these compounds are significantly different in their electronic makeup to imines however they do have a C=N bond in the ring system. When the oxazoline and imidazoline were subjected to the conditions developed for the [2+3]-cycloaddition (10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, 2 eq. ZnBr<sub>2</sub>, THF at 35 °C) no products were seen from either substrate. If the reaction with the vinyl cyclopropane had been successful it would have generated a bicyclic system in one step however the methyl group in the 2-position of the oxazoline and imidazoline is thought to stop the [2+3]-cycloaddition through steric hindrance.

We next looked at the reaction with N=N bonds in order to generate pyrazoles via a [2+3]-cycloaddition between the vinyl cyclopropane and azo compounds. After subjecting the DEAD (**entry 3**, **Table 26**) and the AIBN (**entry 4**, **Table 26**) to the standard reaction conditions for 72 hours it was found that no reaction had occurred and there was decomposition of the DEAD and AIBN.

We also attempted the [2+3]-cycloaddition onto a nitrile bond. For this reaction cyanoacetic acid (**entry 5**), and heptanenitrile (**entry 6**) were used. It was thought that the [2+3]-cycloaddition using a nitrile should have generated a cyclic imine which could have been used in further reactions. However upon reaction under standard conditions for 72 hours only starting material was recovered.

	Trapping agent	Solvent	Temp (°C)	Time (h)	Yield (%)	Cis:Trans
1		THF	35	72	0 (116)	-
2		THF	35	72	0 (117)	-
3		THF	35	72	0 (118)	-
4		THF	35	72	0 (119)	-
5		THF	35	72	0 (120)	-
6		THF	35	72	0 (121)	-

1 mmol scale and had 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, 2 eq ZnBr<sub>2</sub>.

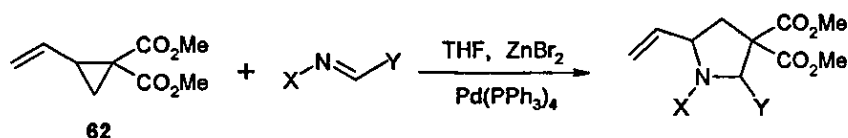
**Table 26** – [2+3]-cycloaddition of other trapping agents with VCP (Scheme 35)

All the cyclisations which have been attempted using these X=Y and X≡Y trapping agents have failed to yield the desired cycloaddition products. In some cases, this could be due to the use of sterically demanding groups which have been shown to cause problems during other cyclisations and also the fact that in the case of the nitrile groups a stronger bond (C≡N instead of C=N) needs to be broken to form the desired product

#### 2.1.4 – Conclusion

A range of imines and other X=Y type compounds have been subjected to [2+3]-cycloaddition chemistry using Pd(PPh<sub>3</sub>)<sub>4</sub> as a catalyst in the presence of ZnBr<sub>2</sub>. The majority of the [2+3]-cycloaddition reactions proceeded well to generating the desired products in moderate to good yields with the most successful imines being the *N*-benzyl imines, followed by *N*-tosyl with the *N*-PMB being the

least successful substrates. However the methodology developed has shown some weakness, firstly aromatics substituted in the *meta* position and secondly highly steric imines failed to react. In the case of *meta* substituted aromatics it is unclear why the reactions failed to give the cycloaddition product as corresponding aromatics substituted in the *ortho* and *para* positions gave the desired pyrrolidines in good yields in most cases. The problem with sterically demanding imines is, however, thought to be the anion formed during the opening of the cyclopropane is unable to react onto the imine due to the bulk of neighboring groups.



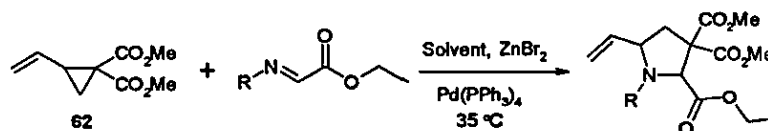
**Scheme 36** – General reaction scheme for [2+3]-cycloaddition with vinyl cyclopropane

## Section 2.2 – Reaction with Ethyl Glyoxylate:

### Preparation of Novel Proline Derivates

#### 2.2.1 – Introduction to Pyrrolidines Derived from Ethyl Glyoxylate

The previous described work in section 2.1 involved the synthesis of *N*-alkyl or aryl pyrrolidines and in order to increase the scope of this chemistry, it was decided to look at imines derived from ethyl glyoxylate. This was done to generate a range of pyrrolidines with a carboxylate ester  $\alpha$  to the nitrogen, i.e. a proline analogue (Scheme 37)



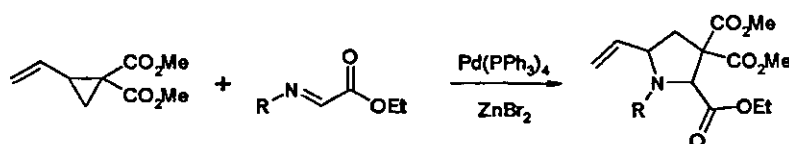
Scheme 37 – C1-Ethyl ester pyrrolidine formation

#### 2.2.2 – Pyrrolidines Derived from Ethyl Glyoxylate Imines Results

The required imines for the [2+3]-cycloaddition step were prepared from a range of amines and ethyl glyoxylate under standard conditions. The first imine examined was the *N*-PMB ethyl ester imine, which was chosen for two reasons. Firstly the *N*-PMB were our initial imines used and secondly it formed an imine with a powerful electron withdrawing group (ester) and a powerfully electron donating group (PMB) attached to the reacting bond. All the stereochemical data was determined by NMR studies of the products with relative stereochemistry being confirmed by X-ray crystal structures.

The *N*-(4-methoxy-phenyl) ethyl ester imine (entries 1-2, Table 27), proved to be very successful under standard conditions (entry 1) with the desired product being formed in only 8 hours in almost quantitative yield (97%). The diastereoselectivity was, however, the most impressive aspect of this work as it

showed only one isomer in both  $^1\text{H}$  and  $^{13}\text{C}$  spectra. This experiment was carried out in the absence of a Lewis acid; with the inclusion of Lewis acid two isomers were formed. It was also decided to determine the effect of TFA on the reaction (**entry 2**), however when this reaction gave no product. It is believed that the TFA was causing decomposition of the cyclopropane. The experiment was then repeated using different electron rich imines: *N*-2,4-dimethoxy-phenyl and *N*-3,5-dimethoxy-phenyl protecting groups (**entries 3-4**). These were performed without the presence of a Lewis acid, as it was found that when using these electron rich groups the Lewis acid was not necessary to activate the imines. However, only the *N*-2,4-dimethoxy-phenyl yielded results, which were comparable to the *N*-4-methoxy-phenyl. The *N*-3,5-dimethoxy-phenyl was also repeated in the presence of Lewis acid, however, still failed to undergo the [2+3]-cycloaddition.

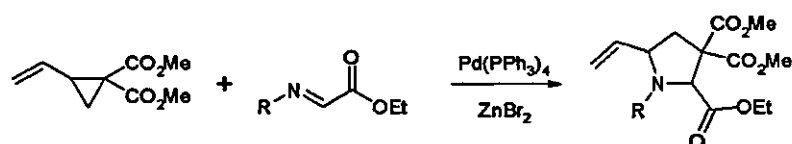


	Imine	Solvent	Temp (°C)	Time (h)	Yield (%)	Cis:Trans
1		THF (no ZnBr <sub>2</sub> )	RT, 35	8	97 (122)	0:1
2		THF, TFA,	RT	16	0 (122)	-
3		THF (no ZnBr <sub>2</sub> )	35	48	94 (123)	0.1
4		THF,	35	48	0 (124)	-

1 mmol scale and had 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, 2 eq. ZnBr<sub>2</sub>.

**Table 27** – Ethyl glyoxylate derived imines [2+3]-cycloaddition with VCP

With the success of the preliminary reactions, it was decided to look at the *N*-benzylimines reaction (entry 1, Table 28), however this proved to be less successful than under standard reaction conditions using the PMB group. The yields obtained for this have only been trace amounts. *N*-Boc protection was next examined (entry 1, Table 33) This underwent cyclisation in reasonable yield (47%), however the diastereoselectivity for this substrate was very poor (1:1 *cis:trans*) A second electron withdrawing group *N*-2-cyano-phenyl (entry 2) was also synthesized in order to examine the possibility of using *ortho* substituent on the aromatic ring next to nitrogen. This reaction went well, giving a good yield (58%) of the desired pyrrolidine.



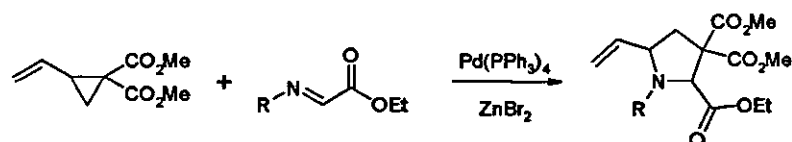
	Imine	Solvent	Temp (°C)	Time (h)	Yield (%)	Cis:Trans
1		THF	35	48	Trace (125)	-
2		THF	RT	48	47 (126)	1:1
3		THF	35	48	58 (127)	1:1

1 mmol scale and had 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, 2 eq ZnBr<sub>2</sub>.

**Table 28** – Ethyl glyoxylate derived imines [2+3]-cycloaddition with VCP

After the use of a powerfully electron donating groups in the [2+3]-cycloaddition, it was decided to attempted the reaction using an electron withdrawing group on the nitrogen. Tosyl was chosen for the initial experiments, however these were initially unsuccessful (entry 1-2, Table 29) with only starting materials being recovered. However when the reaction was allowed to proceed for a longer time (entry 3, Table 29), 96 h rather than 48 h 56% yield of the desired

product was observed, as a white crystalline solid with only one diastereoisomer (*cis*) which was proved by X-ray crystallographic diffraction. *N*-4-Nitro-phenyl was also attempted, however this was unsuccessful yielding no product even with the increase reaction time to 96 h (**entry 4**).

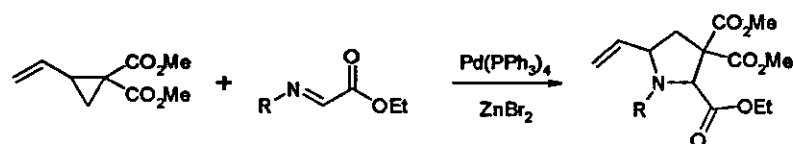


	Imine	Solvent	Temp (°C)	Time (h)	Yield (%)	Cis:Trans
1		THF (no ZnBr <sub>2</sub> )	35	48	0 (128)	-
2		THF	35	48	0 (128)	-
3		THF	35	96	56 (128)	1:0
4		THF	35	96	0 (129)	-

1 mmol scale and had 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, 2 eq. ZnBr<sub>2</sub>.

**Table 29** – Ethyl glyoxylate derived imines [2+3]-cycloaddition with VCP

The **entries 1-2** on **Table 30** shows the use of aliphatic systems on nitrogen and were prepared in moderate yield 42-44% and poor to good selectivity 1.1:5-1.5 (*cis trans*). These were prepared to determine if it was possible to use aliphatic systems on nitrogen. The final entry is however an *N*-oxime ethyl ester imine which was synthesized to determine if oximes could be used as well as imines in this synthesis. The desired pyrrolidine was formed from the oxime in good yield (55%) however the diastereoselectivity for this reaction was poor (1:1)

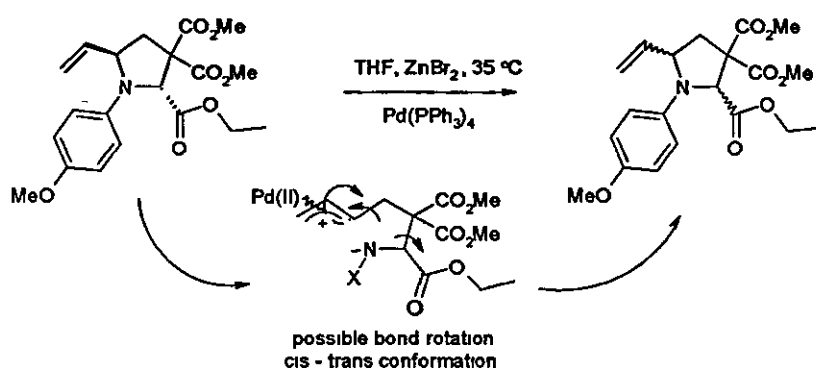


	<i>Imine</i>	<i>Solvent</i>	<i>Temp (°C)</i>	<i>Time (h)</i>	<i>Yield (%)</i>	<i>Cis:Trans</i>
1		THF	35	48	44 (130)	1:1.5
2		THF	35	48	42 (131)	1:5
3		THF	RT	48	55 (132)	1:1

1 mmol scale and had 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, 2 eq. ZnBr<sub>2</sub>.

**Table 30** – Ethyl glyoxylate derived imines [2+3]-cycloaddition with VCP

We also set out to see if the second step in the reaction (ring closing step) of the reaction was reversible, and to this end we examined the effect of reaction time on *cis* to *trans* ratio. It was hoped that by reacting the pyrrolidine for an extended period of time in the presence of the palladium catalyst it would allow the pyrrolidine to ring open and then close again in a different conformation. However there was no change in stereochemistry after a further four days of reacting at 35 °C in the presence of 10 mol% of the catalyst (Scheme 38), which indicated no *cis-trans* equilibrium was occurring.

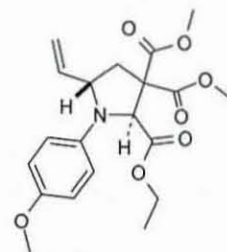
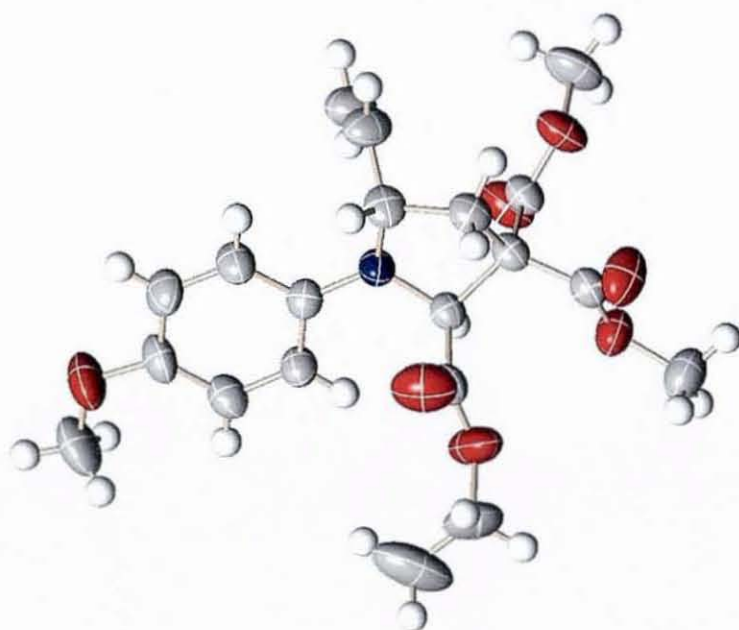


**Scheme 38 – Change in stereochemistry**

### *X-Ray crystal structures*

The most important piece of work which has been done during this project is the synthesis and subsequent crystallization of *N*-(4-methoxy-phenyl)-2-ethyl ester-5-vinylpyrrolidine-3,3-dicarboxylic acid dimethyl ester (**122**) and *N*-(tosyl)-2-ethyl ester-5-vinylpyrrolidine-3,3-dicarboxylic acid dimethyl ester (**128**). It was found that the crystallization of the pyrrolidines formed in the palladium catalyzed [2+3]-cycloaddition used was not easy and was only possible when these reactions were carried out on a multigram scale.

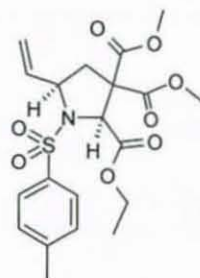
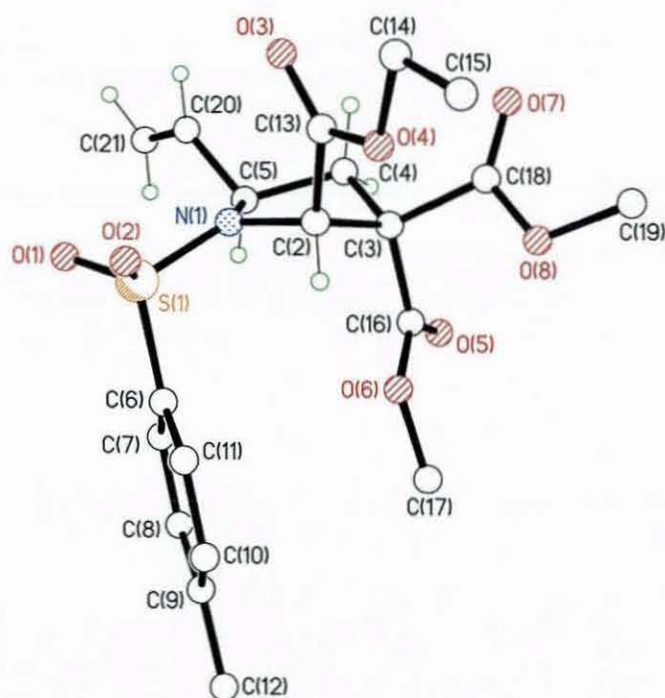
The pyrrolidines which were crystallized were ones which had been shown to have only one diastereoisomer *trans* for the *N*-PMB and *cis* for the *N*-tosyl. Due to the fact that these pyrrolidines were single diastereoisomers and gave unique splitting patterns in the proton NMR it has been possible to go back and look at all the previous pyrrolidines formed and correctly assign the stereochemistry once the X-ray crystal structures were determined.



Relative stereochemistry  
(R, S) or (S, R)

Axel Maier, André Alker –  
Roche X-ray service

**Fig 4** – X-ray crystal structure of *N*-(4-Methoxy-phenyl)-2-ethyl ester-5-vinylpyrrolidine-3,3-dicarboxylic acid dimethyl ester (**122**)



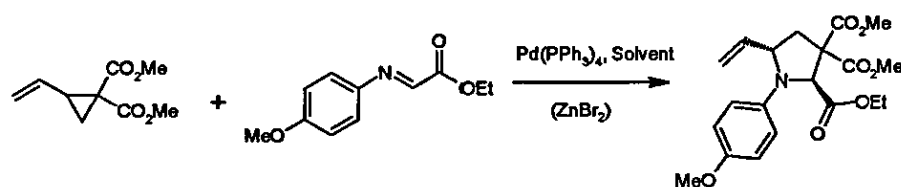
Relative stereochemistry  
(R, S) or (S, R)

Mark Elsegood / EPSRC X-ray  
service Southampton

**Fig 5** – X-ray crystal structure of *N*-(Tosyl)-2-ethyl ester-5-vinylpyrrolidine-3,3-dicarboxylic acid dimethyl ester (**128**)

### 2.2.3 – *N*-(4-Methoxy-Phenyl)-5-Vinyl-Pyrrolidine-2,3,3-Tricarboxylic acid 2-Ethyl Ester 3,3-Dimethyl Ester Results

The initial reactions using *N*-(4-methoxy-phenyl) ethyl ester imine had proved to be highly successful (Table 27) With this success it was decided to look at different reaction conditions. There are three main reasons why this substrate was chosen; firstly it was formed as only one isomer (*trans*); it is also a highly reactive imine, leading to short reaction times, and finally it is one of the only pyrrolidines which has been synthesized as a crystalline product.

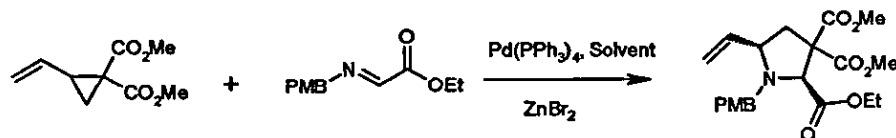


Scheme 39 – *N*-PMB ethyl ester cyclisation

The reaction to prepare *N*-(4-methoxy-phenyl)-5-vinyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester has looked as under a number of conditions (Tables 31-34) We first examined the [2+3]-cycloaddition in the presence of a Lewis acid ( $\text{ZnBr}_2$ ) in a range of solvents (Tables 31-33) A range of common solvents were tried - THF as the control reaction, DCM, toluene, acetonitrile, methanol and DMF. The best solvent which was found for the reaction with and without the Lewis acid present was THF which gave nearly quantitative yield in both cases. However toluene, acetonitrile and methanol all performed well both with and without Lewis acid giving excellent yields of 89-95% DCM however gave slightly poorer yields 65% (with Lewis acid) and 66% (without Lewis acid) However the least successful of the solvents tested was DMF which only gave 35% (with Lewis acid) and 39% (without Lewis acid) of the desired pyrrolidine product

The most unusual feature of the change of having Lewis acid present or not is the diastereoselectivity – in all cases the presence of the Lewis acid caused two diastereoisomers to be formed in the reaction as a 1:1 mixture however when there was no Lewis acid in the reaction mixture there is only the *trans* product formed.

### Reaction with Zinc Bromide

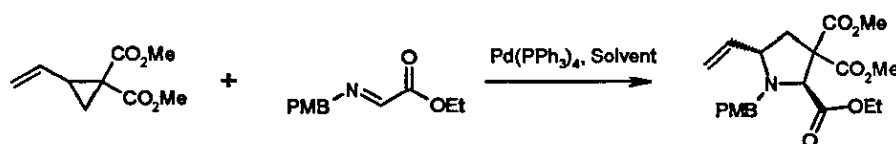


	<i>Solvent</i>	<i>Time (h)</i>	<i>Yield (%)</i>	<i>Cis:Trans ratio</i>
1	THF	16	95 (122)	1:1
2	DCM	16	65 (122)	1:1
3	Toluene	16	89 (122)	1:1
4	Acetonitrile	16	92 (122)	1:1
5	Methanol	16	91 (122)	1:1
6	DMF	16	35 (122)	1:1

1 mmol scale and had 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, 2 eq. ZnBr<sub>2</sub>, 35 °C

**Table 31** – *N*-PMB ethyl ester cyclisations using ZnBr<sub>2</sub>

### Reaction without Zinc Bromide



	<i>Solvent</i>	<i>Time (h)</i>	<i>Yield (%)</i>	<i>Cis:Trans ratio</i>
1	THF	16	97 (122)	0.1
2	DCM	16	66 (122)	0.1
3	Toluene	16	91 (122)	0.1
4	Acetonitrile	16	95 (122)	0.1
5	Methanol	16	94 (122)	0.1
6	DMF	16	39 (122)	0.1

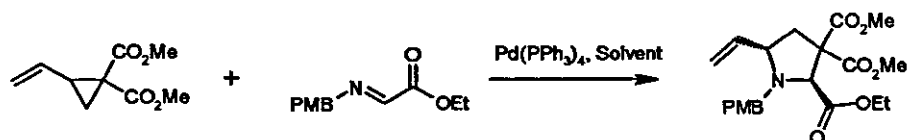
1 mmol scale and had 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, THF at 35 °C

**Table 32** – *N*-PMB ethyl ester cyclisations without using ZnBr<sub>2</sub>

As well as examining in the effect of altering the solvents, the *N*-4-methoxy-phenyl ethyl ester imine has been used to test a number of different reaction conditions including scale and catalyst loading. When the synthesis of the *N*-(4-methoxy-phenyl)-5-vinyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester was carried out on a 10 gram scale, only a slight reduction in yield was observed (90% rather than 97% on a 1 mmol scale) when the reaction was scaled up (entry 1, Table 33).

Due to the fact that large quantities of catalyst were needed on a large scale, it was also decided to attempt the synthesis using a catalyst loading of 1 mol% (entry 2, Table 33). The results from this lower catalyst loading were moderate (39%) and it is thought that further optimization of the reaction conditions would be needed to determine a better catalyst loading, for example longer reaction time or microwave irradiation.

An experiment was also tried using a sonication bath (entry 3, Table 38). The reasoning behind this decision was that sonication creates an energy pattern which has been shown in the literature<sup>39</sup> to reduce the required reaction time of a reaction. The mixture was reacted for 20 minutes under sonication conditions and yielded 48% of the desired pyrrolidine in a 1:2 *cis:trans* ratio.



	Conditions	Product yield (%)	<i>Cis:Trans</i> ratio
1	10 g scale	90 (122)	0.1
2	1 mol% catalyst on 10 g scale	39 (122)	0.1
3	Sonication	48 (122)	1 2

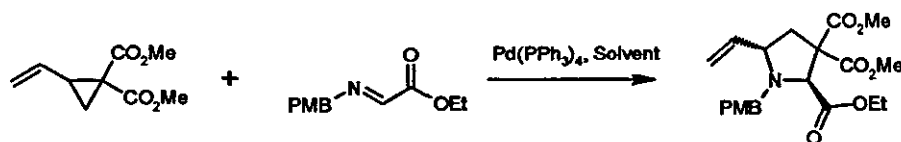
1 mmol scale and had 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, THF, RT for 48 h, no ZnBr<sub>2</sub>

Table 33 – Other PMB ethyl ester [2+3]-cycloadditions

We next turned our attention to the ligand on palladium, so far our chemistry was limited to Pd(PPh<sub>3</sub>)<sub>4</sub>, and the starting point was the bisphosphine dppp (Table

34). The reaction was attempted in the presence of both 1 equivalent of the bisphosphine and also 10 mol% of the bisphosphine ligand. However in both cases the reaction failed to yield the desired pyrrolidine.

Different palladium catalysts have also been looked at, and the palladium(0) catalyst (Table 34, entry 3) reacted to give the desired product in good yield and reasonable selectivity (1:3 *cis:trans*) however the two ligand free palladium(II) catalysts tried (entries 4-5) failed to undergo the [2+3]-cycloaddition reaction.



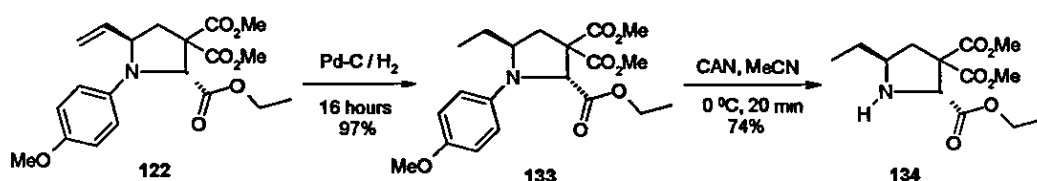
	Conditions	Product yield (%)	Cis:Trans ratio
1	Phosphine ligand (dppp) (1 eq)	0 (122)	-
2	Phosphine ligand (dppp) (10 mol%)	0 (122)	-
3	Pd <sub>2</sub> (dba) <sub>3</sub> catalyst (10 mol%)	92 (122)	1 3
4	PdCl <sub>2</sub> catalyst (10 mol%)	0 (122)	-
5	Pd/C catalyst (10 mol%)	0 (122)	-

1 mmol scale and had 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, THF, RT for 48 h, no ZnBr<sub>2</sub>

**Table 34** – Effect of catalyst and phosphine ligands on [2+3]-cycloadditions

#### *Deprotection of the pyrrolidine nitrogen, using PMB as a protecting group*

We wished to show that the PMB group could be removed from our pyrrolidine. For the *N*-PMB pyrrolidines the deprotection was performed in two steps; firstly hydrogenation of the vinyl group using Pd-C / H<sub>2</sub>, which was done to prevent possible side reactions. After the hydrogenation, the 4-methoxy-phenyl group was removed under the standard conditions, i.e. stirring the substrate with cerium ammonium nitrate (CAN) in acetonitrile at 0 °C for 20 minutes (Scheme 40). It was seen that this method successfully removed the 4-methoxy-phenyl group and did not alter the stereochemistry in the free *N*-H pyrrolidine, as shown by NMR spectroscopy.



**Scheme 40** – Deprotection of *N*-4-methoxy-phenyl pyrrolidine compound

## 2.2.4 – Conclusion

The cyclisation onto ethyl glyoxylate derived imines has proved to be very successful and a range of proline products have been formed. The best example of this range of compounds is the *N*-(4-methoxy-phenyl)-5-vinyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester, which was prepared in a very short reaction time and produced a single diastereoisomer.

It was also possible to crystallize two of the C1-ethyl ester pyrrolidines, one of which being the *trans* *N*-(4-methoxy-phenyl)-5-vinyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester and the other was the *cis* *N*-(toluene-4-sulfonyl)-5-vinyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester which allowed the exact relative stereochemistry to be determined. Overall the proline analogues have been prepared in good yield and in high purity.

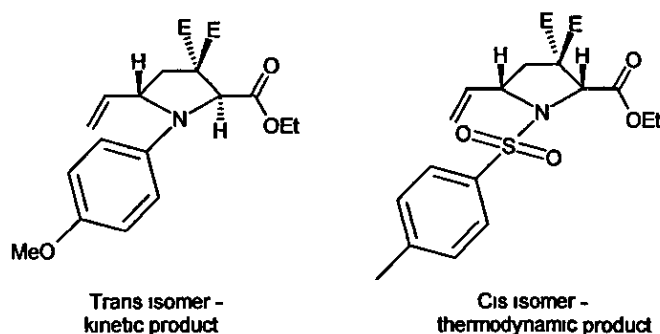
## 2.2.5 – Diastereoselectivity in Palladium Catalyzed [2+3]-Cycloadditions

### *Diastereoselective results*

Control of the diastereoselectivity during the palladium [2+3]-cycloadditions is of great importance. Of particular note in this field were the reactions carried out on the *N*-(4-methoxy-phenyl) ethyl ester imine as this was the first [2+3]-cycloadditions which generated a single isomer. It was later confirmed using X-ray crystal structures that the pyrrolidine formed was *trans*.

The *cis* pyrrolidine product was formed when using the *N*-(tosyl) ethyl ester imine reacted under standard reaction conditions for 96 h. It has been found that the

*trans* product was formed preferentially from an imine which is electron donating on the nitrogen and electron withdrawing on the carbon of the imine bond. However the *cis* product was formed from an imine that was electron withdrawing on both the carbon and the nitrogen of the imine (Scheme 41).



**Scheme 41** – *Cis* and *trans* isomers formed

We believe that it is the electronic properties of the imines which are the largest contributors to the diastereoselectivity of the products formed in the reactions. One aspect of future work in this field could be the formation of other imines with strong electronic properties to determine validity of the conclusions which have been obtained, as it would prove to be very interesting to look at a wider range of both electron donation and electron withdrawing groups on nitrogen.

	<i>Imine</i>	<i>Solvent</i>	<i>Temp (°C)</i>	<i>Time (h)</i>	<i>Yield (%)</i>	<i>Cis:Trans</i>
1		THF (no ZnBr <sub>2</sub> )	35	16	97 (122)	0:1
2		THF	35	96	56 (128)	1:0

1 mmol scale and had 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, no ZnBr<sub>2</sub>.

**Table 35** – Diastereoselectively pure [2+3]-cycloadditions

## 2.2.6 – Asymmetric Palladium Catalyzed [2+3]-Cycloadditions

### Introduction

With some control over the d.e. of the palladium catalyzed [2+3]-cycloaddition, we now wished to look at the enantio- control of the reaction. We set out to do this in two ways: chiral auxiliaries and asymmetric catalysts. Chiral auxiliaries have been used for many years and are designed to be attached to a starting material and then easily removed when the desired reaction has taken place. The second approach, in an attempt to induce chirality, is by using a chiral ligand on the palladium catalyst in the hope that this would induce chirality to the product. There has been a great deal of work done in this field and the approaches to chiral ligands are well known. Trost *et. al.*<sup>40</sup> has performed a great deal of work in this field and has developed many chiral ligands which can be used in palladium catalyzed reactions (Fig 6). The disadvantage of chiral ligands is that they are expensive and a range would need to be tested in order to find the optimum conditions for the best ligand.

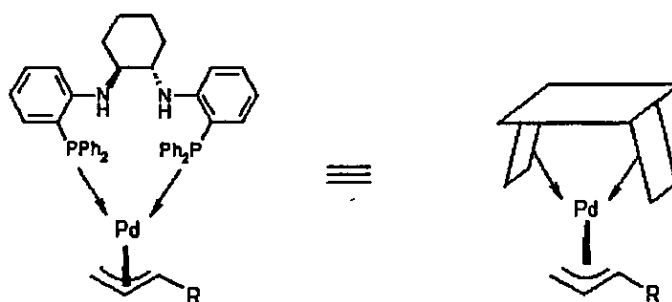
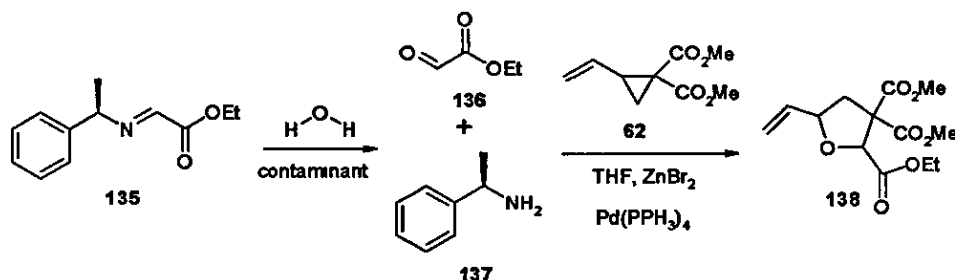


Fig 6 – Chiral ligand blocking vinyl face

### Chiral auxiliaries

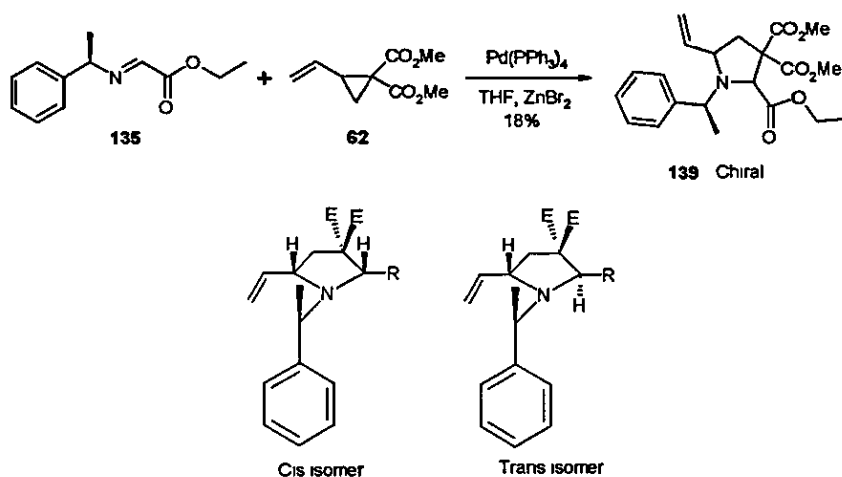
The chiral auxiliary approach was our first choice, with most of our effort being focused on (*R*)-phenylethylamine. This group was chosen as it is similar to benzyl with which we had a great deal of success. The (*R*)-phenylethylamine was reacted with ethyl glyoxylate in the presence of molecular sieves with ether as the solvent for 16 hours to generate the chiral imine in good yield. However when the imine was reacted under standard [2+3]-cycloaddition conditions the product was

not seen in the reaction mixture. It was found by NMR analysis that the chiral imine was hydrolysing during the reaction to give the (*R*)-phenyl ethylamine and ethyl glyoxylate, which reacted with the cyclopropane to give the tetrahydrofuran as the product (Scheme 42).



Scheme 42 – Hydrolysis of the chiral imine

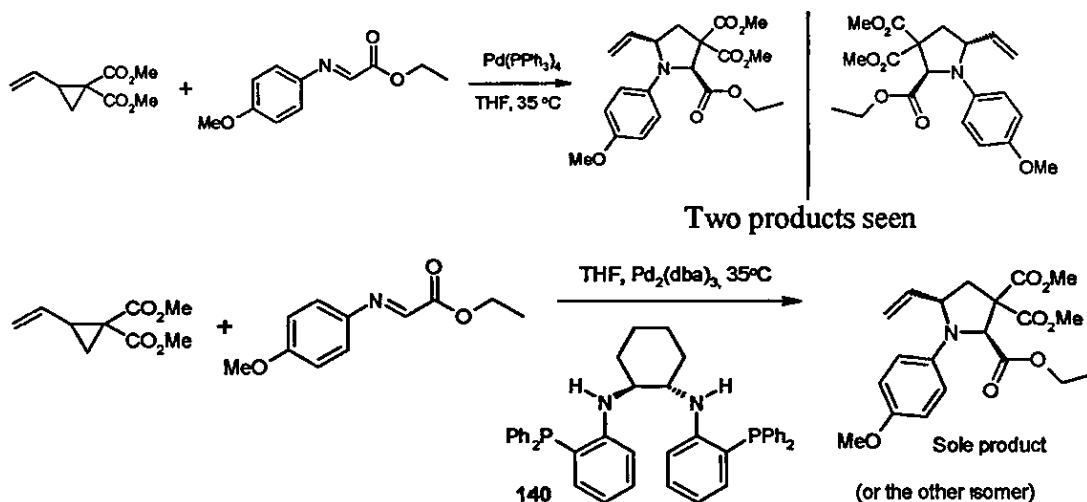
When the reaction was performed under anhydrous conditions it was possible to obtain the desired pyrrolidine product in relatively low yields (18%) with the major product still being the tetrahydrofuran product (43%). Unfortunately, it was shown from the NMR data that the compound had two isomers in roughly 1:1 ratio which could not be separated (Scheme 43). The use of other chiral auxiliaries was not developed further during this project due to the lack of success during the initial work in the area using (*R*)-phenylethylamine. We feel the mistake was having the chiral auxiliary on the nitrogen, as the steric crowding this caused may have effected the reaction



Scheme 43 – Cis and Trans isomers

### Chiral ligands

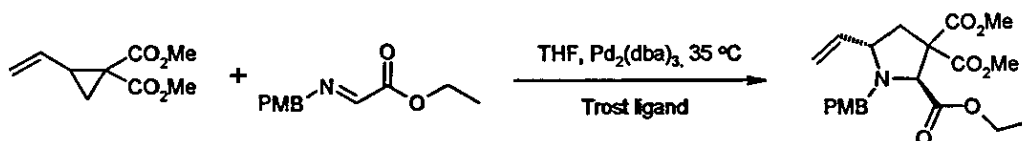
The preparation of the [2+3]-cycloaddition reaction using a chiral ligand on palladium is a different asymmetric route to that of the chiral auxiliaries, as it is dependent on an external source of chirality. The *N*-(4-methoxy-phenyl) ethyl ester imine was chosen as the trapping agent due to its high reactivity, and the fact that under normal reaction conditions the pyrrolidine produces only one diastereoisomer isomer. It was hoped that the use of the Trost ligand<sup>40</sup> (Table 36) would allow the formation of a chiral pyrrolidine in a single step. The Trost ligand was chosen due to its proven reliability during palladium catalysed reactions and it was surmised that this would be the ligand with the greatest chance of creating a chiral pyrrolidine, without the need to examine a range of such ligands (Scheme 44)



**Scheme 44** – Examples of products from standard and chiral reactions

The reaction to generate the Trost ligand-palladium complex proceeded according to the literature with a colour change from purple to orange which is due to complexation between the ligand and the palladium. The imine and vinyl cyclopropane was then added after the reaction had cooled to room temperature. It was found however that when the cycloaddition reaction was carried out at RT, the reaction failed to proceed (entry 1, Table 36). Because of this result the reagents were then added to a fresh ligand-palladium complex at 35 °C (entry 2). After the increase in temperature had proven to be unsuccessful the final variable which was

changed (**entry 3**) was to increase the reaction time in a hope that the product would be formed this reaction also failed to give the [2+3]-cycloaddition product Further work in this area may be of interest as many other chiral ligands are yet to be tried which could prove to be more suitable this type of reaction.



	<i>Chiral ligand</i>	<i>Time (h)</i>	<i>Yield (%)</i>	<i>Cis. Trans ratio</i>
1	Trost ligand ( <b>140</b> )	16	0 ( <b>122</b> )	-
2	Trost ligand ( <b>140</b> )	16	0 ( <b>122</b> )	-
3	Trost ligand ( <b>140</b> )	168	0 ( <b>122</b> )	-

THF with 10 mol% Pd<sub>2</sub>(dba)<sub>3</sub>,

**Table 36** – chiral [2+3]-cycloadditions

## **Section 2.3 Microwave Chemistry**

### **2.3.1 – Introduction to Microwave Assisted Chemical Synthesis**

In the last few years heating chemical reactions using microwave energy has been an increasingly popular technique for organic chemists. This non-classical heating technique is rapidly becoming established in both academia and industry. The microwave region of the electromagnetic spectrum is between IR and radio frequencies with wavelengths from 1 cm to 1 m (30 GHz to 300 MHz). However to avoid interferences with RADAR and telecommunication applications, microwaves for chemical use operate at 2.45 GHz.

Microwaves are a form of electromagnetic energy and like all electromagnetic radiation microwaves have an electrical component as well as a magnetic component. Microwave energy is too weak to break covalent bonds, instead materials can either absorb energy, reflect energy, or they can pass energy. However, few materials are either pure absorbers, pure reflectors, or transparent to microwaves.<sup>42</sup> The chemical composition of the material, as well as its physical size and shape, will affect how it behaves in a microwave field. The way in which microwaves interact with matter can be thought about a penetration depth, i.e. microwaves can usually only penetrate a certain distance into a material. The penetration depth is a function of both the material composition and the frequency of the microwaves. Although most of the early experiments were performed in modified domestic microwave ovens, currently dedicated instruments for chemical synthesis are used which have become readily available, leading to a number of companies producing these devices.<sup>41-43</sup> It can be imagined in a few years most chemists will be using microwave energy to heat chemical reaction in the laboratory in a routine manner.

### 2.3.2 – History of Microwave Irradiation in Chemical Synthesis<sup>41-48</sup>

For centuries the only tools for chemists to apply heat to a reaction process was through direct conduction through a vessel wall. However this is an inefficient source of energy, and potentially dangerous when used with flammable reagents and solvents in reaction mixtures. During the Second World War, RADAR operators noticed that a substance placed in the path of microwave irradiation emitted from the RADAR arrays would keep warm for extended periods of time. The chemical industry made use of microwave irradiation for the first time in 1975<sup>41</sup> In early microwaves samples were usually prepared using common laboratory glassware and open Teflon vessels. However in the 1980s, researchers began using specially designed closed vessels for microwave reactions to achieve reaction temperatures above the atmospheric boiling point of the solvents in the reaction mixture. In order to improve safety in microwave chemistry temperature and pressure monitors were adapted with wavelength attenuators for monitoring reactions and conditions in closed microwave systems. These modifications to commercial microwave systems became the foundation of the laboratory microwave units of today. In 1985 the first laboratory multimode cavity microwave unit was introduced,<sup>41</sup> and although these microwaves were still based on the standard domestic machines the cavity was isolated and ventilated to prevent fumes formed from the reaction process attacking the electronics, thereby making it much safer. In 1986, the first completely focused beam microwave system was introduced to the laboratory environment. Here a single vessel has placed directly in a microwave waveguide which allowed for much greater control during irradiation of the sample.

### 2.3.3 – Types Cavity in Chemical Microwaves<sup>41-48</sup>

#### *Types of cavities*

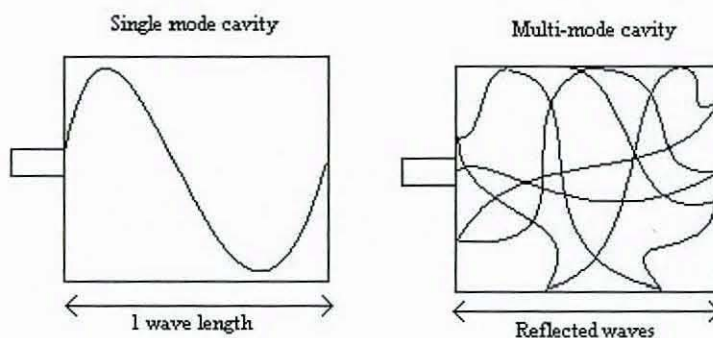
The area in microwaves where materials are exposed to irradiation is called the cavity. Cavities come in many sizes and shapes, depending on the manufacturer and the application for which the machine is used. There are two basic types of cavity, single-mode and multi-mode.

#### *Single-mode cavities*

In single-mode cavities, a standing wave pattern is produced inside the cavity. To do this, the dimensions of the cavity must be carefully controlled to correspond to the characteristic wavelength of the microwaves. For 2.45 GHz microwaves (the frequency domestic and industrial microwaves use), the length of a single wave is 12.2 cm. A single-mode cavity must be a whole-number multiple of this or half of the wavelength to fit inside the cavity (Fig 7). There are specific positions inside the single-mode cavity where items to be heated must be placed. The intensity of the field is greatest at the peaks of the standing wave and drops to zero at the nodes of the wave, which means that there are positions in the single-mode cavity where no heating will occur.

#### *Multi-mode cavities*

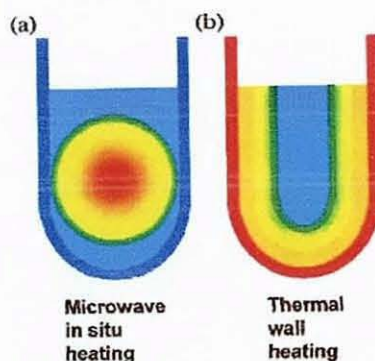
Multi-mode cavities operate by the process of avoiding or disruption of the standing wave pattern inside the cavity, creating as much chaos inside the cavity as possible. There are two ways in which this is achieved. Firstly the dimension of the cavity avoids whole number multiples of the microwave wavelength and secondly by a physical interference of items placed in the cavity. The continual movement of the microwave field results in its homogenization in all directions and all locations throughout the entire cavity (Fig 7).



**Fig 7 – Single and multi mode cavities**

#### 2.3.4 – Heating Using Microwaves<sup>41-48</sup>

In all conventional means for heating reaction mixtures, heating proceeds from a surface to the inside of the reaction vessel. The energy is transferred from a surface to the bulk mixture, and eventually to the reacting species (**Fig 8**). Through mixing, equilibrium temperature conditions can be established and maintained. Microwave heating differs from conventional methods as the reaction vessel must be transparent to the passage of microwaves and heating of the reaction mixture does not proceed from the vessel wall (**Fig 8**). For microwave heating, there must be a component of the reaction mixture which absorbs the penetrating microwaves. When microwaves penetrate the reaction mixture and are absorbed, their energy is converted into heat.<sup>49</sup>

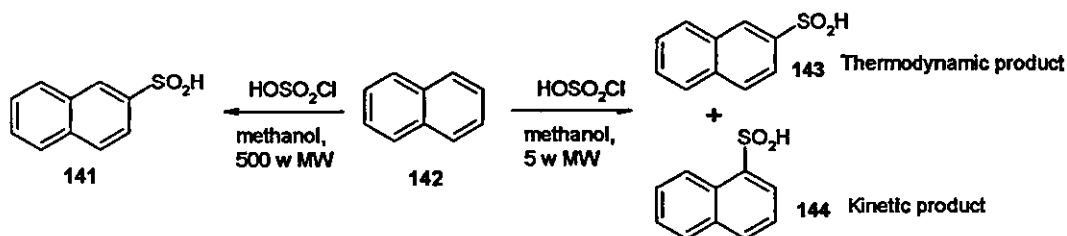


**Fig 8 – Temperature gradient for heating under microwave and thermal conditions<sup>50</sup>**  
(red = hot, blue = cold)

The energy transfer from microwave irradiation to thermal energy occurs by dielectric loss, not conduction and convection as via thermal methods. The easiest way to visualize the mechanism of microwave irradiation is to understand what microwaves are: high frequency oscillating electric and magnetic fields. Anything that is put into this field may be affected if it has the ability to absorb microwave irradiation

### 2.3.5 – Reactions in Microwave Systems

Microwaves give chemists a unique method for controlling reactions. An example of this is chlorosulfonylation of naphthalene, Mingos (now at Oxford University) has shown that the sulphonic group can attach to either the 1 or 2 position of naphthalene (Scheme 45). Low microwave power, like normal heating methods, gave an equal mixture of the two products; however high microwave power, which heats the reaction faster, gave almost 100% of the 2-naphthalenesulphonic acid.<sup>42, 50</sup>



Scheme 45 – Addition of chloro sulphonic acid to naphthalene

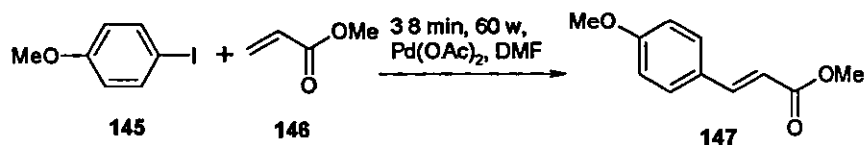
Mingos also showed microwaves can heat solvents above their normal boiling points. Water for example boils at 105 °C under irradiation instead of 100 °C, and acetonitrile, rises to 120 °C (38 °C higher than usual). The reason for this is microwaves heat all the solvent in a flask directly, instead of only the surface area of the reaction vessel, allowing the solvent to reach a higher than usual temperature before bubbles can form.<sup>43</sup>

### 2.3.6 – Microwave Chemistry with Palladium Catalysts

Microwave chemistry has found application in the field of palladium catalyzed chemistry, for example –

#### *Heck reaction*

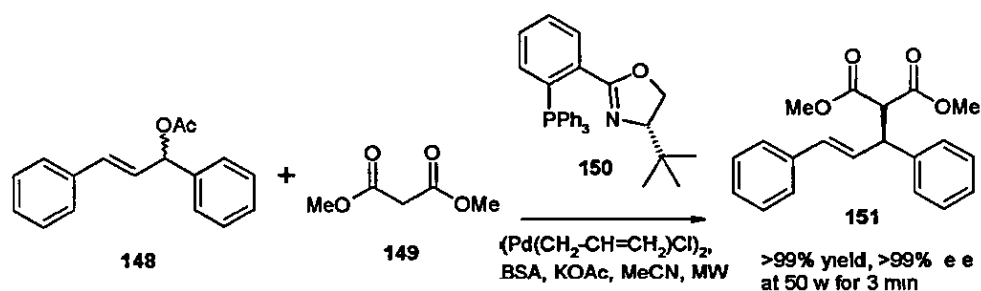
The Heck reaction is the arylation of activated olefins with aryl halides and triflates. This type of reaction generally goes with good regiocontrol to give either linear or branched products. It is, however, a lengthy reaction with times varying from hours to days, however attempts to decrease the reaction time with increased temperature usually causes decomposition of the catalytic system Hallberg *et al* has performed a Heck reaction under microwave irradiation in approximately 4 minutes, whereas with conventional heating would require a reaction time of about 20 hours (Scheme 46) <sup>51</sup>



Scheme 46 – Microwave assisted Heck reaction

#### *Highly selective allylic alkylation*

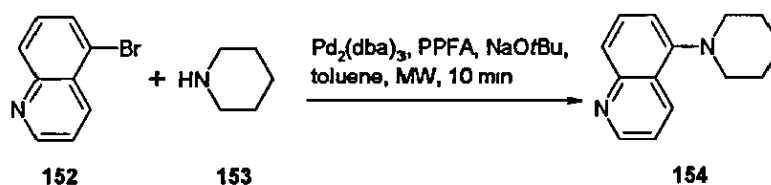
Allylic alkylation has been a common reaction for the past 40 years. However this reaction has a major draw back which is the speed of the reaction, with hours and even days being needed for the product to be formed. However, microwaves are the answer to this problem as they allow for flash heating of the reaction system. Hallberg *et al.* has shown that it is possible to perform these allylic alkylations rapidly (3 min) in excellent yields (>99%) and enantiomeric excess (>99%) (Scheme 47).<sup>52</sup>



**Scheme 47** – Microwave assisted allylic alkylation reaction

#### *Microwave assisted amination*

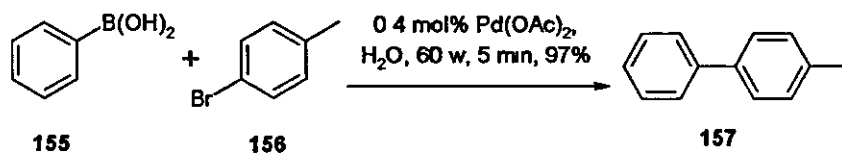
Amination of aromatic halides has become a powerful methodology, since the aryl amine intermediates can be used in the synthesis natural products. Over the last few years, despite the rise in popularity of microwave assisted synthesis, there have only been a very limited number of papers published on using microwaves in amination reactions. Hamann *et al* have developed new aspects of this microwave assisted synthesis and have has shown that it is possible to achieve a 15-75% increase in yield over conventional heating (Scheme 48).<sup>53</sup>



**Scheme 48** – Microwave assisted amination reaction

#### *Suzuki reaction*

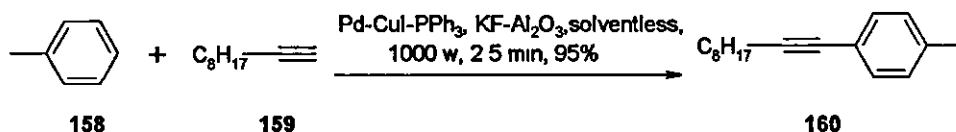
The Suzuki reaction is one of the most versatile, and utilized, reactions for the selective construction of carbon-carbon bonds, especially in the formation of bi-aryl systems.<sup>55</sup> Water is a readily available cheap and non-toxic solvent and is used in some metal-mediated organic reactions however due to problems with solubility of substrates, phase transfer catalysts are some times used. Leadbeater *et al.* showed that is it possible to perform the Suzuki reaction in water without the use of a phase transfer catalyst by using microwave irradiation to superheat the water; thus improving the solubility of the substrates (Scheme 49).<sup>54</sup>



**Scheme 49 – Microwave assisted Suzuki reaction**

### *Sonogashira coupling*

The Sonogashira coupling of terminal alkynes with aryl halides is an efficient route into arylalkynes, and there have been numerous uses for this chemistry including several natural product syntheses. This reaction is usually performed in organic solvents such as THF, DMF or benzene. Kabalka *et. al* have developed this reaction for use with microwave in a solvent less reaction. The development of a solvent less reaction system is important in the context of microwave chemistry as solvent vapour in the reaction could be ignited. The results show that this particular reaction is highly efficient giving high yields (95%) in very short reaction times (Scheme 50).<sup>55</sup>



**Scheme 50 – Microwave assisted Sonogashira coupling**

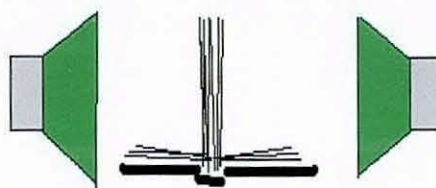
As can be seen in these selected examples, microwave assisted synthesis is already being used for a wide range of palladium catalyzed reactions. It is also likely that in the future more applications will be found for microwave assisted synthesis particularly in areas where the reaction times under conventional heating need to be reduced

### 2.3.7 – Microwaves

The two types of machines which were used in this work are very different, both in their design and way in which the samples are irradiated. The CEM ‘Discover’ and Emrys ‘Optimizer’ are both focused beam machines, which means only the sample is irradiated whereas the CEM MDS 81D is an older cavity type microwave, where all the internal space of the microwave is irradiated.

#### *CEM MDS 81D*

This machine is an old style chemical microwave (approximately 17 years), and uses a process called a “cavity irradiation” which is the same process as used in all domestic microwaves; in these cavity irradiation chemical microwaves, the sample is placed in a large hollow space and then irradiated. The problem with this method is that ‘hot and cold spots’ develop in the microwave where reflected microwave beams cross one another. These ‘hot spots’ continually move so it is impossible to know the exact amount of irradiation that a sample is receiving. However using this approach it is possible to irradiate many samples at once (**Fig 10**).

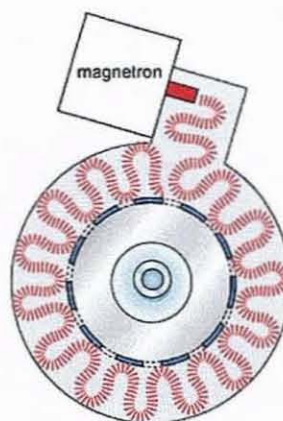


**Fig 10** – CEM MDS 81D microwave and irradiation type

#### *CEM Discover*

This is a more modern chemical microwave and operates on a different and more advanced principle. The CEM discover is a focused beam microwave, which

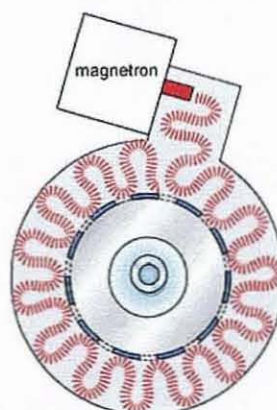
means that rather than irradiating a large volume with imprecise control, it irradiates a small area which can be constantly monitored and adjusted. By doing this it is possible to very accurately maintain a specific energy in the reaction vessel. This is of great importance as it allows control of the operation of the microwave and knowledge that the sample is being fully, but not over, irradiated (Fig 11).



**Fig 11** – CEM discover microwave and irradiation type

#### *Emrys Optimizer*

Of the three microwaves used, the Emrys Optimizer is the most technologically advanced although it still used the principle of a focused beam to irradiate the samples. This microwave is a standard piece of equipment at Roche and contains a built in auto-sampler and computer system to allows for rapid throughput of samples.

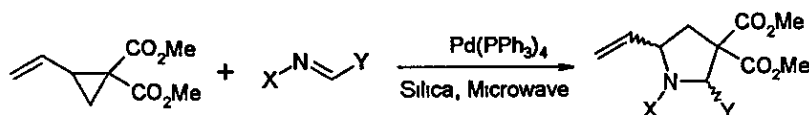


**Fig 12** – Emrys Optimizer microwave and irradiation type

### 2.3.8 – Results for Microwave Irradiation

#### CEM MDS 81D results

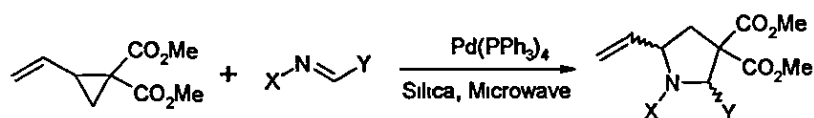
Our preliminary work was carried out on a CEM MDS 81D, and due to the age of the machine was impossible to have absolute control over the power supplied by this microwave. One of the major aspects of working with this machine is that the samples needed to be adsorbed onto a solid support before being reacted to avoid ignition of solvent vapor or explosion of a sealed tube. The result of this meant it was difficult to directly compare the results to those done under thermal conditions, or solution microwave reactions.



Scheme 51 – CEM MDS 81D reaction

The results which were obtained were however interesting and this microwave provided a useful first insight. The CEM MDS 81D is essentially a domestic microwave therefore there were limited variables which could be exploited. It was decided to use 700 watts as a standard irradiation power, and varied the time as appropriate. The initial sample was irradiated for 3 min using the *N*-4-methoxy-phenyl ethyl ester imine. The results were very encouraging as after purification it was found that there was a 92% yield of the desired product, however the diastereoselectivity was poor (1:1 *cis:trans*) (Table 37, entry 1).

After this initial success it was decided to test the conditions to determine the optimum procedure for the irradiation. The first variable was to determine if the reaction would proceed without catalyst present, but the results obtained suggest that the catalyst was still required under microwave irradiation (Table 37, entry 2). Zinc bromide was then added to the reaction mixture as in previous work it was found that a Lewis acid reduced reactivity. This was also found to be the case under microwave conditions as there was a significant drop in yield with the addition of zinc bromide (Table 37, entry 3) from 92% to 75%.

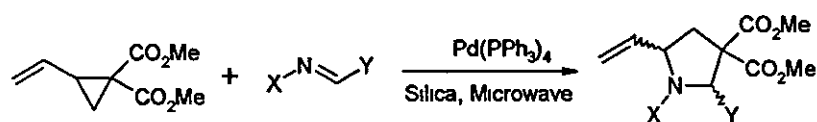


	<i>Imine</i>	<i>Adsorbent</i>	<i>ZnBr<sub>2</sub></i>	<i>Other conditions</i>	<i>Time (min)</i>	<i>Yield (%)</i>	<i>Cis:Trans ratio</i>
1		Silica	No	N/A	3	92 (122)	1:1
2		Silica	No	No catalyst	3	0 (122)	1:1
3		Silica	Yes	N/A	3	75 (122)	1.1

1 mmol scale and had 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, 700 w

**Table 37** – Results for reactions with CEM MDS 81D

The solid support was also examined, the reaction was performed on fluorocil, alumina and an absence of an adsorbent to see which would be the most successful adsorbent. The alumina (**Table 38, entry 1**) gave no product when irradiated however the fluorocil (**Table 38, entry 2**) and the absence of an adsorbent (**Table 38, entry 3**) material both gave positive results (82% for fluorocil and 79% when no adsorbent was used). It appears from these results that it is necessary to use either an acidic support or no support as the neutral alumina proved to be unsuccessful. It is also interesting to note that the stereochemistry was greatly improved when no support was used in the reaction, although the yields were significantly reduced.

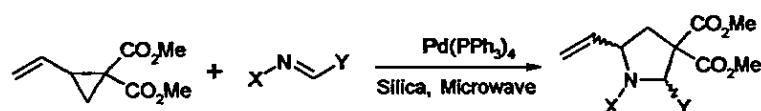


	<i>Imine</i>	<i>Adsorbent</i>	<i>ZnBr<sub>2</sub></i>	<i>Other conditions</i>	<i>Time (min)</i>	<i>Yield (%)</i>	<i>Cis:Trans ratio</i>
1		Alumina	No	N/A	3	0 (122)	-
2		Fluorocil	No	N/A	3	82 (122)	1:1
3		None – neat reagents	No	N/A	3	79 (122)	0:1

1 mmol scale and had 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, 700 w

**Table 38** – Results for reactions with CEM MDS 81D

The final test reaction (**Table 39, entry 1**) was performed using a sample prepared on a solid support which was then allowed to stand for 10 minutes without any irradiation, since during the preparation of the microwave samples there was a colour change in the reagents (yellow to red) and an exothermic reaction which suggested that there was some reaction occurring. It was found upon workup that there was an 87% yield of the desired pyrrolidine product; however it is unclear why there was this rapid reaction. We do however believe that there is a co-catalytic effect caused by the silica in the reaction, but the precise mechanism is unknown.

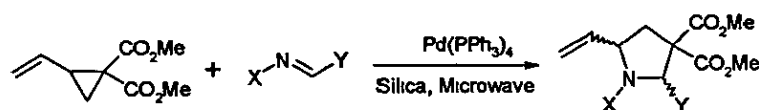


	<i>Imine</i>	<i>Adsorbent</i>	<i>ZnBr<sub>2</sub></i>	<i>Other conditions</i>	<i>Time (min)</i>	<i>Yield (%)</i>	<i>Cis:Trans ratio</i>
1		Silica	No	No MW	3	87 (122)	1.1

1 mmol scale and had 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, 700 w

**Table 39** – Results for reactions with CEM MDS 81D

As had been seen the addition of a Lewis acid to the palladium [2+3]-cycloaddition reaction when *N*-PMB ethyl ester imine is the trapping agent reduces the yield of the pyrrolidine. However under thermal conditions, a Lewis acid is usually required, it was therefore decided to see whether an imine which required a Lewis acid for the [2+3]-cycloaddition would also need it under microwave irradiation conditions **Entries 1-2 on Table 40** show the results, for a reaction using the *N*-2-nitrile-phenyl ethyl ester imine. The reactions with (**entry 1**) and without (**entry 2**) ZnBr<sub>2</sub> have approximately the same yields, 75% and 78% respectively. It was therefore decided to not use ZnBr<sub>2</sub> in future reactions when using the CEM MDS 81D, as we believe that the silica is acting as a Lewis acid.

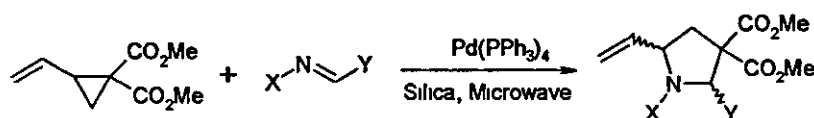


	<i>Imine</i>	<i>Adsorbent</i>	<i>ZnBr<sub>2</sub></i>	<i>Other conditions</i>	<i>Time (min)</i>	<i>Yield (%)</i>	<i>Cis:Trans ratio</i>
1		Silica	Yes	N/A	3	75 (127)	1:1
2		Silica	No	N/A	3	78 (127)	1:1

1 mmol scale and had 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, 700 w

**Table 40** – Results for reactions with CEM MDS 81D

The Table below shows three reactions which were performed in order to achieve a shorter reaction time for the palladium catalysed [2+3]-cycloaddition reaction. The usual reaction times for the [2+3]-cycloaddition reaction is approximately 2 days depending on the substrate used. It was thus decided to test a small selection of different groups using the microwave, and benzyl (**entry 1**), tosyl (**entry 2**) and PMB (**entry 3**) protecting groups were all attempted and all showed reactivity which was approximately the same as under thermal condition, however the selectivity was very poor (1:1)



	<i>Imine</i>	<i>Adsorbent</i>	<i>ZnBr<sub>2</sub></i>	<i>Other conditions</i>	<i>Time (min)</i>	<i>Yield (%)</i>	<i>Cis:Trans ratio</i>
1		Silica	No	N/A	3	67 (109)	1:1
2		Silica	No	N/A	3	61 (115)	1:1
3		Silica	No	N/A	3	55 (85)	1:1

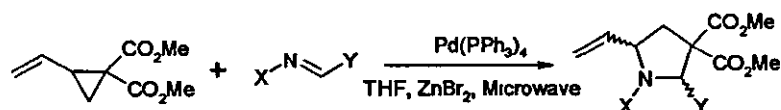
1 mmol scale and had 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, 700 W

**Table 41** – Results for reactions with CEM MDS 81D

The initial microwave reactions proved to be very successful for forming the desired pyrrolidines very rapidly, however the diastereoselectivity of the reaction was poor. The CEM MDS 81D is a very simple machine to use however it was extremely old for a working microwave and therefore slightly unreliable in the exact power output, and the inability to perform the reactions in a solution phase is also a major problem. The reaction times of the CEM MDS 81D were however very rapid with the desired pyrrolidine products being formed in only 3 minutes rather than 2 days as had been seen under the thermal conditions.

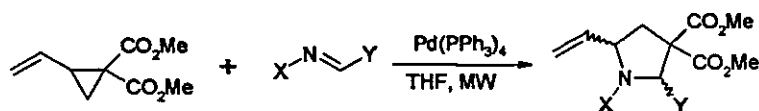
### CEM Discover results

The CEM Discover provided a more advanced microwaves generator. The major advantage of this system is that many options which are available; the ability to set temperatures, pressures and power for a particular solvent. This meant that the reaction conditions were controlled to a far higher degree. This control, and also the fact the samples were carried out in the solution phase, meant that the results could be compared to the original reactions carried out under thermal conditions.



Scheme 52 – CEM Discover accelerated reaction

The first of the products to be tested was the *N*-4-methoxy-phenyl ethyl ester imine. This substrate when reacted under thermal condition at 35 °C had given almost quantitative yields in 8 hours. However under microwave irradiation at 50 Watts a 91% yield was seen after 10 minutes with the same stereochemical outcome as the thermal conditions. This reaction proved the effectiveness of microwave conditions and paved the way for its use with different substrates



	Imine	Solvent	Power (w)	Time (min)	Yield (%)	Cis:Trans
1		THF	50	10	91 (122)	0.1

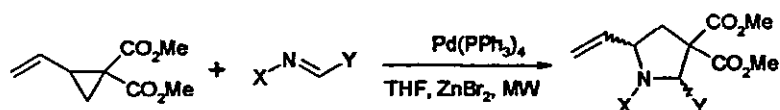
1 mmol scale and had 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>

Table 42 – [2+3]-cycloaddition using CEM Discover microwave

The next group of the substrates used in the CEM discovers were *N*-PMB imines (Table 43, entry's 1-4) as these had proven difficult to cyclise under thermal condition in good yields. The imines chosen were the 4-bromo-phenyl (entry 1), 4-nitro-phenyl (entry 2), 4-methoxy-phenyl (entry 3) and the 4-nitrile-phenyl (entry 4) as these had all given low yields under thermal conditions. The microwave

irradiation results for these substrates were less than encouraging as only the 4-bromo-phenyl (**entry 1**) and the 4-methoxy-phenyl (**entry 3**) formed the desired pyrrolidines, however the yield for the 4-bromo-phenyl was significantly improved from 24% under thermal conditions to 54% using microwave irradiation. The yield of 4-methoxy-phenyl imine remained similar to that of the thermal conditions. It is thought that the problems in the 4-nitro-phenyl (**entry 2**) and the 4-nitrile-phenyl (**entry 4**) are due to decomposition of the imine.

One of the most important reactions performed under microwave conditions was the reaction using a tosyl imine (**entry 5, Table 43**) which had been shown to have a very long reaction time. Under the microwave irradiation conditions the reaction time was reduced from 96 hours to 10 minutes, there was also an increase in yield from 56% to 74% without any change in diastereoselectivity from thermal conditions.

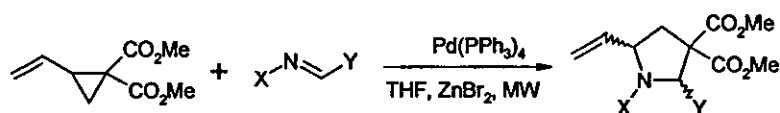


	<i>Imine</i>	<i>Solvent</i>	<i>Power (w)</i>	<i>Time (min)</i>	<i>Yield (%)</i>	<i>Cis:Trans</i>
1		THF	50	10	54 (86)	10:1
2		THF	50	10	0 (82)	-
3		THF	50	20	63 (85)	1:0
4		THF	50	10	0 (83)	-
5		THF	50	10	74 (126)	1 0

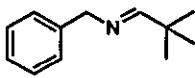
1 mmol scale and had 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, 2 eq ZnBr<sub>2</sub>

**Table 43** – [2+3]-cycloaddition using CEM Discover microwave

Benzyl imines had proven to be a highly successful substrate group for the [2+3]-cycloaddition however there have been some imines which had proven to be unreactive, for example *meta* substituted aromatics and bulky groups on the carbon of the imine. It would therefore be interesting to compare a range of successful imines under both thermal and microwave conditions, and several benzyl imines were irradiated in an attempt to undergo the [2+3]-cycloaddition (Table 44, entries 1-6). The initial tests were performed on substrates which were known to be successful under thermal conditions to allow for a direct comparison. *N*-Benzyl phenyl imine (entry 1), *N*-benzyl 4-pyridineimine (entry 2), *N*-benzyl PMB imine (entry 3) and *N*-benzyl pentane imine (entry 4) were all tried under microwave conditions. The results were as expected, with a dramatic decrease in the reaction times for all the substrates and comparable yields and stereochemistry to the thermal conditions. The next examples chosen of the benzyl imines were the 3-pyridine (entry 5) and the *t*-butyl (entry 6) groups both of which had failed under thermal conditions. After irradiation it was found that the 3-pyridine had been successful formed in good yield (82%), however the *t*-butyl substrate had still failed to give the desired pyrrolidine product.



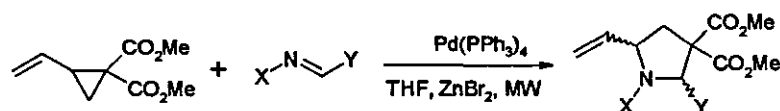
	Imine	Solvent	Power (w)	Time (min)	Yield (%)	Cis:Trans
1		THF	50	20	85 (92)	10:1
2		THF	50	10	86 (96)	7:1
3		THF	50	20	89 (104)	1:0
4		THF	50	10	72 (109)	8:1
5		THF	50	10	82 (98)	1:0

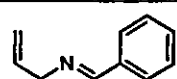
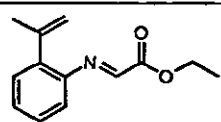
6		THF	50	10	0 (110)	-
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1 mmol scale and had 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, 2 eq ZnBr<sub>2</sub>

**Table 44** – [2+3]-cycloaddition using CEM Discover microwave

Our long term plan involved the use of some RCM chemistry. To allow us to do this we required some substrates which contained as alkene bond, and one of the substrates chosen was a simple *N*-allyl imine and the second was an aromatic styrene imine substituted with a methyl vinyl group. The results for these reactions were encouraging with the desired pyrrolidines being formed in good yield and fast reaction times (Table 45).



	Imine	Solvent	Power (w)	Time (min)	Yield (%)	Cis:Trans
1		THF	50	20	71 (161)	1:1
2		THF	50	20	88 (162)	6.1

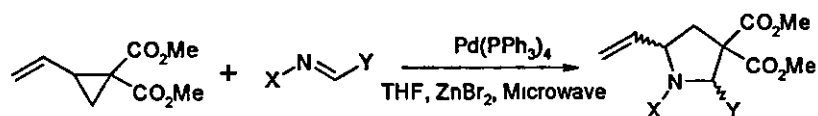
1 mmol scale and had 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, 2 eq ZnBr<sub>2</sub>

**Table 45** – [2+3]-cycloaddition using CEM Discover microwave

Overall the reactions performed using microwave irradiation conditions with the CEM 'Discover' showed significant improvement over those done under thermal conditions. It was found that all reaction yields were increased compared with the reaction being carried out under thermal conditions except for *N*-(benzyl) *t*-butyl imine, which failed to undergo the palladium catalyzed [2+3]-cycloaddition, as it had done under thermal conditions, and more significantly the reaction times had been dramatically reduced to only 10 minutes rather than the 2 days under thermal conditions.

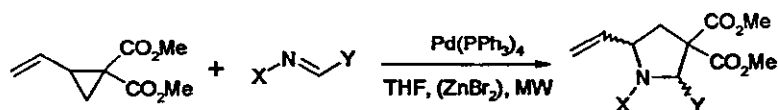
### Emerys Optimizer results

While at Roche (Basel) there was an opportunity to use an Emerys 'Optimizer' microwave. This microwave proved to be very useful for examining many reactions in rapid succession using the inbuilt auto-sampler. The substrates which were used in the Emerys 'Optimizer' were mainly ones which we have had to make in the synthesis in some natural products. However before any work could be performed on new substrates, it was decided to test the new microwave on known imines to determine its effectiveness.



Scheme 53 – [2+3]-cycloaddition using Emerys Optimizer

With the change in equipment, we first looked at two of our most reliable imines the *N*-4-methoxy-phenyl ethyl ester imine **122** (Table 46, entry 1) and the *N*-tosyl ethyl ester imine **126** (Table 46, entry 2), as both of these had performed well under thermal conditions and microwave conditions. The results were as expected both giving the desired product in good yield and fast reaction times with retention of stereochemistry from the thermal conditions.



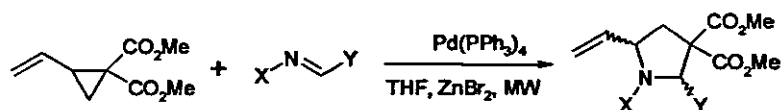
	Imine	Solvent	Power (w)	Time (min)	Yield (%)	Cis:Trans
1		THF	50	10	91 ( <b>122</b> )	0:1
2		THF	50	10	75 ( <b>128</b> )	0.1

1 mmol scale and had 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, (2 eq ZnBr<sub>2</sub>)

Table 46 – [2+3]-cycloaddition using Emery's Optimizer microwave

With the success of the initial test reactions, it was decided to examine reactions using the substrates which would eventually lead towards the synthesis of natural products (see Chapter 2.6). Table 47 shows reworks of reactions which used *N*-benzyl pentane imine as the trapping agent. These reactions proceeded well giving a 72% yield on a 1 mmol scale (entry 1) however it was necessary to have a large quantity of this particular pyrrolidine so a scaled up reaction (entry 2) was carried out with only a slight loss of yield (68%). Both of these proved to have a stereochemical ratio of 8 : 1 in favor of the *cis* product

The final reactions carried out using the Emerys Optimizer on Table 47 entries 3-4 used similar imines as before. The results were not promising, as the pyrrolidines were prepared in either trace amounts for the 1-butene derived imine (entry 3) or had contamination which it was not possible to remove with the 1-allyl derived imine entry 4.



	Imine	Solvent	Power (W)	Time (min)	Yield (%)	Cis:Trans
1		THF	50	10	72 (109)	8 : 1
2		THF	50	10	68 (109) 5 g scale	8.1
3		THF	50	10	Trace (163)	-
4		THF	50	10	Contaminated (164)	8.1

10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, ZnBr<sub>2</sub>

Table 47 – [2+3]-cycloaddition using Emerys Optimizer microwave

As the Emerys Optimizer proved to be very similar to the CEM Discover it was not surprising that these microwaves performed almost identically. The only advantages that the Emerys Microwave had over the previous microwaves tested

was the auto sampling feature, which allowed many samples to be run overnight and also the fact that larger sample vessels could be used, allowing for multigram reactions, which was useful in the preparation of natural product precursors.

### 2.3.9 – Microwave Chemistry Conclusion

A large number of microwave reactions have been performed, and the advantages of this technology were clearly evident. As it allows the formation of pyrrolidine in 3-10 minutes where, as under thermal conditions, it would have taken two days or more to achieve the similar results. The speed at which the pyrrolidines are formed is not the only advantage of microwave irradiation, as it was also seen that the microwave allowed the reaction of aromatic imines substituted in the *meta* position, which was not observed under thermal reaction conditions.

When using the CEM 'Discover' or Emerys 'Optimizer' the stereochemistry was retained from that observed under the thermal solution reaction conditions, however when the CEM MDS 81D was used, which required a solid support, there was a mixture of diastereoisomers formed. Both the CEM discover and Emerys Optimizer allowed control over the conditions as it was possible to alter, time, temperature and pressure at the touch of a button. The CEM MDS 81D is the quicker of the microwaves to undergo the [2+3]-cycloaddition (approximately 3 minutes) however this is due to the much higher power of the microwave (700 watts compared to the Discovery's and Optimizer's 50 watts).

Overall it can be concluded that the microwave reactions proved to be successful. It is known that microwave reactions have been used with palladium catalyst, however it was unclear whether this would apply to our [2+3]-cycloaddition reaction, but with the success of our research into this area of chemistry it is clear that microwave enhanced chemistry is applicable to this reaction type.

### 2.3.10 – Silica Enhanced Reactions Introduction

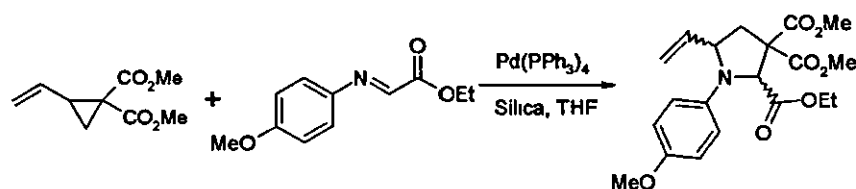
During our work on the microwave chemistry we observed an unusual aspect, in which silica appeared to be a co-catalyst for the [2+3]-palladium cyclisation reaction. This effect was discovered during the first stage of the microwave enhanced chemistry using the CEM MDS 81D, which required the use of a solid support. Careful observation while preparing the samples showed an increase in temperature and discolouration of the material from yellow to red. Instead of reacting it under microwave conditions, extractions of the sample underwent NMR spectroscopy, the results indicated that the desired [2+3]-cyclisation had occurred in only the time needed to work up the reaction which had taken approximately 10 minutes.

This result was dramatically faster than any previous pyrrolidine formations, the fastest reaction observed before had been that using *N*-(4-methoxy-phenyl) ethyl ester imine which had only gone to completion after 8 hours under thermal conditions, however both the diastereoisomers were formed in the reaction on silica. One theory about the way that the silica acts is through co-ordination, to the vinyl cyclopropane and imine in the same way as a Lewis acid.

### 2.3.11 – Silica Enhanced Palladium Catalyzed [2+3]-Cycloaddition Results

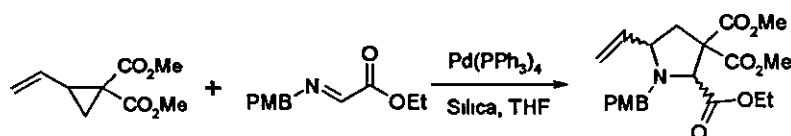
#### *Determine the volume of silica*

The initial work in the field of the silica-enhanced [2+3]-cycloaddition reactions examined the amount of silica which was needed in order to give the desired co-catalytic effect. This work used the most successful imine (*N*-(4-methoxy-phenyl) ethyl ester imine) as the reaction times for this cyclisation under thermal conditions had been determined as 8 hours to go to completion (Scheme 54).



**Scheme 54** – Silica enhanced reaction

After we had found that using silica in the palladium [2+3]-cycloaddition increased the rate of reactions, it was decided that further exploration was needed. The reactions were carried out under three conditions, the first (**entry 1**) being the standard reaction conditions, the second (**entry 2**) was with a small volume of silica using THF as a solvent, and the last (**entry 3**) was a large volume of silica (2 g) without any solvent present. The reagents were mixed with a minimum volume of THF which was immediately removed in *vacuo*. When the large volume silica was added to the reaction mixture it was observed that although the reaction rate was greatly increased, to the point where it is impossible to determine the exact rate of the reaction, two isomers which were formed in roughly 1:1 ratio. In the reaction with the smaller volume of silica in THF, there was not only an increase in reaction rate, compared with the standard reaction without silica, but also retention in stereochemistry from thermal conditions



	<i>Imine</i>	<i>Solvent</i>	<i>Silica</i>	<i>Time</i>	<i>Yield (%)</i>	<i>Cis:Trans</i>
1		THF	None	8 h	97 ( <b>122</b> )	0:1
2		THF	Spatula tip	45 min	94 ( <b>122</b> )	0:1

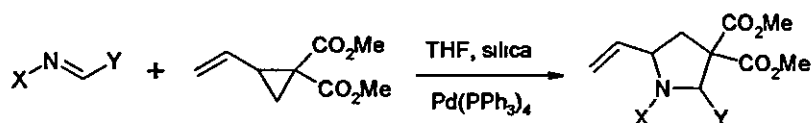
3		None	2 g	10 min	95 (122)	1:1
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1 mmol scale and had 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>.

**Table 48** – [2+3]-Cycloaddition varying the silica volume

### *Cyclisations using silica*

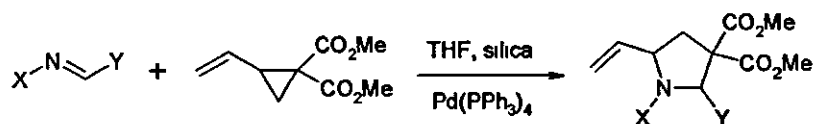
After better conditions had been established (a spatula tip of silica, 16 h at RT) the next aspect of the work focused on examining a range of different imines to determine the tolerance of the silica to different groups. A number of different imines with a range of different groups on both the nitrogen and carbon of the imine were reacted in the presence of a small amount of silica (**Scheme 55**)



**Scheme 55** – Silica enhanced reaction

The first of the reactions to be attempted was with the *N*-tosyl ethyl ester imine, the reaction proceeded as expected with a yield of 57%. This is comparable to the results generated under thermal conditions without silica (**entry 1**). A second electron withdrawing group, *N*-4-nitro-phenyl ethyl ester imine (**entry 2**) was selected however this substrate failed to undergo the [2+3]-cycloaddition.

The final two entries on **Table 49** were standard reactions which had been performed under both microwave irradiation and under the thermal reaction conditions. It was therefore logical to try these substrates under the silica enhanced conditions to determine any change in reactivity. As was seen previously the silica caused an increase in the reaction rate allowing the products to be formed in only 16 hours, with comparable yields and stereochemistry to the standard conditions



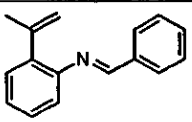
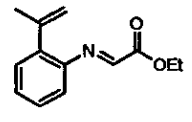
	<i>Imine</i>	<i>Solvent</i>	<i>Temp</i> (°C)	<i>Time (h)</i>	<i>Yield</i> (%)	<i>Cis:Trans</i>
1		THF, silica	RT	16	57 (128)	1:0
2		THF, silica	RT	16	0 (129)	-
		THF, silica	RT	16	62 (85)	1:1
		THF, silica	RT	16	75 (109)	8:1

1 mmol scale and had 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>,

**Table 49** – Results for reaction with silica added

We next looked at imines derived from amines which had an alkene bond; these were chosen because we hoped to use these in RCM reactions. The reactions with the *N*-alkene imines performed well, with most of the desired pyrrolidines being formed in good yield and comparable stereochemistry to the standard conditions, with the advantage that the reactions times were dramatically reduced.

	<i>Imine</i>	<i>Solvent</i>	<i>Temp</i> (°C)	<i>Time</i> (h)	<i>Yield</i> (%)	<i>Cis:Trans</i>
1		THF, silica	RT	16	79 (161)	1.1
2		THF, silica	RT	16	81 (165)	5.1

3		THF, silica	RT	16	0 (166)	-
4		THF, silica	RT	16	58 (162)	10:1

1 mmol scale and had Pd(PPh<sub>3</sub>)<sub>4</sub>, THF, ZnBr<sub>2</sub>, spatula tip of silica, 16 h.

**Table 50** – Results for reaction with Emery's Optimizer microwave

### 2.3.12 – Conclusion

The silica-enhanced reactions were performed by preparing the sample under the standard [2+3]-cycloaddition, the only change being the addition of a spatula tip of silica to the reaction mixture. The reactions were carried out using a range of the imines which had been used under standard conditions to determine the how well the silica catalyzed the cycloaddition. It was seen that the addition of the silica had increased the reaction rate for the pyrrolidine formation from 48 hours or greater, to less than 16 hours.

The reason why this effect occurs is unknown however maybe linked to a Lewis acid effect, as many other Lewis acids have been tried using [2+3]-cycloadditions, however without a dramatic change in reaction rate. It is also not due to any acidic properties of the silica, as other acids were tried without success. However there remains to be a great deal of work yet to be done to determine what is causing this effect.

## Section 2.4 – Grubbs Ring Closing Metathesis

### 2.4.1 – Introduction to Grubbs Ring Closing Metathesis

Ring closing metathesis is one of the most powerful reactions developed in the last two decades, and a review of ring closing metathesis had appeared in the literature.<sup>57</sup> Ring closing metathesis can be defined as the “metal catalyzed redistribution of carbon-carbon double bonds to form new ring systems”,<sup>56</sup> and it is a powerful tool for the transformation of two alkenes to a ring or indeed multiple ring systems with an alkene. The metathesis catalysts developed over the years have the ability to use a wide range alkenes and eneynes in a variety of ways including cross metathesis, ring-closing metathesis, ring opening metathesis polymerization, and acyclic diene metathesis polymerization. The real breakthrough in RCM came in 1993, when Grubbs *et. al.* reported the use of an easy-to-handle ruthenium alkylidene complex which also gave excellent results in RCM.<sup>57</sup> In 1995 the ruthenium complex now widely known as “Grubbs 1<sup>st</sup> generation catalyst”, was reported and has since become the benchmark catalyst for this type of reaction.<sup>58-59</sup>

#### *Grubbs catalysts*

Grubbs First Generation Catalyst **64** effects ring-closing metathesis, olefin cross-metathesis, and ROMP.<sup>60</sup> Among its numerous advantages include its high activities, tolerance for functional groups and protic media. However, this catalyst is limited in its substrate tolerance. Grubbs Second Generation Catalyst **65** however is a more active analogue of the first-generation Grubbs catalyst,<sup>59</sup> and it can also be used for ring-closing metathesis, cross metathesis, and ROMP.<sup>59</sup> However the Grubb’s second generation catalyst can ring close alkenes with excellent functional-group tolerance (Fig 13)<sup>59, 61</sup>

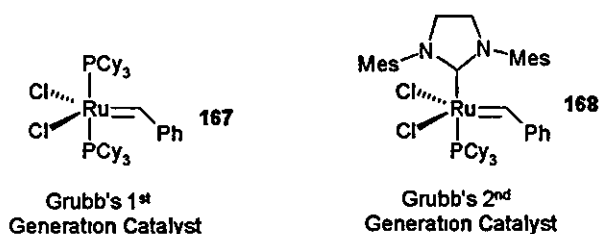
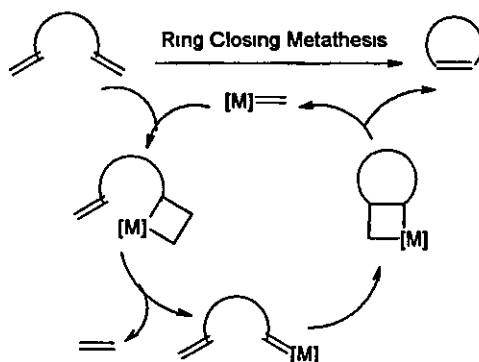


Fig 13 – Grubb's first and second generation catalysts

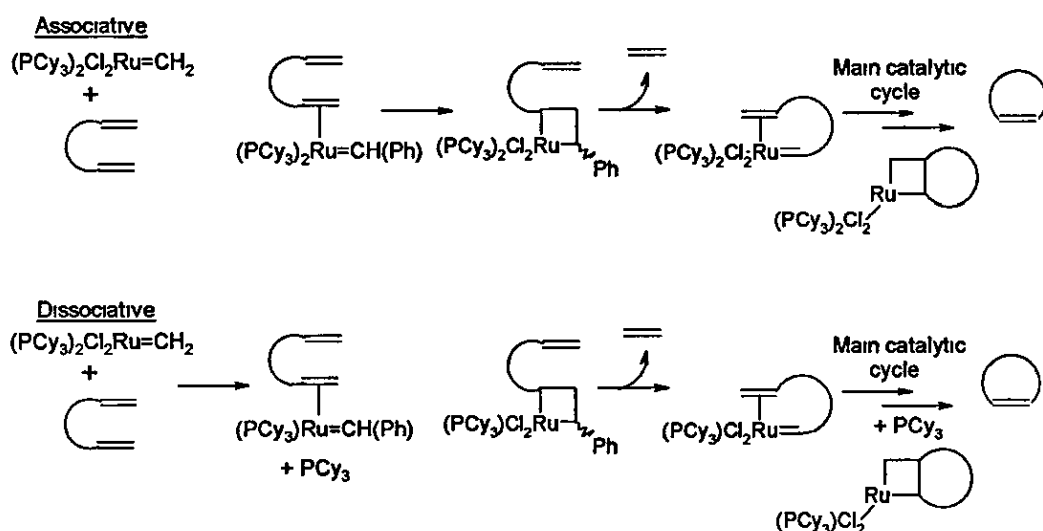
### 2.4.2 – Mechanism in Ring Closing Metathesis

In ring closing metathesis, the [2+2]-cycloaddition of an alkene to a metal-carbon double bond to generate a metallacyclobutane complex is an important step. These metallacyclobutane can break down via a retro [2+2]-cycloaddition reaction either to give the ring closed product or reform the initial substrate (Scheme 56). The generally accepted mechanism of metathesis reactions (the Chauvin mechanism) consists of a sequence of [2+2]-cycloadditions/cycloreversions involving alkenes, metal carbenes, and metallacyclobutane intermediates. Since all individual steps of the catalytic cycle are reversible, an equilibrium mixture of uncoordinated alkenes and metalla-cyclic alkenes is obtained. It is therefore necessary to shift this equilibrium in one direction in order to form the metathesis product. In the case of RCM the forward process is entropically driven by loss of ethene and therefore the desired cycloalkene accumulates in the reaction mixture (Scheme 56) <sup>57, 62-64</sup>



Scheme 56 – Chauvin mechanism

The RCM reaction has provided a challenging mechanistic problem as model and theoretical studies have provided evidence for at least two distinct mechanisms.<sup>50</sup> The "associative" pathway, which assumes that the alkene coordinates to the catalyst to form the intermediate 18-electron alkene complex, followed by the metathesis steps to form the product (Scheme 57).<sup>59</sup> And the "dissociative" pathway, which assumes that on binding to the alkene, a phosphine is displaced from the metal center to form a 16-electron olefin complex. This undergoes metathesis forming the ring closed product. The catalyst is regenerated by co-ordination of the phosphine ligand (Scheme 57).<sup>59</sup> Katz *et. al.* found that the cross coupled products appeared before there was a significant build up of the scrambled acyclic olefin.<sup>64</sup> This result supported the "dissociative" pathway mechanism



**Scheme 57 – Types of initial mechanism**

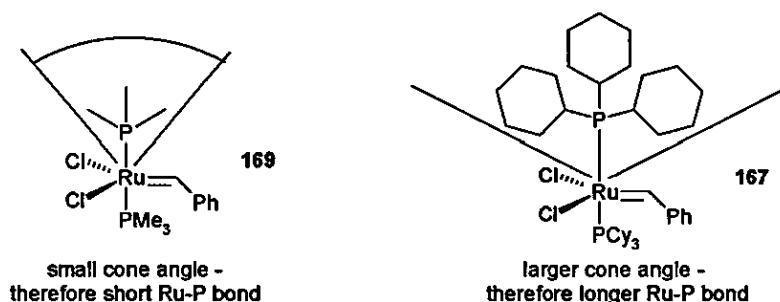
### 2.4.3 – Activity and Reactions of Grubbs Catalyst

Ligand effects on catalyst activity refers to the "dissociative" pathway (Scheme 57), because this pathway is thought to account for around 95% of the catalyst turnover. Therefore catalyst activity is related to three constants: the equilibrium constant for olefin binding, the equilibrium constant for phosphine

dissociation, and the rate constant for metallacyclobutane formation. There are two main ways these constants can be affected, changing the halogens on the ruthenium and changing the phosphines on the ruthenium.<sup>59</sup>

**Halogens** – The catalyst activity decreases as the halogens increase in size  $\text{Cl} \rightarrow \text{I}$ , as the alkene binds *trans* to one of the halogens. Steric crowding in the halogen alkene-carbene plane, results in a decline in catalytic activity from Cl to I.

**Phosphines** – The catalyst activities increase as both the cone angle and the electron donating ability of the phosphines increase. As the cone angle of the phosphine increases (the angle between the ruthenium and the phosphorus ligands) the phosphine is dissociated from the sterically crowded 18-electron alkene complex giving an increase in alkene binding. The relief of steric crowding also stabilizes the monophosphine alkene complex (**Fig 14**) Therefore bulkier phosphines will favor the overall equilibrium for alkene binding<sup>59, 65-67</sup>

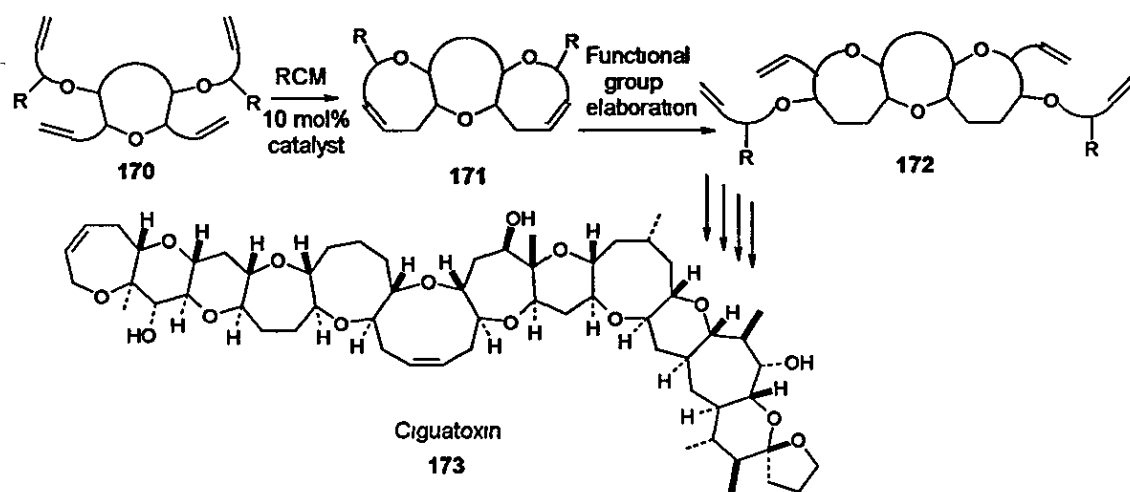


**Fig 14** – Dissociation of the phosphine ligand caused by bulky groups

#### 2.4.4 – Applications of RCM to Natural Product Synthesis

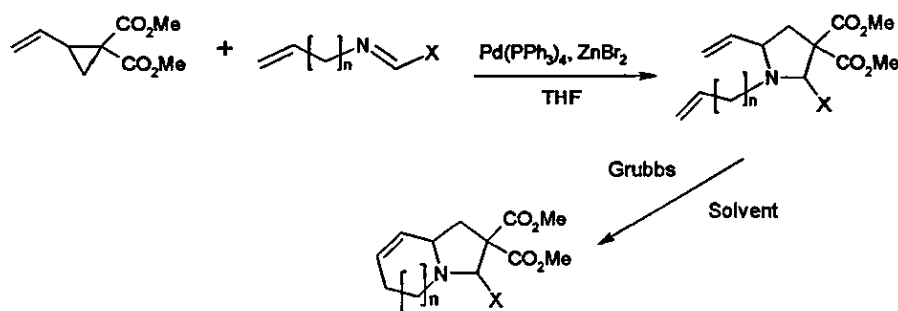
Grubbs-type catalysts tolerate a wide spectrum of functional groups, and this has allowed metathesis to rapidly evolve into a useful tool for target-oriented synthesis. The complex natural products brevetoxin and ciguatoxin and other polyether natural products provide interesting targets for this chemistry. In the synthesis of ciguatoxin, when the substrate was reacted with Grubbs catalyst the product is formed in respectable yield (50%) **171** (**Scheme 58**). These intermediates can then be manipulated to generate a second substrate **172** which is capable of

undergoing RCM. By repeating the ring closure and side chain elaboration steps very complex natural products can be effectively synthesized e.g. ciguatoxin 173.<sup>56</sup>



**Scheme 58 – Polyether synthesis**

It was hoped that the Grubbs ring closing metathesis reactions could be used in conjunction with our chemistry. If successful, it should allow the formation of bicyclic ring systems using the vinyl group from pyrrolidine ring and a terminal alkene on the nitrogen of the pyrrolidine. The reason for the importance of this reaction to our chemistry lies in its use for natural product synthesis. The route to many of the natural product targets from our chemistry is the [2+3]-cycloaddition followed by RCM as outlined below (**Scheme 59**).

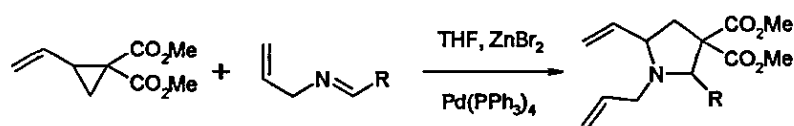


**Scheme 59 – Synthesis for RCM reaction**

## 2.4.5 – Results for RCM and Related Reactions

### Results for allyl pyrrolidines

As stated in the Introduction, one of the goals for this project was to develop the methodology to a point where natural products could be synthesized. Due to the fact many natural products contain a bicyclic system, it was decided to attempt ring closure on a range of *N*-alkenyl pyrrolidines. To this end, a range of pyrrolidines were required (Scheme 60). The *N*-alkenyl imines chosen were mainly derived from a selection of aromatic systems; however an aliphatic group was also examined

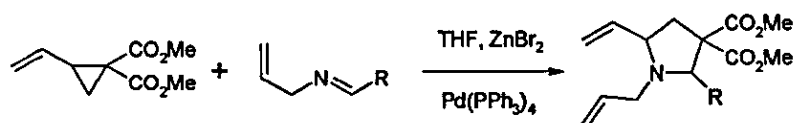


Scheme 60 – *N*-Allyl pyrrolidine formation

The first of the aromatic RCM precursors to be synthesized used the allyl-phenyl imine as it was thought that this simple aromatic system would not only be formed in good yields but also would be capable of RCM. As can be seen in Table 51, the required imine was formed in good yields (81%) and the stereoselectivity was also excellent (1:0 *cis:trans*). The synthesis of toluenes and pyridines substituted in the *para* and *ortho* positions (entries 2-5) were also examined. The *meta* position was not attempted as has been seen in previous reactions the *meta* substituent was not examined as it has shown to be unreactive in the [2+3]-cycloaddition. Toluene derivatives (entries 2-3) were synthesized in reasonable to good yield (54% *para* and 72% *ortho*). It was also decided to attempt the [2+3]-cycloaddition using a pyridine (entries 4-5) in order to determine the difference in reactivity between it and phenyl. However, both pyridines failed to undergo the [2+3]-cycloaddition reaction, giving only starting materials.

Other aromatic systems were also examined for example the entries 6-10, Table 51 look at PMB which is a strongly electron donating group (entry 6). The pyrrolidine derived from *N*-allyl PMB imine was prepared in good yield (51%), however poor selectivity (1.3:1, *cis:trans*). The *N*-allyl 4-bromo-phenyl pyrrolidine

(entry 2) was synthesized, the desired pyrrolidine was formed in good yield (58%) and a diastereoselectivity of 2:1, (*cis.trans*). The next two pyrrolidines synthesized (entry's 3-4, table 51) the 3-thiophene and the 3-furan were synthesis to determine the effect of the oxygen and sulfur heteroaromatics on the RCM reaction. The 3-furan was prepared in good yield (49%) but the thiophene failed to undergo the [2+3]-cycloaddition. An alkane (entry 5) was also attempted, however this proved to be an unsuccessful substrate.

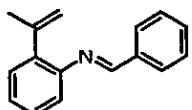
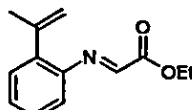
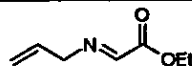
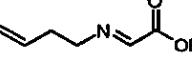
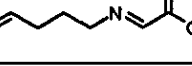


	Imine	Solvent	Temp (°C)	Time (h)	Yield (%)	Cis:Trans
1		THF,	RT	48	81 (161)	1:0
2		THF	RT	48	54 (174)	5:1
3		THF	RT	48	72 (175)	2:1
4		THF	RT	48	0 (176)	-
5		THF	RT	48	0 (177)	-
6		THF	RT	48	51 (178)	1.3:1
7		THF	RT	48	58 (179)	2:1
8		THF	RT	48	0 (180)	-
9		THF	RT	48	49 (181)	1:0
10		THF	RT	48	0 (182)	-

1 mmol scale 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>, ZnBr<sub>2</sub>

Table 51 – N-allyl pyrrolidines

As well as the simple allyl group described above other groups suitable for RCM were also examined (entries 1-5, Table 52). The pyrrolidines were prepared however the phenyl derived pyrrolidine (entry 1) only gave a trace of the desired however 58% of the ethyl ester pyrrolidine (entry 2) was isolated with good selectivity for both products (1.6 in favour of the *cis* for the phenyl and 1:10 favour of the *cis* for the ethyl ester). *N*-Allyl (entry 3), *N*-butene (entry 4) and *N*-pentene (entry 5) were all attempted however only the *N*-allyl, *N*-butene was prepared successfully, in good to excellent yields

	Imine	Solvent	Temp (°C)	Time (h)	Yield (%)	Cis:Trans
1		THF	RT	48	Trace (166)	6:1
2		THF	RT	48	58 (162)	10:1
3		THF	RT	48	61 (183)	1:0
4		THF	RT	48	82 (165)	1:0
5		THF	35	48	0 (184)	-

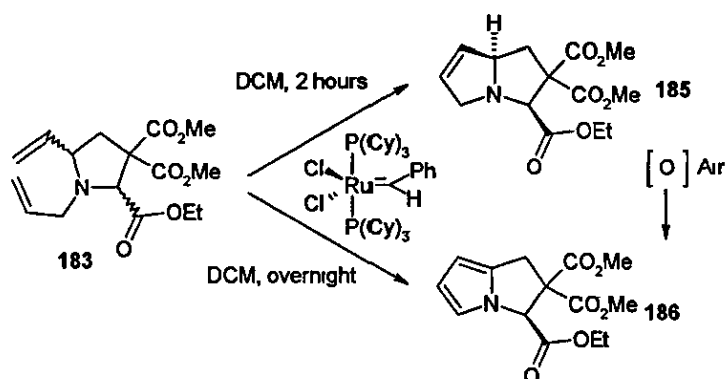
1 mmol scale and had Pd(PPh<sub>3</sub>)<sub>4</sub>, ZnBr<sub>2</sub>

**Table 52** – [2+3]-Cycloaddition of *N*-allyl imines with vinyl cyclopropane

#### Reaction time variations in ring closing metathesis reactions

Standard Grubbs RCM conditions on *N*-(allyl)-2-ethyl ester-5-vinylpyrrolidine-3,3-dicarboxylic acid dimethyl ester were first examined. This was chosen since 5 membered rings are among the easiest to form, 5 mol% of Grubbs first generation catalyst at room temperature in distilled de-gassed DCM under positive pressure of nitrogen for 16 hours was used. This reaction was also carried out under the same conditions for 2 hours to determine the optimum time for the

RCM reaction (Scheme 61). It can be seen in Table 53 that when the time of the reaction was increased from 2 hours (entry 1) to 16 hours (entry 2) there was oxidation of the ring closed product. However, when the pyrrolidine substrate was reacted for a longer time there was a significant increase in the yield of the ring closed product.



Scheme 61 – Grubbs reactions over time

	Reactant	Time	Product	Yield (%)
1		2 hours	 (185)	43
2		Over night (16 hours)	 (186)	76

\* Both products had 1:0 *cis trans* diastereoselectivity

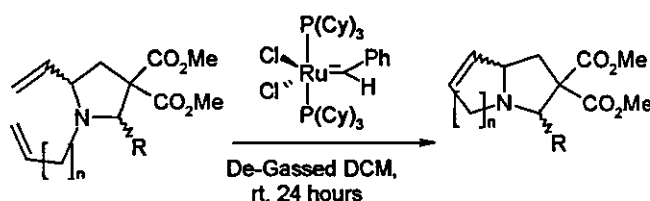
Table 53 – Grubbs reactions over time

The stereochemistry of the ring closed products was determined by NOE's of the resulting bicycles. The NOE's were possible because of the increased rigidity of the fused bicyclic system over the pyrrolidine precursors. It was found that only the *cis* product was formed under the RCM conditions, however this is likely to be due to the pyrrolidine precursor being solely the *cis* product as well. The NOE data was also backed up by comparing the ring closed products proton NMR to the proton

NMR's of the two crystalline pyrrolidines formed (see Page 60) which confirmed the *cis* product was being formed as a single diastereoisomer.

#### *Results of RCM under classical synthesis conditions*

With a range of *N*-alkene pyrrolidines available (Tables 51-52), we now applied Grubb's RCM conditions (Scheme 62). The only change to this procedure was the reaction time as Grubb's suggests a time of 2 hours for the reaction to go to completion, however for our substrates TLC monitoring suggested a time of 24 hours was better.



**Scheme 62** – Standard Grubbs reaction

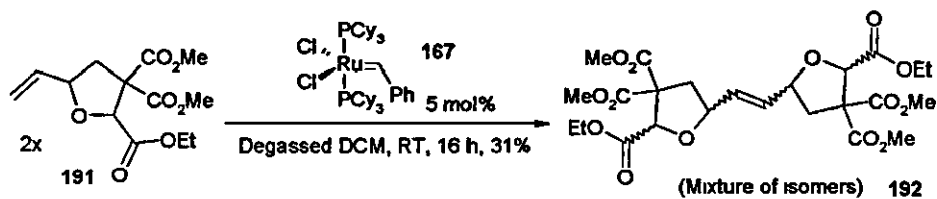
Reactions with the 1-butene ethyl ester imine also proved to be very successful as this particular substrate ring closed readily under the reaction conditions to generate the bi-cyclic core in an excellent yield (82%) (entry 1). Entry 2 of Table 54 is the same reaction conditions under microwave irradiation conditions. When this reaction was performed, RCM under microwave irradiation was unknown but since this result was achieved several papers have been published on the subject.<sup>68-70</sup> The irradiation conditions meant that there was a dramatic reduction in the time of the reaction to only 20 minutes with little difference in yield (76%)

When the RCM reaction was attempted using the *N*-allyl C1-phenyl pyrrolidine (Table 54, entry 3), the RCM failed and only starting materials were recovered from the reaction mixture. The two pyrrolidines with the *N*-2-isopropylphenyl (Table 54, entry 4-5) also proved to be unsuccessful under RCM conditions. However, the likely problem here is the nature of the tri-substituted alkene

	Reactant	Product	Yield (%)	Cis:Trans
1		 (187)	82	1.0
2		 (187)	76	1.0
3		 (188)	0	-
4		 (189)	0	-
5		 (190)	0	-

Table 54 – Grubbs RCM reactions

The application of cross metathesis reactions for the formation of dimers of heterocycles was also examined. A tetrahydrofuran was decided upon instead of a pyrrolidine to ease characterization. This cross metathesis proved to be moderately successful as the desired product was produced in low yield (31%), however, it was a mixture of isomers. This has proven that these substrates can undergo cross metathesis reactions if required (Scheme 63).



Scheme 63 – Cross metathesis

#### 2.4.6 – Conclusion

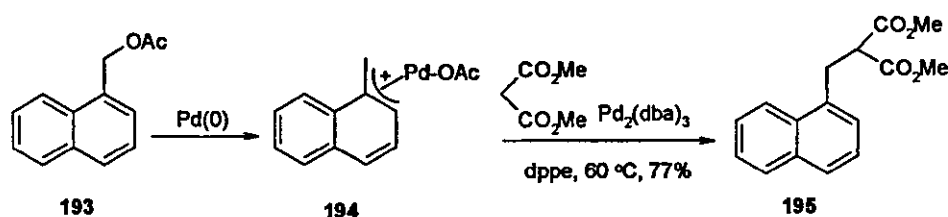
It is clear from the results obtained that the Grubbs ring closing metathesis reactions for our particular system is very sensitive, as there have been very few successes in the ring closing step except with the simplest systems i.e. *N*-butyl and *N*-allyl which containing an ethyl ester group  $\alpha$  to the nitrogen of the pyrrolidine or oxygen of the THF. There have been some very interesting results from this work as several conditions have been tried for this reaction, and positive results were seen from microwave irradiation (Table 54) which at the time was unprecedented.

All the pyrrolidines which were synthesised in Table 51 were tested using both the conditions outlined above and also using Grubb's 2<sup>nd</sup> generation catalyst (5 mol%) with 1 eq of PTSA in the reaction mixture. PTSA was indicated in a paper<sup>72</sup> to improve the reactivity of nitrogen containing substrates; however none of the conditions for these substrates proved to be successful. It is believed that the absence of the ethyl ester group in the  $\alpha$  position of the pyrrolidine ring dramatically decreases the reactivity during the RCM reactions.

## Section 2.5 – Aromatic Cyclopropanes and their Cyclisation

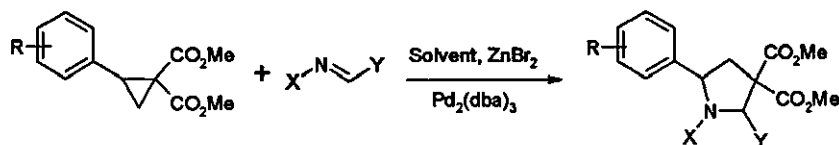
### 2.5.1 – Introduction to Aromatic Cyclopropanes

During the [2+3]-cycloaddition, based the reaction developed by Tsuji,<sup>9</sup> the mechanistic pathway is thought to involve a  $\pi$ -allyl complex. It was decided to investigate if this effect could be duplicated using an aromatic ring, rather than a vinyl group. There is some literature precedent for this type of reaction taking place as Legros *et. al.*<sup>4</sup> described the formation of aromatic  $\pi$ -allyl complexes when using naphthalene derivatives (Scheme 64). His work prompted us to form a range of aromatic cyclopropanes in the hope that these new cyclopropanes could cyclise in the same way as vinyl cyclopropanes to generate pyrrolidines and furans.

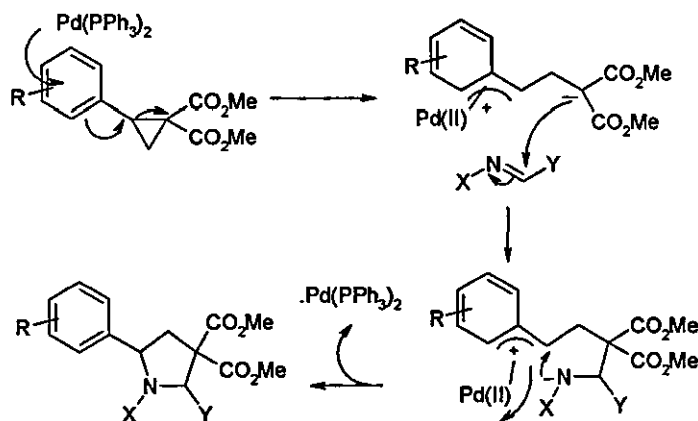


Scheme 64 –  $\pi$ -Allyl formation of a naphthalene group<sup>4</sup>

Aromatic cyclopropanes can be prepared by a reaction between a vinyl aromatic and diazomalonate in the presence of a catalytic amount of rhodium acetate dimer.<sup>72</sup> The intermediate  $\pi$ -allyl complex would generate a 1,3-dipole which would be able to react with an imine or an aldehyde in the same way in which the vinyl cyclopropane reacts (Scheme 65-66).



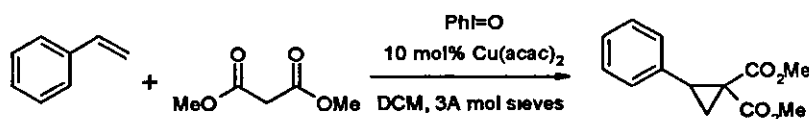
Scheme 65 – General reaction scheme



**Scheme 66** – Formation of aromatic pyrrolidine (general procedure)

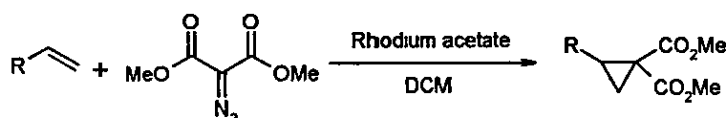
## 2.5.2 – Procedures Used in the Formation of Aromatic Cyclopropanes

There have been two methods used in the preparation of phenyl cyclopropane, both of which used a carbene to form the cyclopropane. In the first procedure the carbene precursor was formed using a strong oxidizing agent (iodosobenzene) in the presence of a copper catalyst (copper acetylacetonate) (Scheme 67).<sup>73</sup>

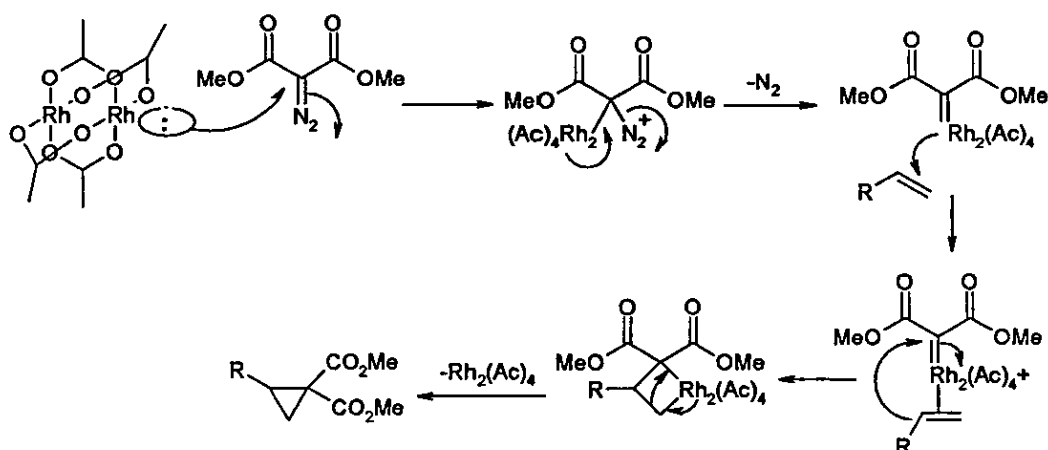


**Scheme 67** – Aromatic cyclopropane formation using an oxidizing agent<sup>73</sup>

However, although this method was attempted several times, the reaction mixture could not be purified. With the lack of a usable product, we moved onto a more traditional rhodium method of cyclopropane formation. The method used diazomalonate which is synthesized from dimethyl malonate and tosyl azide.<sup>74</sup> The diazomalonate was then reacted with rhodium acetate in the presence of DCM (Scheme 68-69).



**Scheme 68** – General reaction scheme

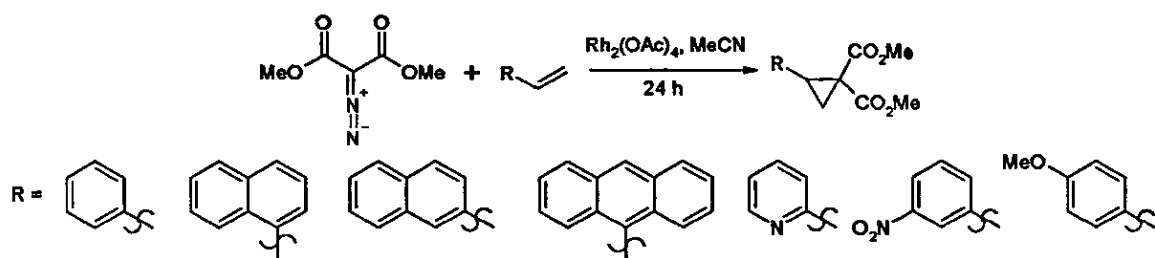


**Scheme 69** –Formation of aromatic cyclopropane using rhodium acetate

### 2.5.3 – Aromatic Cyclopropane Results

The substrates chosen were those which would form a good  $\pi$ -allyl system (such as naphthalene and anthracene), or those which had interesting electronic properties (such as 3-nitro-phenyl and the 4-methoxy-phenyl) (Scheme 70)

When rhodium acetate was used to generate the cyclopropanes, the phenyl, 1-naphthalene, 2-naphthalene, 9-anthracene, 4-methoxy-phenyl 3-nitro-phenyl and 2-pyridine cyclopropanes were successfully formed. The aromatics were carefully chosen as they have a range of different regio-isomers in the case of the naphthalene (entries 2-3), and also different electronic effects using both electron withdrawing and electron donating groups on the phenyl (entries 6-7). Although all the cyclopropanes were prepared in reasonable yields these are not optimized conditions and with further work it is expected that even better yields could be achieved (Table 55)



	<i>Aromatic vinyl</i>	<i>Product</i>	<i>Yield (%)</i>
1	Styrene	(196)	82
2	2-vinyl naphthalene	(197)	65
3	1-vinyl naphthalene	(198)	75
4	9-vinyl anthracene	(199)	83
5	2-vinyl pyridine	(200)	71
6	4-vinyl PMB	(201)	69
7	3-Nitrostyrene	(202)	58

**Table 55 – Aromatic cyclopropanes formed**

## 2.5.4 – Aromatic Cyclisations Introduction

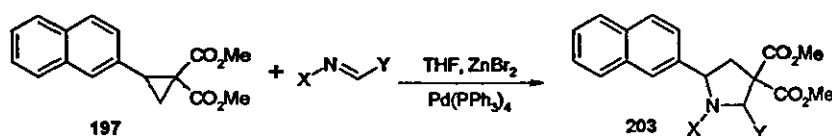
With the aromatic cyclopropanes in hand, they were all subjected to cyclisation under the standard reaction conditions; zinc bromide (2 eq), palladium tetrakis(triphenyl phosphine) (10 mol%) in THF in the presence of either the *N*-PMB ethyl ester imine or ethyl glyoxylate. The *N*-PMB ethyl ester imine and using ethyl glyoxylate were chosen as trapping agents as they had proved to be the most reactive imine and aldehyde and therefore should form the cycloaddition product in the shortest time. Work by Legros<sup>4</sup> had described the formation of aromatic  $\pi$ -allyl complex when using naphthalene derivatives, and it is thought these were successful because one of the naphthalene rings has less aromatic character than the other which leads to an increased reactivity in the less aromatic ring

## 2.5.5 – Results for the [2+3]-Cycloaddition Using Aromatic Cyclopropanes

### *Results for 2-naphthalene cyclopropane*

We first looked at the 2-naphthalene cyclopropanes; these were chosen because they were the most readily available naphthalene systems. Also it was thought that the naphthalene cyclopropane would have a better chance of generating the  $\pi$ -allyl complex and therefore reacting than the phenyl cyclopropane (Scheme 71).

During the optimization of the [2+3]-cycloaddition using the 2-naphthalene cyclopropanes, a number of conditions needed to be varied, including reaction time, catalyst, temperature, solvent and Lewis acid. The initial results (Table 56, entries 1-3) indicated that even with longer reaction times and increased temperatures in the presence of a Lewis acid there was no formation of the pyrrolidine product from the [2+3]-cycloaddition.



**Scheme 71** – Formation of aromatic pyrrolidine (general procedure)

	<i>Imine</i>	<i>Time</i> (d)	<i>Catalyst / solvent</i>	<i>Temp</i> (°C)	<i>Yield</i> (%)	<i>Cis:Trans</i>
1		7	Pd(PPh <sub>3</sub> ) <sub>3</sub> / THF	RT	0 (203)	-
2		7	Pd <sub>2</sub> (dba) <sub>3</sub> / THF	50	Trace (203)	-
3		7	Pd <sub>2</sub> (dba) <sub>3</sub> / THF / no ZnBr <sub>2</sub>	50	0 (203)	-

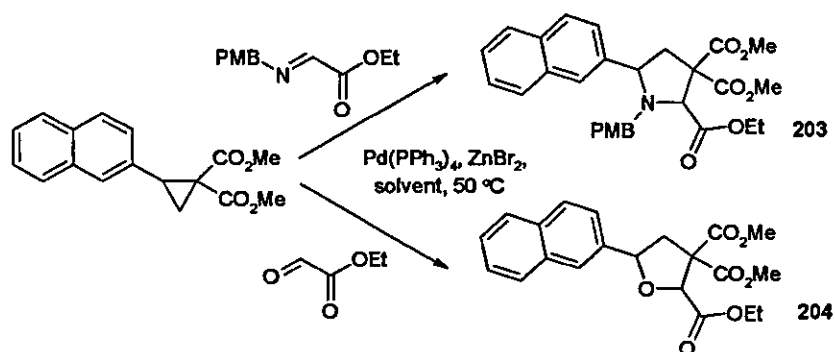
1 mmol scale, 10 mol% Pd<sub>2</sub>(dba)<sub>3</sub>

**Table 56** – 2-Naphthalene cyclisation results according to **Scheme 71**

After initial reactions had determined that the optimum conditions involved a temperature of 50 °C using 10 mol% Pd<sub>2</sub>(dba)<sub>3</sub> catalyst and zinc bromide, it was decided to test a range of solvents (**entries 1-8, Table 57**). In these reactions, the 2-naphthalene cyclopropane was reacted with both *N*-4-methoxy-phenyl ethyl ester imine and ethyl glyoxylate to see any changes in reactivity between imines and aldehydes. The solvents which were chosen are some of the most commonly used and comprise of toluene (**entries 1-2**), DMF (**entries 3-4**), acetonitrile (**entries 5-6**) and THF (**entries 7-8**). These reactions were monitored by TLC, until there appeared to be no further reaction (14 days). The results showed that the highest yielding solvent was toluene followed by THF, acetonitrile was significantly less reactive and DMF only gave a trace of the desired products.

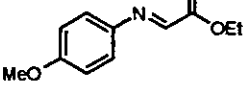
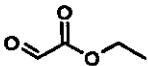
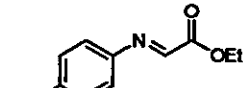
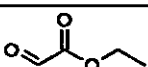
Work was also done using the palladium tetrakis(triphenyl)phosphine catalyst, to compare the catalyst with the Pd<sub>2</sub>(dba)<sub>3</sub> catalyst. Both the *N*-4-methoxy-phenyl

ethyl ester imine (**entry 9**) and ethyl glyoxylate (**entry 10**) underwent the [2+3]-cycloaddition reactions however the yields were significantly lower than with  $\text{Pd}_2(\text{dba})_3$  catalyst (41% for the pyrrolidine and 40% for the tetrahydrofuran)



**Scheme 72** – Product formed from [2+3]-cycloadditions with 2-naphthalene cyclopropane

	Imine	Time (d)	Catalyst / solvent	Temp ( $^\circ\text{C}$ )	Yield (%)	Cis:Trans
1		14	$\text{Pd}_2(\text{dba})_3$ / toluene / $\text{ZnBr}_2$	50	51 (203)	0 1
2		14	$\text{Pd}_2(\text{dba})_3$ / toluene / $\text{ZnBr}_2$	50	55 (204)	1:1.2
3		14	$\text{Pd}_2(\text{dba})_3$ / DMF / $\text{ZnBr}_2$	50	Trace	-
4		14	$\text{Pd}_2(\text{dba})_3$ / DMF / $\text{ZnBr}_2$	50	Trace	-
5		14	$\text{Pd}_2(\text{dba})_3$ / acetonitrile / $\text{ZnBr}_2$	50	27 (203)	0 1
6		14	$\text{Pd}_2(\text{dba})_3$ / acetonitrile / $\text{ZnBr}_2$	50	33 (204)	1 1 2

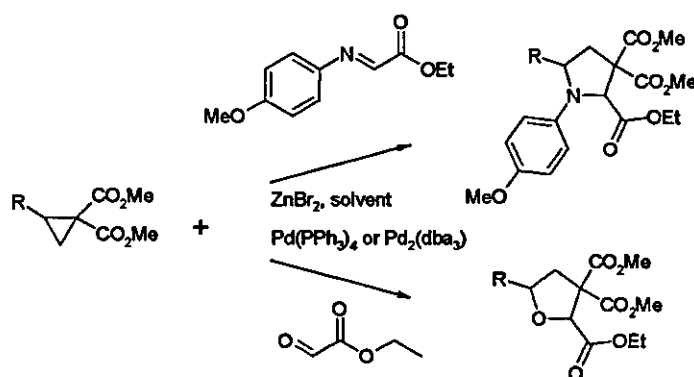
7		14	$\text{Pd}_2(\text{dba})_3 / \text{THF}$ $/ \text{ZnBr}_2$	50	48 (203)	0:1
8		14	$\text{Pd}_2(\text{dba})_3 / \text{THF}$ $/ \text{ZnBr}_2$	50	53 (204)	1:1.2
9		14	$\text{Pd}(\text{PPh}_3)_3 /$ $\text{THF} / \text{ZnBr}_2$	50	41 (203)	0:1
10		14	$\text{Pd}(\text{PPh}_3)_3 /$ $\text{THF} / \text{ZnBr}_2$	50	40 (204)	1:1.5

1 mmol scale, 10 mol% Pd(0) catalyst

**Table 57** – 2-Naphthalene cyclisation results according to **Scheme 72**

#### *Results for reaction with other aromatic cyclopropanes*

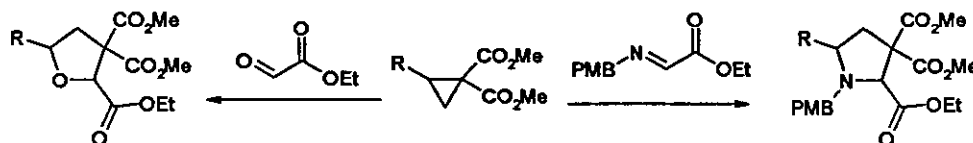
After the initial experiments to optimize the reaction conditions using the 2-naphthalene cyclopropane, it was a natural progression to look into the [2+3]-cycloaddition of the other aromatic cyclopropanes which had been synthesized. These were reacted under the optimum conditions of 50 °C for fourteen days using  $\text{Pd}_2(\text{dba})_3$  as the catalyst. The cyclisation reactions were performed with both *N*-4-methoxy-phenyl ethyl ester imine and ethyl glyoxylate as trapping agents to look into changes in reactivity between these two functional groups (**Scheme 73**)



**Scheme 73** – Pyrrolidine formations

The initial cyclisations which were attempted failed due to the short time that the substrates were reacted (only 7 days). It was discovered by careful monitoring of TLC's for long periods from the reaction mixture that it is necessary to react the substrates for fourteen days. However, after the optimum time and temperature for the cyclisation reaction had been determined the cyclisation of the aromatic cyclopropanes was achieved.

The reason why this cyclisation occurs during the [2+3]-cycloaddition is thought to be through the formation a  $\pi$ -allyl complex in the aromatic ring. The examples below (Table 58) gives details of aromatic systems, phenyl (entries 1-2), 1-naphthalene (entries 3-4) and 9-anthracene (entries 5-6). The fact that these reactions were for the most part successful is a significant point as it clearly shows that an aromatic system will form  $\pi$ -allyl complexes, which was thought to be unlikely to form with single aromatic rings.

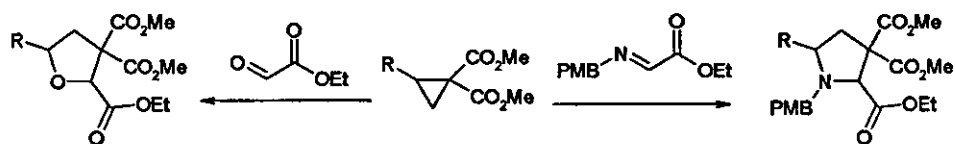


	Product	Time (d)	Conditions	Temp (°C)	Yield (%)	Cis:Trans
1		14	$\text{Pd}_2(\text{dba})_3 /$ toluene / $\text{ZnBr}_2$	50	43 (205)	1:1
2		14	$\text{Pd}_2(\text{dba})_3 /$ toluene / $\text{ZnBr}_2$	50	48 (206)	1.4
3		14	$\text{Pd}_2(\text{dba})_3 /$ toluene / $\text{ZnBr}_2$	50	Isolated as impure compound (207)	-

4		14	$\text{Pd}_2(\text{dba})_3 /$ toluene / $\text{ZnBr}_2$	50	62 (208)	1:3
5		14	$\text{Pd}_2(\text{dba})_3 /$ toluene / $\text{ZnBr}_2$	50	Isolated as impure compound (209)	-
6		14	$\text{Pd}_2(\text{dba})_3 /$ toluene / $\text{ZnBr}_2$	50	42 (210)	1 4

**Table 58 – [2+3]-Cycloaddition using aromatic cyclopropanes**

In order to fully examine the effect of aromatic cyclopropanes in the [2+3]-cycloaddition reaction, it was decided to use substituted phenyls with strongly electron poor (3-nitro-benzene) and strongly electron rich groups (PMB). The cyclisation using the *N*-PMB ethyl ester imine with the PMB cyclopropane (Table 59, entries 1) and the two 3-nitro-phenyl cyclopropane cyclisations (Table 59, entries 3-4) proved to be very successful giving moderate yields of the cyclised products



	Product	Time (d)	Conditions	Temp (°C)	Yield (%)	Cis:Trans
1		14	Pd <sub>2</sub> (dba) <sub>3</sub> / toluene / ZnBr <sub>2</sub>	50	42 (211)	1:1.3
2		14	Pd <sub>2</sub> (dba) <sub>3</sub> / toluene / ZnBr <sub>2</sub>	50	Isolated as impure compound (212)	-
3		14	Pd <sub>2</sub> (dba) <sub>3</sub> / toluene / ZnBr <sub>2</sub>	50	45 (213)	1:3
4		14	Pd <sub>2</sub> (dba) <sub>3</sub> / toluene / ZnBr <sub>2</sub>	50	49 (214)	1:1.1

**Table 59** – [2+3]-Cycloaddition using aromatic cyclopropanes

### 2.5.6 – Aromatic Cyclopropane Conclusion

As can be seen from the results obtained many of the desired pyrrolidines and tetrahydrofurans were generated in good yields, after the optimized conditions had been found. It is interesting to note that the actual conditions needed to cyclise the aromatic cyclopropanes are very different from the optimum condition needed when using the vinyl cyclopropane, with changes in catalyst, temperature, and the overall reaction time needing to be modified in order to generate the product in good

yields. Unfortunately, there was not sufficient time to test this reaction only using Lewis acid as it is possible that coordination between the Lewis acid and the aromatic ring may have caused ring opening of the cyclopropane.

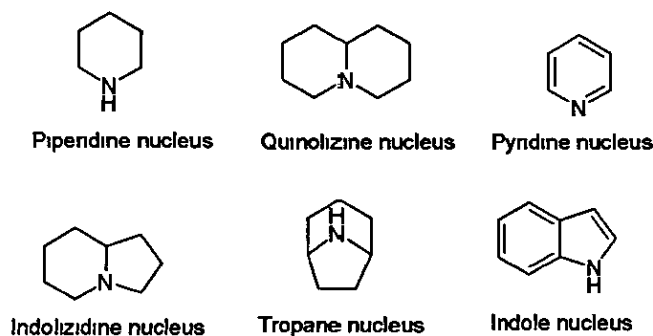
It would have been an interesting series of experiments to have carried out these reactions under microwave irradiation as we believe that there would have been a significant reduction in reaction time. The need to reduce reaction time is especially important in these reactions due to the fact that all the other trapping agents would have likely caused a dramatic increase in reaction time

## **Section 2.6 – Natural Product Synthesis**

### **2.6.1 – Introduction to the Alkaloids**

The alkaloids are compounds known for their potent pharmacological activities. Such is the bioactivity of some alkaloids that using even tiny amounts can immobilize an elephant or a rhinoceros. Others are important in modern medicines, and properties include activity as analgesics, anti-spasmodics, anti-hypertensives, anti-psychotics, and anti-cancer agents.

The defining characteristic of alkaloids is they contain a nitrogen atom in a ring system. The majority of naturally occurring alkaloids are found in plants as the salts of common carboxylic acids such as citric, lactic, oxalic, acetic, malic and tartaric acids,<sup>75</sup> however some alkaloids are derived from insect or amphibian sources.<sup>75</sup> Their amine character produces an alkaline solution in water which is the origin of their name - alkaloids. There is a wide variety of structural types of alkaloid e.g. monocyclic, bi-cyclic, tri-cyclic, tetra-cyclic etc, as well as cage structures. However all contain one of a number of different types of nitrogen heterocycles (Fig 15).<sup>1</sup>



**Fig 15 – Examples of some heterocyclic alkaloid cores**

Many of the alkaloids found in Nature are intentionally synthesized as a defense against predators both due to their characteristic bitter taste and accompanying toxicity which help to repel insects and herbivores. Alkaloids have

become so important in nature that there have developed complicated ecological inter-relationships between several insects and alkaloids.<sup>1,75-79</sup>

### 2.6.2 – History of Alkaloids

The history of alkaloid chemistry is long and varied, ranging from simple compounds to highly complex natural products, which even today are either hard or appear impossible to synthesize in the laboratory. Many of the earliest isolated pure compounds with a biological activity were the alkaloids.

The use of the alkaloids in modern medicine began around 300 years ago, at a time when malaria was prevalent in Europe, having been introduced through the Middle East. As the Spanish and Portuguese explorers began to colonize South America, they discovered a treatment for malaria from the bark of the *Cinchona* trees. The use of *Cinchona* bark to treat malaria was first reported in Europe in 1633. The reason for the success of the *Cinchona* bark as a medicine is due to quinine **215** (Fig 16) which was isolated originally from *Cinchona* approximately 300 years ago, and is one of the principal anti-malarial compounds found in plants. Malaria is still a major problem throughout the world, and, although synthetic anti-malarial drugs have largely replaced quinine as the treatment for malaria since the beginning of World War II, quinine is still often used as the drug of choice in resistant strains of malaria.<sup>75-77</sup>

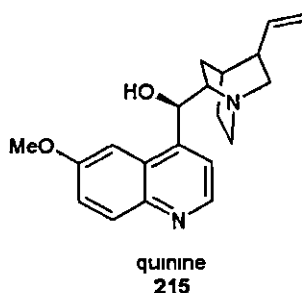


Fig 16 – Quinine

Among the most famous of the alkaloids are the *Solanaceae* or tropane alkaloids. These alkaloids have been used throughout recorded history as poisons,<sup>1</sup> but recent research into their biological properties has shown that many of these alkaloids have valuable pharmaceutical properties and drug companies around the world are currently creating drugs based on the structure of these natural products.

Another well known example of a group of alkaloids are the morphine alkaloids derived from the opium poppy, *Papaver somniferum*, which are powerful pain relievers and narcotics described as long ago as 3500 B C. Morphine is the principal alkaloid isolated from opium and was first isolated in its pure form between 1803 and 1806 (Fig 17); it was widely used for pain relief beginning from the 1830's. Other derivatives of morphine have been developed and are used as pain killers or as animal tranquilizers.<sup>75-77</sup>

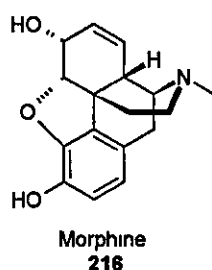


Fig 17 – Morphine

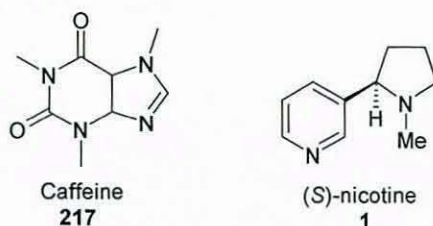
### 2.6.3 – Definition of Alkaloids

Alkaloids are found in around 20% of vascular plants and also many species of insects and amphibians. All types of alkaloids are important in nature and in the pharmaceutical industry. The basic unit in the biogenesis of the alkaloids is amino acids and any non-nitrogen containing rings or side chains are derived from terpene or other units. Alkaloids are usually highly biologically active which makes them key targets in the pharmaceutical industry. Characteristic properties of an alkaloid are –

- Contains nitrogen - usually derived from an amino acid.
- Bitter tasting, generally white solids.
- They give a precipitate with heavy metal iodides

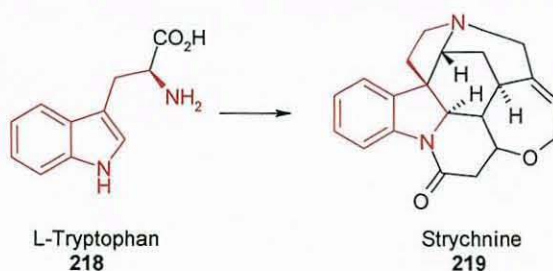
- Alkaloids are basic - they form water soluble salts. Most alkaloids are well-defined crystalline substances which unite with acids to form salts. In plants, they may exist in the free state, as salts or as *N*-oxides.

However there are some exceptions to even these rules; caffeine **217**, which is a purine derivative, does not precipitate like most alkaloids, and also nicotine **1** is a brown liquid rather than a white solid (**Fig 18**).



**Fig 18** – Caffeine and (*S*)-nicotine

The most common amino acids which alkaloids are derived from are proline, phenylalanine, tryptophan **218**, tyrosine and histidine. It is interesting to note that it is the cyclic amino acids which are most commonly used in the biosynthesis of alkaloids such as in strychnine **219** (**Scheme 74**). Strychnine can be isolated from the dried seeds of *Strychnos vux vomica*, a small Australian tree, and is so physiologically active only 60 mg can kill an adult.<sup>1, 75-77</sup>



**Scheme 74** – Possible biosynthesis of strychnine

## 2.6.4 – Rings in Alkaloids

All alkaloids have structures which contain one or more rings; there is however a great diversity in both the functionalization and the structures of these

rings. The ring systems in alkaloids contain monocyclic, bicyclic or polycyclic ring systems. Although all types contain alkaloids which are biologically active, it is the polycyclic rings which exhibit the greatest potency in modern drugs such as reserpine (220), vinblastine (221) (Fig 19) and strychnine (219) (Scheme 74).

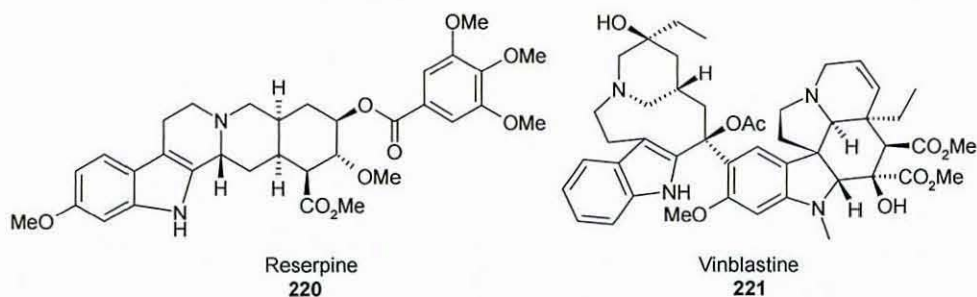


Fig 19 – Reserpine and vinblastine

### 2.6.5 – Introduction to Natural Product Synthesis

Pyrrolidines are found in a large number of natural products including plants and insects,<sup>1, 75-77</sup> and have been shown to give rise to a number of interesting enzymes inhibitors and have neuroexcitatory activities amongst many other properties. Selected examples of some pyrrolidines containing natural products are –

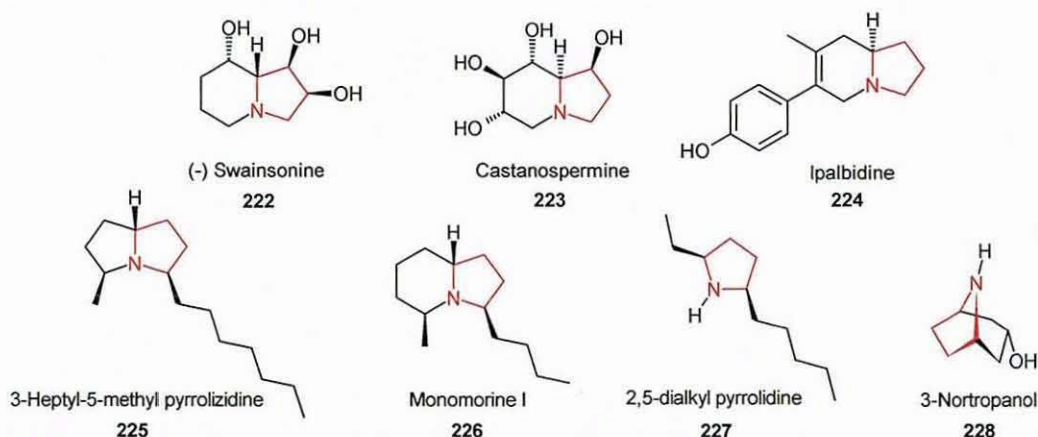


Fig 20 – Pyrrolidine containing natural products

- **Swainsonine (222)** – is a *D*-mannose-mimic causing poisoning and teratogenicity. It is found in a large number of plants such as *A. argillophilus*, *A. oxyphysus* and *A. wootonii*.
- **Castanospermine (223)** – is a naturally occurring alkaloid and inhibitor of glucosidase-I and has been isolated from *Castanospermum australe* seeds.
- **Ipalbidine (224)** – is a naturally occurring indolizidine alkaloid that is a non-addictive analgesic. It is isolated from *Ipomoea alba L.* seeds.

Natural products which have been studied in some detail during the project have been some of the simplest alkaloids, and were chosen due to their ease of synthesis. It was thought that the structures of these compounds would be synthesized via the [2+3]-cycloaddition chemistry which has been developed.

- **3-Heptyl-5-methyl pyrrolizidine** – this natural product is from the venom of the cryptic thief ant *Solenopsis spp. cf. tennesseensis*.<sup>1</sup>



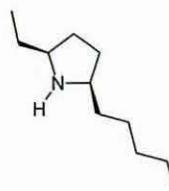
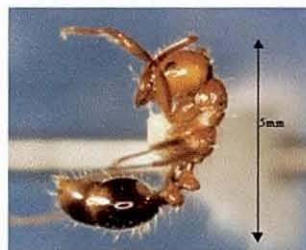
Fig 21 – Cryptic thief ant

- **Monomorphine I** – Monomorphine I is a naturally occurring pheromone of Pharaoh ants, and is used in marking territory and routes to food sources.<sup>1</sup>



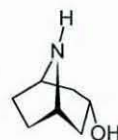
Fig 22 – Pharaoh ant

- (+) **2,5-dialkyl pyrrolidine** – (+) 2,5-dialkyl pyrrolidine is also obtained from two species of ants *Solenopsis* (fire ant) and *Monomorium spp*, and is used in their defensive systems.<sup>1</sup>



**Fig 23** – *Solenopsis* Fire ant

- (+) **3-Nortropanol** – an alkaloid from *Atropa belladonna*, *Hyoscyamus niger*, *Datura spp.* and several other plants from the same family, *Solanaceae*. This is highly toxic and has some hallucinogenic properties.<sup>1</sup>

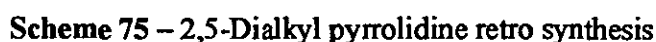


**Fig 24** – *Atropa belladonna* (deadly nightshade)

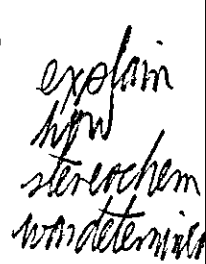
## 2.6.6 – Work Towards Natural Product Synthesis

### 2,5-Dialkyl pyrrolidines

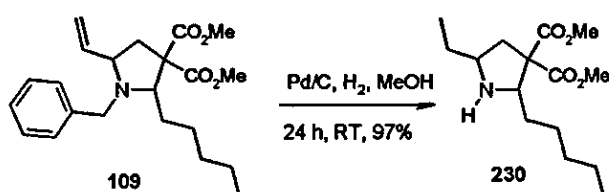
A retro-synthetic analysis for 2,5-dialkyl pyrrolidines is shown in **Scheme 75**. Benzyl was selected as a nitrogen protecting group as it should give the best yields during the [2+3]-cycloaddition step, and secondly it is readily removed during hydrogenolysis, which would also convert the vinyl group to the desired ethyl. The next stage would be to remove both ester groups, after which the [2+3]-cycloaddition would be carried out between the vinyl cyclopropane and benzyl-pentane imine (**Scheme 75**).



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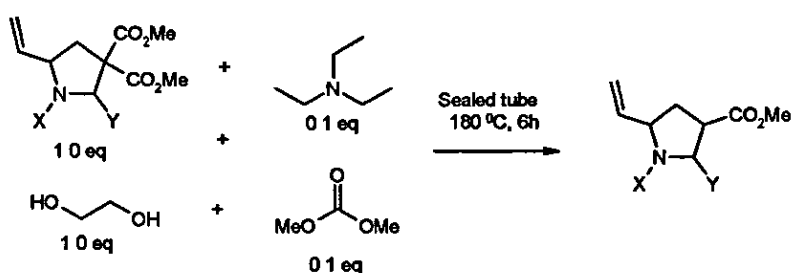
Table 60 – [2+3]-cycloadditions on route to natural product synthesis

After the initial success in the formation of the palladium catalyzed [2+3]-cycloaddition to form the core pyrrolidine of 2,5-dialkyl pyrrolidine, it was decided to test the chemistry by reacting the substrate under hydrogenolysis conditions to determine if the benzyl/vinyl double bond would be removed in this single step. This is a standard literature method where a balloon of hydrogen is used to create a hydrogen atmosphere in a RBF containing a stirred solution of the substrate and Pd/C in methanol, and in this example the product was formed in 97% yield (Scheme 76)



**Scheme 76** – Hydrogenation of vinyl and benzyl groups

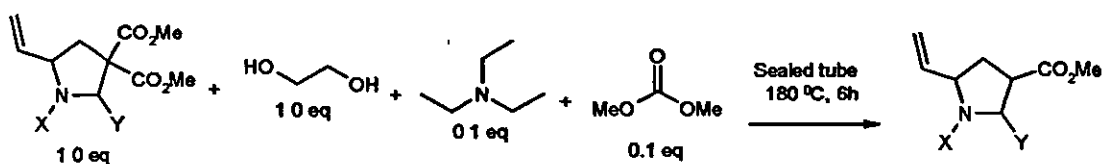
In order to form the required natural product, modification was needed. The most difficult was the removal of the gem diester. After an exhaustive literature search, two methods were found which could remove a single ester group from a gem diester; heating to high temperature with stearic acid (2 eq),<sup>80</sup> or a pressure reaction at high temperatures with ethylene glycol (1 eq), triethyl amine (0.1 eq), pyrrolidine (1 eq) and methyl carbonate (0.1 eq) (Scheme 77).<sup>81</sup>



**Scheme 77** – Ester removal

An attempt at the stearic acid procedure although appearing to have been successful from the  $^1\text{H}$  NMR, was however contaminated with a considerable amount of steric acid which could not be removed (entry 1, Table 61) In the original paper detailing this procedure, the substrates used were of low molecular mass and could be easily distilled.

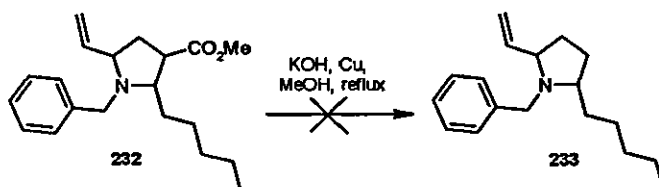
The second method attempted (entries 2-3, Table 61) was more successful and involved the use of ethylene glycol (1 eq), triethyl amine (0.1 eq), pyrrolidine (1 eq) and methyl carbonate (0.1 eq) to remove the ester.<sup>81</sup> The desired products was formed in reasonable yield, for both the *N*-PMB ethyl ester imine and the *N*-benzyl pentane imine.



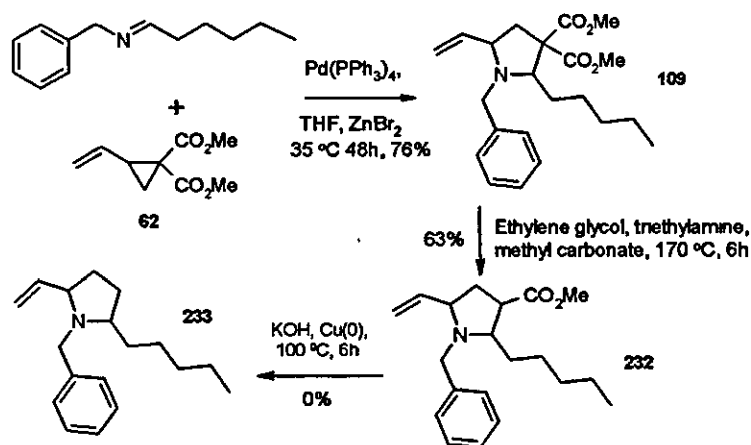
	<i>Product</i>	<i>Conditions</i>	<i>Yield (%)</i>	<i>Cis:Trans</i>
1	 (231)	Stearic acid (2 eq), 200 °C, 16 hours. <sup>81</sup>	0 (stearic acid contamination)	-
2	 (231)	Ethylene glycol (1 eq), triethyl amine (0.1 eq), pyrrolidine (1 eq) and methyl carbonate (0.1 eq). 1 <sup>st</sup> ester removal. <sup>82</sup>	73	10.1
3	 (232)	Ethylene glycol (1 eq), triethyl amine (0.1 eq), pyrrolidine (1 eq) and methyl carbonate (0.1 eq). 1 <sup>st</sup> ester removal. <sup>82</sup>	63	8.1

Table 61 – Ester removal

We next turned our attention to the removal of the second ester. The procedure used, KOH in methanol at reflux for 24 h is a literature procedure for removing an ester which is distant from a heteroatom in a ring system (Scheme 78)<sup>82</sup>



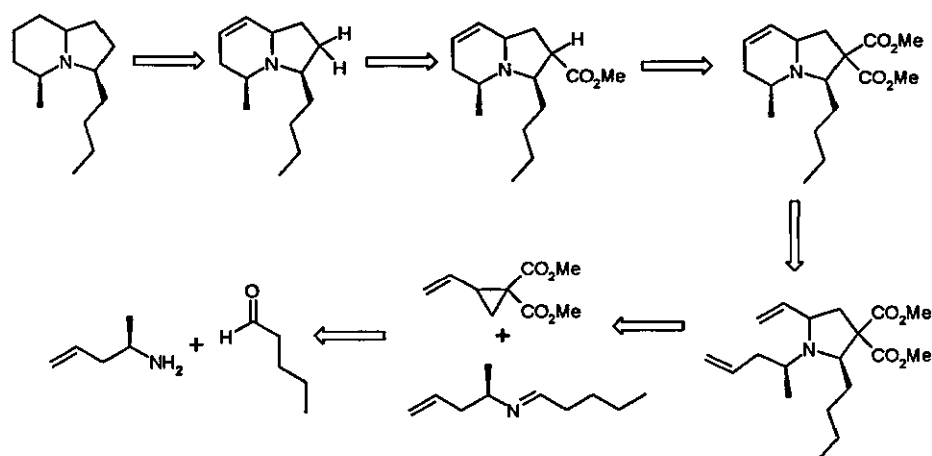
Scheme 78 – Reaction to remove the 2<sup>nd</sup> ester



Scheme 79 – Overall synthesis towards 2,5-dialkyl pyrrolidine

### Monomorine I

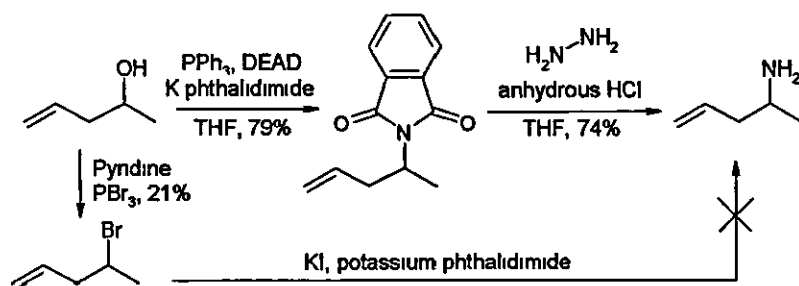
The retro-synthetic analysis of this natural product begins with the reduction of the double bond which would be generated during the RCM step. The two esters would then need to be removed which would give the pyrrolidine product formed from the [2+3]-cycloaddition between the vinyl cyclopropane and imine (Scheme 80)



**Scheme 80** – Monomorine I Retro synthesis

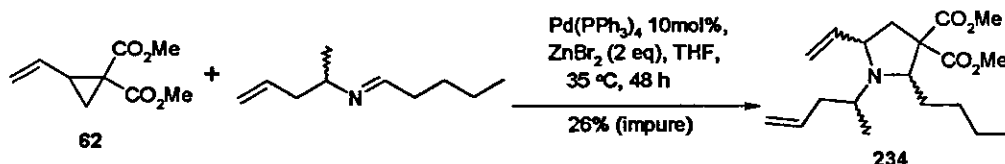
Due to a lack of commercially available *N*-alkene amines, it has been necessary to examine the formation of *N*-alkene amines in order to synthesize the imines required for our natural product targets. The two routes which were looked into both involve an alcohol starting material; the initial method looked at conversion of the alcohol to a bromide which would then be converted to the acid using the Gabriel synthesis. The second approach used a Mitsunobu coupling between alcohol and phthalimide which could be then converted to the amine

Although the formation of the bromo alkene from the alcohol was successful (Scheme 81), in poor yield (21%), the subsequent transformation into the desired amine via the Gabriel synthesis<sup>83</sup> failed to form the amine. The route finally decided upon which involved a Mitsunobu coupling followed by a deprotection using anhydrous hydrazine and anhydrous HCl to form the desired amine. The Mitsunobu reaction<sup>84</sup> was used to successfully form the phthalimide from the alcohol in good yields (79%) This was then deprotected using anhydrous hydrazine in ether and anhydrous HCl in ether, also in good yields (74%) (Scheme 81)



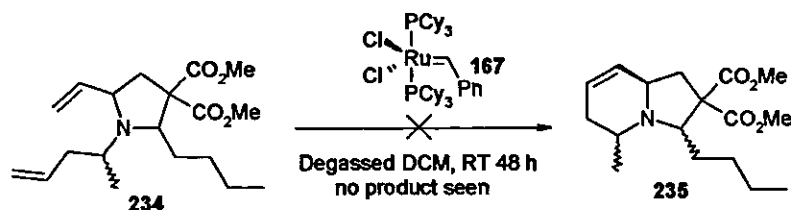
**Scheme 81 – Amine formation**

The next step towards the synthesis of Monomarine I looked at the palladium catalyzed [2+3]-cycloaddition reaction. However even under the optimum conditions, there was only a 26% yield of the required pyrrolidine in only moderate diastereoselectivity (2:1 in favour of the *cis* product). The conditions used in these cyclisations were the optimized conditions developed during the project of 35 °C for 48 h in the presence of 2 eq of ZnBr<sub>2</sub> and 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>. It is felt that for a practical synthesis of a natural product, the yield needs to be significantly higher the product also needs to be isolated in a purer form (**Scheme 82**).

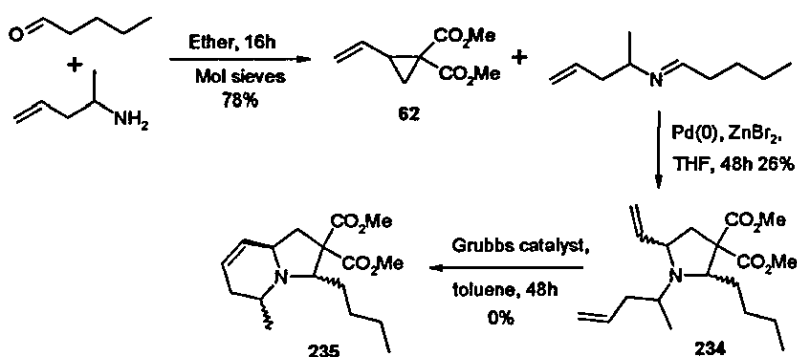


**Scheme 82 – Key step in the formation of Monomarine I**

The next logical step as outlined by our retro-synthetic analysis was the RCM to generate the 6,5-bicyclic ring system. When the Monomarine I pyrrolidine precursor was subjected to the RCM conditions no product was seen from the reaction (**Scheme 83**).



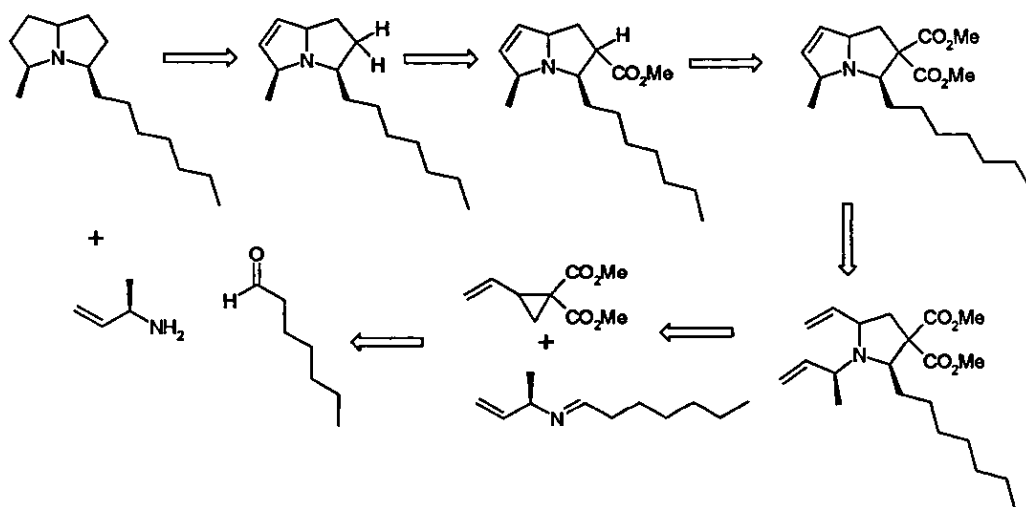
**Scheme 83 – RCM step in the formation of Monomarine I**



**Scheme 84** – Overall synthesis of Monomarine I

### *3-Heptyl-5-methyl pyrrolizidine*

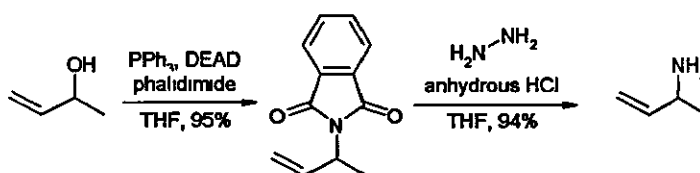
The retro-synthetic analysis for 3-heptyl-5-methyl pyrrolizidine is very similar to that of Monomarine I. The initial step in the retro-synthesis would be the reduction of the double bond formed during the RCM step. The two esters would need to be removed next to give the core pyrrolizidine product, which would be generated via the palladium catalyzed [2+3]-cycloaddition from the vinyl cyclopropane and imine. The imine would be formed from the corresponding amine and aldehyde (Scheme 85)



**Scheme 85** – 3-Heptyl-5-methyl pyrrolizidine retro-synthesis

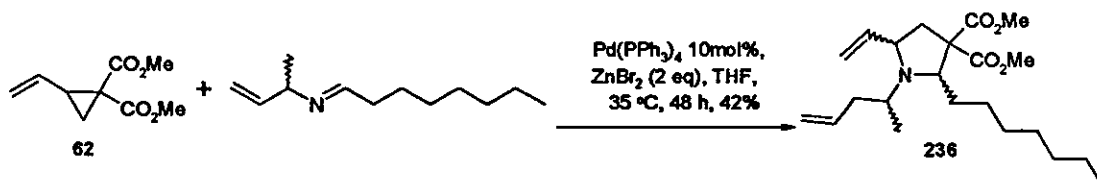
As with Monomarine I, there was a lack of commercially available *N*-alkene amines which had the correct substitution pattern. Due to the fact that we had already examined Mitsunobu coupling between alcohols and phthalimide followed by subsequent conversion to the amine, this approach was followed in the synthesis of 3-heptyl-5-methyl pyrrolizidine's amine precursor.

The Mitsunobu reaction<sup>85</sup> was successful in the formation of the phthalimide protected amide from the alcohol in excellent yields (95%). This was then deprotected using anhydrous hydrazine in ether and anhydrous HCl in ether, also in excellent yields (94%) (Scheme 86).



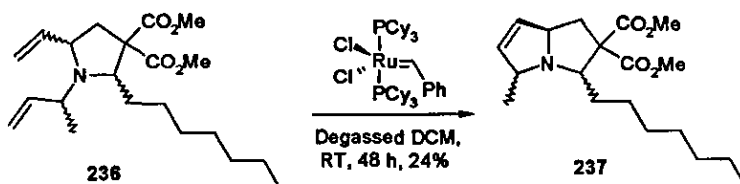
Scheme 86 – Amine formation

After the amine was converted to the imine, the next step is the cyclisation of the key intermediate which was achieved using the [2+3]-cycloaddition conditions of 35 °C for 48 h in the presence of 2 eq of ZnBr<sub>2</sub> and 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub> were used. Although this product is only slightly different to the Monomarine I precursor the cyclisation step was more successful giving a 42% yield of the desired pyrrolizidine, although the pyrrolizidine was contaminated and it proved to difficult purify. The selectivity for this pyrrolizidine was still very poor (1.5:1 *Cis:Trans*) (Scheme 87).

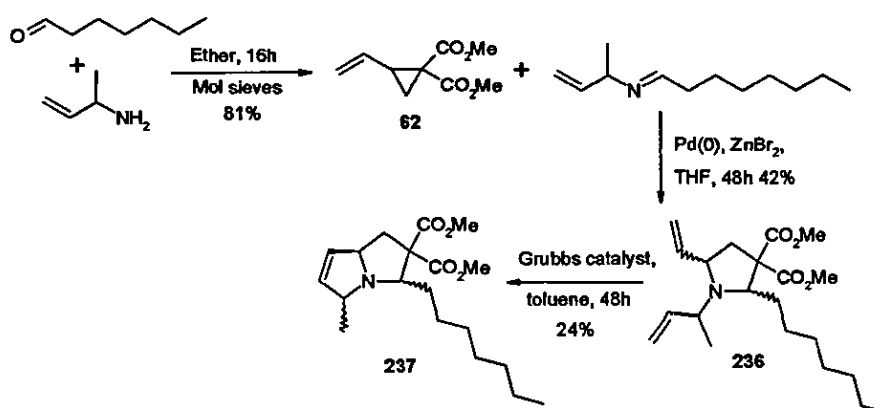


Scheme 87 – [2+3]-cycloaddition in the formation of  
3-heptyl-5-methyl pyrrolizidine

After the pyrrolidine core of the desired natural products was synthesized, the next step in the synthesis of 3-heptyl-5-methyl pyrrolizidine was the application of ring closing metathesis. This proceeded well, with the desired 5,5-bicyclic product being formed in 24% yield.



**Scheme 88** – RCM step in the formation of 3-heptyl-5-methyl pyrrolizidine

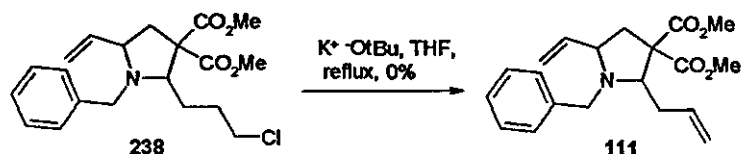


**Scheme 89** – Overall synthesis of 3-heptyl-5-methyl pyrrolizidine

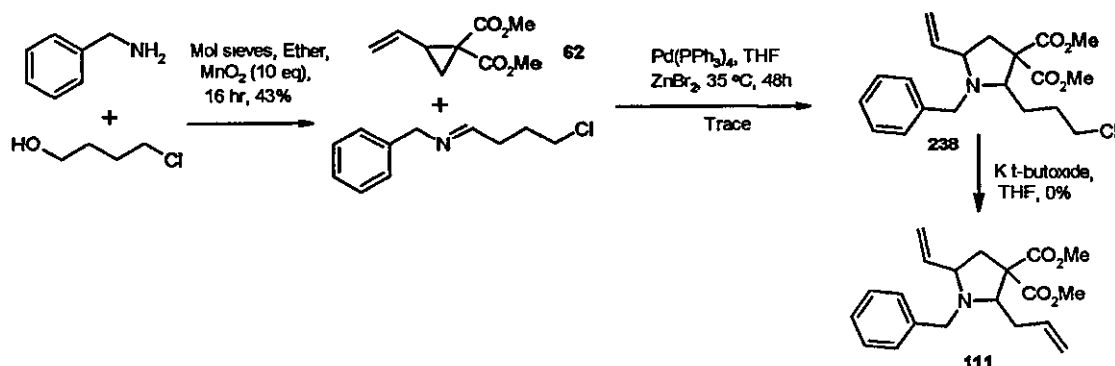
### 3-Nortropanol

The retro-synthesis of the plant based alkaloid 3-nortropanol begins with the deprotection of the bridged nitrogen, where the benzyl group was chosen for ease of removal and likelihood of a high yielding reaction during the [2+3]-cycloaddition step. The next stage in the retro-synthesis would be the addition to the double bond in the seven membered ring by a hydroxyl group, after which the gem di-esters would be removed. A RCM reaction would then be done to generate the bridged intermediate from the pyrrolidine. The key pyrrolidine formation step could be performed via the palladium catalyzed [2+3]-cycloaddition from the corresponding vinyl cyclopropane and imine (**Scheme 90**).





**Scheme 92** – Elimination reaction to generate C1 allyl pyrrolidine



**Scheme 93** – Overall synthesis of 3-nortropanol

### 2.6.7 – Conclusion

In the synthesis of these products there have been many different challenges, of which the most difficult was the removal of the gem diester. Unfortunately the first attempt, stearic acid and phosphorus catalyst,<sup>80</sup> proved to be a very troublesome reaction, as although the ester was successfully removed, the product was contaminated with stearic acid which we found was impossible to separate from the pyrrolidine. In the original paper the products were volatile and therefore could be distilled from the steric acid, however with our pyrrolidines this was not possible. For this reason the removal of the gem diester was attempted via the second method, which involved heating of the pyrrolidine, ethylene glycol, triethyl amine and methyl carbonate at 170 °C in a sealed tube.<sup>81</sup> This proved to be more efficient as the pyrrolidine was readily removed from the other reagents, and we attempted to remove the second ester was removed using potassium hydroxide and copper in methanol,<sup>82</sup> which failed to afford the pyrrolidine product.

The gem diester removal was the most challenging problem which we had to overcome but there were many others, such as the ring closing metathesis which was needed to form the bi-cyclic system of many of the target natural products. Although this should have been a relatively simple reaction (as we had tried some substrates previously) the reaction failed in almost every instance. However results were obtained using Grubb's 2<sup>nd</sup> generation catalyst in dry toluene at reflux, but only in low to moderate yields.

So far the synthesis of any natural products has been far from complete as although many of the challenging obstacles have been overcome enroute to the products there are still many more which need to be addressed. Any future work on this [2+3]-cycloaddition chemistry should look at completing this work.

## Section 2.7 – Overall Conclusions

The development of this novel palladium catalyzed [2+3]-cycloaddition has proceeded well. Over the course of this project a great deal of knowledge on all aspects of this reaction have been gained. The most significant knowledge was gained during the early reactions when it was important to determine the reactivity of the different substrates. The *N*-benzyl imines were of particular note as many examples of these were formed and thus a wide cross section of reactivity could be determined which we hope will be useful in planning future reactions.

The biggest success of the project was however the development of the ethyl glyoxylate derived imines especially the *N*-PMB and *N*-tosyl imines, as it has been possible to crystallize both this products. This was very useful in determining the diastereoselectivity of not only these two compounds but all the other pyrrolidine products formed. As well as this the *N*-PMB ethyl ester imine has also been employed as a test substrate do to its high reactivity, including our attempts at asymmetric catalysis using Trost's ligand which although unsuccessful as given new ideas on the future work which could be done in this field.

Overall the early work was of great interest however the project had a definitive goal from the out set which was the development of the palladium catalyzed [2+3]-cycloaddition toward the synthesis of natural product targets. No natural products were formed but the methodology which we have developed had reached a stage where it has been possible to generate the pyrrolidine cores for four natural products 2,5-dialkyl pyrrolidine, Monomorine I, 3-heptyl-5-methyl pyrrolizidine and 3-nortropanol. The synthesis of these natural products has been a challenge but it has allowed us to look at combining both classical synthesis methods and the palladium catalyzed [2+3]-cycloaddition which is the core of our work.

## Chapter 3 – Experimental

### **3.1 General Experimental**

#### **3.1.1 Solvents**

The solvents used were either freshly distilled or purchased –

DCM	– Distilled over phosphorus pentoxide
Ethyl acetate	– Distilled over calcium chloride
Light Petrol 40-60	– Distilled over calcium chloride
Diethyl ether	– Purchased from Fisher Scientific UK
THF	– Distilled with sodium and benzophenone
Ethanol	– Purchased from Fisher Scientific UK
Methanol	– Purchased from Fisher Scientific UK
Acetonitrile	– Purchased from Aldrich Chemical Company
Dimethyl sulfoxide	– Purchased from Aldrich Chemical Company
Acetone	– Purchased from Aldrich Chemical Company

#### **3.1.2 Reagents**

Most of the reagents used have been purchased from Lancaster Research Chemicals and Aldrich. Thanks go to Roche for supplying a large number of chemicals including significant quantities of *trans*-1,4-dibromobut-2-ene, and PdCl<sub>2</sub>. GSK also supplied a quantity of palladium chloride and Chamwood Catalysis supplied palladium on activated carbon.

#### **3.1.3 FT-IR**

Infrared spectra were recorded as thin films on NaCl plates using a Perkin-Elmer Paragon 1000 Fourier Transform spectrometer. Only significant absorptions ( $\nu_{\max}$ ) are reported and all absorptions are reported in wave numbers (cm<sup>-1</sup>). The following abbreviations are used w, weak; m, medium; s, strong; br, broad.

### 3.1.4 $^1\text{H}$ NMR

Proton magnetic resonance spectra were recorded at 250 and 400 MHz using Brüker AC-250 or Brüker DPX-400 spectrometer. Chemical shifts ( $\delta_{\text{H}}$ ) are quoted in parts per million (ppm) and are referenced to the residual protonated solvent peak. The following abbreviations are used s, singlet; d, doublet; dd, doublet of doublet; t, triplet; q, quartet; m, multiplet; br, broad. Coupling constant ( $J$ ) is quoted in Hertz to the nearest 0.1 Hz.

### 3.15 $^{13}\text{C}$ NMR

Carbon magnetic resonance spectra ( $^{13}\text{C}$  NMR) were recorded at 101 MHz using Brüker DPX-400 spectrometer. Chemical shifts ( $\delta_{\text{H}}$ ) are quoted in parts per million (ppm) and are referenced to the residual protonated solvent peak.

### 4.1.6 Mass Spectrums

High resolution mass spectra were recorded on a JEOL JMS-SX102 by Fast Atom Bombardment (FAB), and electron spray ionization (ESI) ionization capabilities at a resolution of 60,000 and a mass range of 2,500 at 10kV accelerating voltage. Elemental analysis was performed by Mr J Kershaw department of chemistry Loughborough University.

### 3.1.7 $[\alpha]_D^{20}$

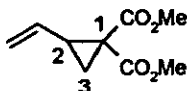
The measurement of optical rotation was performed using a POLAAR 2001 spectrophotometer using a 10 mm cell.

### 3.1.8 X-Ray

The EPSRC National Crystallography service operates a Bruker-Nonius KappaCCD FR591 rotating anode with a molybdenum target, with low and high temperature capabilities (80-500K) via an Oxford cryostream.

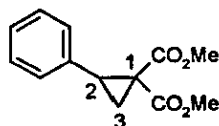
### Section 3.02 – Vinyl Cyclopropane and Aromatic Cyclopropanes

#### 2-Vinyl-cyclopropane-1,1-dicarboxylic acid dimethyl ester (62)<sup>38</sup>



Dimethylmalonate (80) (5.90 mL, 52.00 mmol) was added to a stirred solution of sodium methoxide (prepared from sodium (1.150 g, 50 mmol) and methanol (20 mL)). To the mixture was then added a methanolic solution (20 mL) of *trans*-1,4-dibromobut-2-ene (79) (5.350 g, 25.00 mmol). The mixture was refluxed for 3 hours and cooled to RT. A white precipitate of sodium bromide formed was filtered off and the filtrate concentrated *in vacuo* to give a pale yellow oily residue. This was partitioned between Et<sub>2</sub>O (30 mL) and distilled water (30 mL). The layers were separated and the organic layer was washed with distilled water (2 x 30 mL) and brine (2 x 30 mL), dried over MgSO<sub>4</sub> and concentrated *in vacuo* to give a oil (5.420 g, 73%) the product was then purified by column chromatography (SiO<sub>2</sub>, Et<sub>2</sub>O P.E. 40-60; 1:4, R<sub>f</sub> = 0.250) to afford 2-vinyl-cyclopropane-1,1-dicarboxylic acid dimethyl ester (62) as a colourless oil (4.750 g, 64%);  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2955m (CH str), 1735s (C=O), 1638m, 1332s, 1275s, 1211s, 1132s;  $\delta_{\text{H}}$  (250 MHz; CDCl<sub>3</sub>) 1.38 (1H, dd, J= 5.0 and 9.0, C3-CH(H)), 1.52 (1H, dd, J= 5.0 and 7.5, C3-CH(H)), 2.40 (1H, dd, J= 7.5 and 9.0, C2-CH(H)), 3.55 (6H, s, 2 x OCH<sub>3</sub>), 4.94-5.14 (2H, m, CH=CH<sub>2</sub>), 5.22-5.28 (1H, m, CH=CH<sub>2</sub>);  $\delta_{\text{C}}$  (101 MHz; CDCl<sub>3</sub>) 19.95 (C3-CH<sub>2</sub>), 30.75 (C2-CH), 35.23 (C1-C), 51.89 (OCH<sub>3</sub>), 52.05 (OCH<sub>3</sub>), 117.98 (CH<sub>2</sub>=CH), 132.66 (CH<sub>2</sub>=CH), 167.12 (C=O), 169.33 (C=O);  $m/z$  (EI) 184 (M<sup>+</sup>, 14%), 152 (66), 124 (63), 93 (49), 71 (65), 65 (64), 59 (100); Accurate mass for C<sub>9</sub>H<sub>12</sub>O<sub>4</sub> – 184.0735, found – 184.0737.

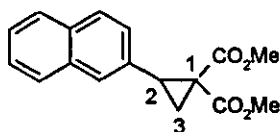
## 2-Phenyl-cyclopropane-1,1-dicarboxylic acid dimethyl ester (196)<sup>74</sup>



### General procedure

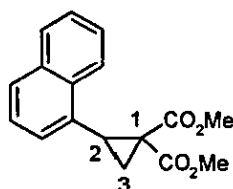
A solution of dimethyl diazomalonate<sup>88</sup> (0.790 g, 5.00 mmol) in anhydrous DCM (15 mL) was added via syringe to a stirred solution of  $\text{Rh}_2(\text{OAc})_4$  (0.004 mg, 0.020 mmol) and styrene (0.520 g, 5.00 mmol). The mixture was stirred at RT for 24 hours, after which time the DCM was removed in vacuo and the resulting slurry filtered through a plug of cotton wool to remove the excess  $\text{Rh}_2(\text{OAc})_4$ . The resulting mixture was purified using column chromatography ( $\text{SiO}_2$ , Et<sub>2</sub>O/P.E. 40-60; 1:4,  $R_f$  = 0.45) to afford 2-phenyl-cyclopropane-1,1-dicarboxylic acid dimethyl ester (196) (0.960 g, 82%) as a colourless oil;  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  3027w, 2951m (CH str), 1727s (C=O), 1437s, 1376m, 1332s, 1279s, 1217s, 1130s, 1032m, 988w, 920w, 792w, 749m;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 1.60 (1H, dd,  $J=5.2$  and  $9.2$ , C3-CH(H)), 2.08 (1H, dd,  $J=5.2$  and  $8.2$ , C3-CH(H)), 3.11 (1H, dd,  $J=8.2$  and  $9.2$ , C2-CH), 3.22 (3H, s, O-CH<sub>3</sub>), 3.60 (3H, s, O-CH<sub>3</sub>), 7.06-7.14 (5H, m, 5 x Ar-CH);  $\delta_{\text{C}}$  (101 MHz,  $\text{CDCl}_3$ ) 18.96 (C3-CH<sub>2</sub>), 32.13 (C2-CH), 37.23 (C1-C), 52.03 (O-CH<sub>3</sub>), 52.64 (O-CH<sub>3</sub>), 127.05 (Ar-CH), 127.90 (Ar-CH), 128.24 (Ar-CH), 128.41 (Ar-CH), 128.56 (Ar-CH), 144.52 (Ar-C), 166.87 (C=O), 170.06 (C=O),  $m/z$  (EI) 234 ( $\text{M}^+$ , 14%), 202 (27), 170 (60), 121 (69), 115 (100), 91 (13), 77 (9), 59 (14), Accurate mass for  $\text{C}_{13}\text{H}_{14}\text{O}_4$  – 234.0892, found – 234.0890

**2-Naphthalen-2-yl-cyclopropane-1,1-dicarboxylic acid dimethyl ester (197)<sup>74</sup>**



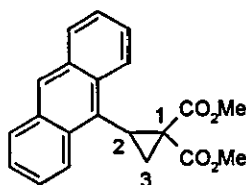
Prepared following the general procedure for compound (196), 2-Naphthalen-2-yl-cyclopropane-1,1-dicarboxylic acid dimethyl ester (197) (0.930 g, 65%) was prepared as a pale yellow oil using 2-vinyl naphthalene (0.770 g, 5.00 mmol),  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  2950s (CH str), 1731s (C=O), 1599m, 1434s, 1334s, 1282s, 1017m, 893m, 861s, 820s, 747s, 645w;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 1.73 (1H, dd,  $J=5.2$  and  $9.2$ , C3-CH(H)), 2.23 (1H, dd,  $J=5.2$  and  $8.0$ , C3-CH(H)), 3.18 (3H, s, O-CH<sub>3</sub>), 3.30 (1H, dd,  $J=8.0$  and  $9.2$ , C2-CH), 3.70 (3H, s, O-CH<sub>3</sub>), 7.31-7.34 (4H, m, 4 x Ar-CH), 7.62-7.67 (3H, m, 3 x Ar-CH);  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 19.28 (C3-CH<sub>2</sub>), 32.75 (C2-CH), 37.63 (C2-C), 52.21 (O-CH<sub>3</sub>), 52.80 (O-CH<sub>3</sub>), 126.19 (Ar-CH), 126.66 (Ar-CH), 127.19 (Ar-CH), 127.61 (Ar-CH), 127.79 (Ar-CH), 127.83 (Ar-CH), 128.08 (Ar-CH), 132.22 (Ar-C), 132.73 (Ar-C), 133.17 (Ar-C), 167.03 (C=O), 170.22 (C=O);  $m/z$  (EI) 284 ( $\text{M}^+$ , 83%), 220 (75), 192 (30), 171 (100), 155 (27), 139 (39), 127 (27), 115 (26), 91 (13), 77 (10), 59 (27); Accurate mass for  $\text{C}_{17}\text{H}_{16}\text{O}_4$  – 284.1048, found – 284.1046.

**2-Naphthalen-1-yl-cyclopropane-1,1-dicarboxylic acid dimethyl ester (198)<sup>74</sup>**



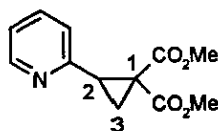
Prepared following the general procedure for compound (196), 2-Naphthalen-1-yl-cyclopropane-1,1-dicarboxylic acid dimethyl ester (198) (1 070 g, 75%) was prepared as a pale yellow oil using 1-vinyl naphthalene (0.770 g, 5.00 mmol),  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  2919s (CH str), 1724s (C=O), 1648w, 1508w, 1435m, 1284m, 1208m, 1128m, 803w, 760m;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 1.79 (1H, dd,  $J=5.0$  and  $9.1$ , C3-CH(H)), 2.36 (1H, dd,  $J=5.1$  and  $8.1$ , C3-CH(H)), 2.97 (3H, s, O-CH<sub>3</sub>), 3.65 (1H, dd,  $J=8.1$  and  $9.1$ , C2-CH), 3.81 (3H, s, O-CH<sub>3</sub>), 7.18-7.47 (4H, m, 4 x Ar-CH), 7.67-7.74 (2H, m, 2 x Ar-CH), 8.08 (1H, m, Ar-CH);  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 18.88 (C3-CH<sub>2</sub>), 30.41 (C2-CH), 36.74 (C1-C), 51.91 (O-CH<sub>3</sub>), 52.98 (O-CH<sub>3</sub>), 124.26 (Ar-CH), 125.01 (Ar-CH), 125.45 (Ar-CH), 125.60 (Ar-CH), 125.70 (Ar-CH), 126.21 (Ar-CH), 128.27 (Ar-CH), 130.75 (Ar-C), 132.94 (Ar-C), 133.38 (Ar-C), 167.10 (C=O), 170.39 (C=O);  $m/z$  (EI) 284 ( $\text{M}^+$ , 3%), 220 (18), 171 (36), 165 (100), 153 (15), 139 (6), 115 (5), 59 (5); Accurate mass for  $\text{C}_{17}\text{H}_{16}\text{O}_7$  – 284.1048, found – 284.1044

**2-Anthracen-9-yl-cyclopropane-1,1-dicarboxylic acid dimethyl ester (199)**<sup>74</sup>



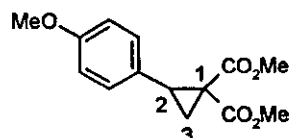
Prepared following the general procedure for compound (196), 2-Anthracen-9-yl-cyclopropane-1,1-dicarboxylic acid dimethyl ester (199) (1.390 g, 83%) was prepared as a yellow oil using 9-vinyl anthracene (1.020 g, 5.00 mmol);  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2949m (CH str), 1726s (C=O), 1435s, 1315s, 1256s, 1130s, 1001m, 913m, 887s, 842m, 736s, 687m;  $\delta_{\text{H}}$  (250 MHz,  $\text{CDCl}_3$ ) 2.24 (1H, dd,  $J=4.7$  and 8.6, C3-CH(H)), 2.30 (1H, dd,  $J=4.7$  and 8.5, C3-CH(H)), 2.75 (3H, s, O-CH<sub>3</sub>), 3.69 (1H, dd,  $J=8.5$  and 8.6, C2-CH), 3.83 (3H, s, O-CH<sub>3</sub>), 7.12-7.39 (5H, m, 5 x Ar-CH), 7.81-7.84 (2H, m, 2 x Ar-CH), 8.32-8.37 (2H, m, 2 x Ar-CH);  $\delta_{\text{C}}$  (101 MHz,  $\text{CDCl}_3$ ) 24.13 (C3-CH<sub>2</sub>), 29.11 (C2-CH), 37.63, 51.77 (O-CH<sub>3</sub>), 53.20 (C1-C), 124.76 (Ar-CH), 124.89 (Ar-CH), 125.06 (Ar-CH), 125.18 (Ar-CH), 125.56 (Ar-CH), 126.15 (Ar-C), 126.27 (Ar-C), 127.33 (Ar-C), 127.52 (Ar-C), 128.35 (Ar-CH), 128.53 (Ar-C), 128.63 (Ar-CH), 129.00 (Ar-CH), 129.33 (Ar-CH), 167.68 (C=O), 170.43 (C=O);  $m/z$  (EI) 334 ( $\text{M}^+$ , 27%), 302 (14), 242 (11), 215 (100), 202 (26), 180 (11), 152 (10), 91 (23), 84 (56), 59 (17); Accurate mass for  $\text{C}_{21}\text{H}_{18}\text{O}_4$  – 334.1205, found – 334.1202.

**2-Pyridin-2-yl-cyclopropane-1,1-dicarboxylic acid dimethyl ester (200)<sup>74</sup>**



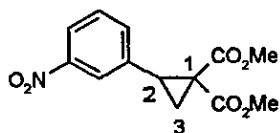
Prepared following the general procedure for compound (196), 2-Pyridin-2-yl-cyclopropane-1,1-dicarboxylic acid dimethyl ester (200) (0.840 g, 71%) was prepared as a colourless oil using 2-vinylpyridine (0.530 g, 5.00 mmol),  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  2951m (CH str), 1731s (C=O), 1592s, 1436s, 1333s, 1274s, 1132s, 998m, 878w, 806m;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 1.82 (1H, dd,  $J=4.5$  and 9.0, C3-CH(H)), 2.34 (1H, dd,  $J=4.5$  and 7.3, C3-CH(H)), 3.10 (1H, dd,  $J=7.3$  and 9.0, C2-CH), 3.48 (3H, s, O-CH<sub>3</sub>), 3.77 (3H, s, O-CH<sub>3</sub>), 7.09 (1H, m, Ar-CH), 7.29 (1H, m, Ar-CH), 7.56 (1H, m, Ar-CH), 8.41 (1H, m, Ar-CH);  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 20.37 (C3-CH<sub>2</sub>), 32.91 (C2-CH), 37.91 (C1-C), 52.28 (O-CH<sub>3</sub>), 52.87 (O-CH<sub>3</sub>), 121.86 (Ar-CH), 123.84 (Ar-CH), 136.16 (Ar-CH), 148.95 (Ar-CH), 155.38 (Ar-C), 167.23 (C=O), 170.20 (C=O);  $m/z$  (EI) 235 ( $\text{M}^+$ , 4%), 204 (46), 172 (85), 144 (43), 117 (100), 89 (20), 78 (13), 59 (12); Accurate mass for  $\text{C}_{10}\text{H}_{13}\text{NO}_4$  – 235.0844, found – 235.0839.

**2-(4-Methoxy-phenyl)-cyclopropane-1,1-dicarboxylic acid dimethyl ester (201)<sup>74</sup>**



Prepared following the general procedure for compound (196), 2-(4-methoxy-phenyl)-cyclopropane-1,1-dicarboxylic acid dimethyl ester (201) (0.910 g, 69%) was prepared as a colourless oil using 4-methoxystyrene (0.670 g, 5.00 mmol);  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  2952m (CH str), 1733s (C=O), 1516s, 1436s, 1332m, 1229s, 1174s, 1130s, 1039m, 968w, 893w, 836m, 761w;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 1.63 (1H, dd,  $J=5.1$  and  $9.3$ , C3-CH(H)), 2.07 (1H, dd,  $J=5.1$  and  $8.0$ , C3-CH(H)), 3.09 (1H, dd,  $J=8.0$  and  $9.3$ , C2-CH), 3.29 (3H, s, Ar-O-CH<sub>3</sub>), 3.68 (3H, s, O-CH<sub>3</sub>), 3.69 (3H, s, O-CH<sub>3</sub>), 6.72 (2H, d,  $J=8.8$ , 2 x Ar-CH), 7.03 (2H, d,  $J=8.8$ , 2 x Ar-CH);  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 19.20 (C3-CH<sub>2</sub>), 32.14 (C2-CH), 37.62 (C1-C), 52.16 (O-CH<sub>3</sub>), 52.86 (O-CH<sub>3</sub>), 55.13 (Ar-O-CH<sub>3</sub>), 113.56 (Ar-CH), 127.74 (Ar-C), 127.88 (Ar-C), 129.89 (Ar-CH), 166.88 (C=O), 170.25 (C=O);  $m/z$  (EI) 264 ( $\text{M}^+$ , 28%), 232 (29), 200 (86), 173 (17), 151 (80), 145 (100), 103 (15), 77 (15), 59 (10); Accurate mass for  $\text{C}_{14}\text{H}_{16}\text{O}_5$  – 264.0997, found – 264.1007.

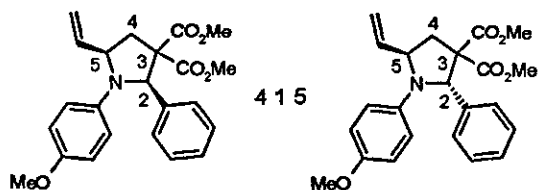
**2-(3-Nitro-phenyl)-cyclopropane-1,1-dicarboxylic acid dimethyl ester (202)<sup>74</sup>**



Prepared following the general procedure for compound (196), 2-(3-nitro-phenyl)-cyclopropane-1,1-dicarboxylic acid dimethyl ester (202) (0.810 g, 58%) was prepared as a yellow oil using 3-nitrostyrene (0.760 g, 5.00 mmol),  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  2953m (CH str), 1730s (C=O), 1531s, 1436s, 1351s, 1277s, 1220s, 1199s, 1131s, 1024w, 934w, 896w, 812m, 792m, 733m, 685m;  $\delta_{\text{H}}$  (250 MHz; CDCl<sub>3</sub>) 1.78 (1H, dd,  $J=5.4$  and  $8.8$ , C3-CH(H)), 2.19 (1H, dd,  $J=5.4$  and  $7.8$ , C3-CH(H)), 3.24 (1H, dd,  $J=7.8$  and  $8.8$ , C2-CH), 3.36 (3H, s, O-CH<sub>3</sub>), 3.75 (3H, s, O-CH<sub>3</sub>), 7.43 (1H, m, Ar-CH), 7.50 (1H, m, Ar-CH), 8.02-8.05 (2H, m, 2 x Ar-CH);  $\delta_{\text{C}}$  (101 MHz; CDCl<sub>3</sub>) 19.09 (C3-CH<sub>2</sub>), 31.30 (C2-CH), 37.22 (C1-C), 52.46 (O-CH<sub>3</sub>), 52.99 (O-CH<sub>3</sub>), 122.44 (Ar-CH), 123.42 (Ar-CH), 129.19 (Ar-CH), 134.76 (Ar-CH), 137.03 (Ar-C), 148.02 (Ar-C-NO<sub>2</sub>), 166.52 (C=O), 169.49 (C=O);  $m/z$  (EI) 279 ( $M^+$ , 24%), 247 (57), 216 (19), 166 (100), 150 (61), 132 (29), 115 (53), 103 (60), 89 (24), 75 (40), 59 (47), Accurate mass for C<sub>13</sub>H<sub>13</sub>NO<sub>6</sub> – 279.0742, found – 279.0746

### Section 3.03 – Pyrrolidines Derived from *N*-(4-methoxybenzene) Imines

*N*-(4-Methoxy-phenyl)-2-phenyl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (81)

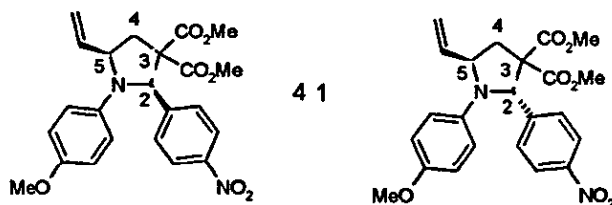


#### General procedure

To a solution of *N*-(4-methoxy-phenyl)-phenyl imine (0.190 g, 1.00 mmol), zinc bromide (0.460 g, 2.00 mmol) and  $\text{Pd}(\text{PPh}_3)_4$  (0.110 g, 0.100 mmol) in THF (10 mL) was added a 2-vinyl-cyclopropane-1,1-dicarboxylic acid (62) (0.190 g, 1.00 mmol). This mixture was stirred for 72 h at 35 °C, the solvent was evaporated *in vacuo* and the residue partitioned between EtOAc (30 mL) and distilled water (30 mL). The organic layer was separated and washed with aq. HCl (1M 2 x 30 mL), saturated  $\text{NaHCO}_3$  solution (30 mL), and saturated brine solution (2 x 30 mL). The organic layer was dried using  $\text{MgSO}_4$ , filtered and concentrated *in vacuo* to afford the crude pyrrolidine product as a dark brown heavy oil. This was then purified using column chromatography ( $\text{SiO}_2$ , EtOAc:PE. 40-60; 1:4,  $R_f$  - 0.35) to yield *N*-(4-methoxy-phenyl)-2-phenyl-3,3-dicarboxylic acid dimethyl ester-5-vinyl pyrrolidine (81) (0.240 g, 60%) as a yellow-brown oil;  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  2998w, 2951w (CH str), 1737s (C=O), 1511, 919m, 814m, 702m;  $\delta_{\text{H}}$  (250 MHz,  $\text{CDCl}_3$ ) 2.38 (1H, dd,  $J=8.6$  and 13.5, C4-C(H)H), 2.48 (1H, dd,  $J=8.6$  and 13.5, C4'-C'(H)H), 2.74 (1H, dd,  $J=5.6$  and 13.5, C4-C(H)H), 3.15 (1H, dd,  $J=5.6$  and 13.5, C4'-C'(H)H), 3.26 (3H, s, O-C(H)<sub>3</sub>), 3.28 (3H, s, O-CH<sub>3</sub>), 3.55 (3H, s, O-CH<sub>3</sub>), 3.59 (3H, s, O-C(H)<sub>3</sub>), 3.65 (3H, s, O-CH<sub>3</sub>), 3.67 (3H, s, O-C(H)<sub>3</sub>), 3.91 (1H, m, C5'-N-C(H)), 4.61 (1H, m, C5-N-CH), 4.98-5.35 (5H, m, C2'-N-C(H), C'H<sub>2</sub>=CH, CH<sub>2</sub>=CH), 5.52 (1H, m, C'H<sub>2</sub>=C(H)), 5.76 (1H, s, C2-N-CH), 5.92 (1H, m, C'H<sub>2</sub>=CH), 6.34 (2H, d,  $J=9.0$ , 2 x Ar-CH), 6.48 (2H, d,  $J=9.0$ , 2 x Ar-C(H)), 6.59 (2H, d,  $J=9.0$ , 2 x Ar-CH), 6.62 (2H, d,  $J=9.0$ , 2 x Ar-C(H)), 7.14-7.34 (10H, m, 5 x Ar-CH, 5 x Ar-C(H)),  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 36.55 (C4-CH<sub>2</sub>), 38.33 (C4'-CH<sub>2</sub>), 52.62 (C2'-CH), 53.31 (C2-

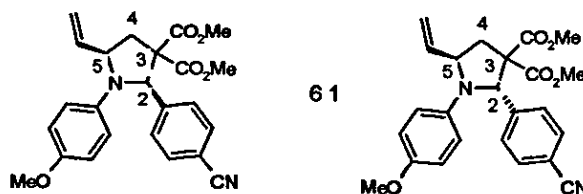
$\underline{\text{CH}}$ ), 53.62 ( $\text{C5}-\underline{\text{CH}}$ ), 55.93 ( $\text{C5}'-\underline{\text{C}}'\text{H}$ ), 59.93 ( $\text{O}-\underline{\text{CH}}_3$ ), 56.00 ( $\text{O}-\underline{\text{C}}'\text{H}_3$ ), 60.38 ( $\text{O}-\underline{\text{CH}}_3$ ), 60.97 ( $\text{O}-\underline{\text{C}}'\text{H}_3$ ), 64.81 ( $\text{C3}'-\underline{\text{C}}'$ ), 64.94 ( $\text{C3}-\underline{\text{C}}$ ), 67.10 ( $\text{O}-\underline{\text{CH}}_3$ ), 71.74 ( $\text{O}-\underline{\text{C}}'\text{H}_3$ ), 114.69 ( $\text{Ar}-\underline{\text{CH}}$ ), 114.74 ( $\text{Ar}-\underline{\text{CH}}$ ), 115.47 ( $\text{Ar}-\underline{\text{C}}'\text{H}$ ), 115.49 ( $\text{Ar}-\underline{\text{C}}'\text{H}$ ), 116.45 ( $\underline{\text{C}}'\text{H}_2=\underline{\text{CH}}$ ), 117.11 ( $\underline{\text{CH}}_2=\underline{\text{CH}}$ ), 128.03 ( $\text{Ar}-\underline{\text{C}}'\text{H}$ ), 128.20 ( $\text{Ar}-\underline{\text{CH}}$ ), 128.38 ( $\text{Ar}-\underline{\text{CH}}$ ), 128.70 ( $\text{Ar}-\underline{\text{C}}'\text{H}$ ), 128.76 ( $\text{Ar}-\underline{\text{CH}}$ ), 128.98 ( $\text{Ar}-\underline{\text{C}}'\text{H}$ ), 133.37 ( $\text{Ar}-\underline{\text{C}}$ ), 138.61 ( $\underline{\text{CH}}_2=\underline{\text{CH}}$ ), 139.01 ( $\text{Ar}-\underline{\text{C}}$ ), 139.97 ( $\underline{\text{CH}}_2=\underline{\text{C}}'\text{H}$ ), 140.93 ( $\text{Ar}-\underline{\text{C}}'$ ), 142.31 ( $\text{Ar}-\underline{\text{C}}'$ ), 151.38 ( $\text{Ar}-\underline{\text{C}}$ ), 152.69 ( $\text{Ar}-\underline{\text{C}}'$ ), 168.16 ( $\underline{\text{C}}'=\text{O}$ ), 168.31 ( $\underline{\text{C}}=\text{O}$ ), 171.21 ( $\underline{\text{C}}'=\text{O}$ ), 171.29 ( $\underline{\text{C}}=\text{O}$ );  $m/z$  (EI) 395 ( $\text{M}^+$ , 100%), 251 (82), 196 (21), 175 (25), 84 (42), 49 (59), Accurate mass for  $\text{C}_{23}\text{H}_{25}\text{NO}_5$  – 395.1732, found – 395.1728

***N*-(4-Methoxy-phenyl)-2-(4-nitro-phenyl)-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (82)**



Prepared following the general thermal procedure for compound (81), *N*-(4-methoxy-phenyl)-2-(4-nitro-phenyl)-3,3-dicarboxylic acid dimethyl ester-5-vinyl pyrrolidine (82) (0.130 g, 29%) was prepared as a yellow oil using *N*-(4-methoxy-phenyl)-(4-nitro-phenyl) imine (0.260 g, 1.00 mmol) for 96 hours,  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2950w (CH str), 1736s (C=O), 1604w, 1510s, 1435m, 1374s, 1243s, 1037m, 989w, 870w, 814w, 731w;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 2.44 (1H, dd,  $J=2.4$  and 11.0, C4-CH(H)), 2.54 (1H, dd,  $J=9.0$  and 11.6, C4-CH(H)), 2.69 (1H, dd,  $J=2.4$  and 11.0, C4'-CH'(H)), 3.09 (1H, dd,  $J=9.0$  and 11.6, C4'-CH'(H)), 3.31 (3H, s, Ar-O-CH<sub>3</sub>), 3.58 (3H, s, Ar-O-CH<sub>3</sub>), 3.63 (3H, s, O-CH<sub>3</sub>), 3.67 (3H, s, O-CH<sub>3</sub>), 3.70 (3H, s, O-CH<sub>3</sub>), 3.71 (3H, s, O-CH<sub>3</sub>), 4.00 (1H, m, C5-N-CH), 4.70 (1H, m, C5'-N-CH), 5.02-5.07 (2H, m, CH=CH<sub>2</sub>), 5.23-5.32 (2H, m, CH=CH<sub>2</sub>), 5.37 (1H, s, C2-N-CH), 5.61 (1H, m, CH'=CH<sub>2</sub>), 5.86 (1H, s, C2'-N-CH), 5.97 (1H, m, CH=CH<sub>2</sub>), 6.32 (2H, d,  $J=9.2$ , 2 x Ar-CH), 6.45 (2H, d,  $J=9.2$ , 2 x Ar-CH), 6.58 (2H, d,  $J=9.2$ , 2 x Ar-CH), 6.62 (2H, d,  $J=9.2$ , 2 x Ar-CH), 7.27 (2H, d,  $J=8.5$ , 2 x Ar-CH-OMe), 7.55 (2H, d,  $J=8.5$ , 2 x Ar-CH-OMe), 8.05 (2H, d,  $J=8.8$ , 2 x Ar-CH-NO<sub>2</sub>), 8.14 (2H, d,  $J=8.8$ , 2 x Ar-CH-NO<sub>2</sub>);  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 36.50 (C4-CH<sub>2</sub>), 38.06 (C4'-CH<sub>2</sub>), 52.52 (C2-CH), 52.55 (C2'-CH), 52.71 (C5-CH), 52.86 (C5'-CH), 53.49 (O-CH<sub>3</sub>), 55.57 (O-CH<sub>3</sub>), 60.14 (O-CH<sub>3</sub>), 61.04 (O-CH<sub>3</sub>), 64.37 (C3-C), 64.58 (C3'-C), 116.62 (CH<sub>2</sub>=CH), 117.12 (CH<sub>2</sub>=CH), 123.63 (Ar-CH), 124.00 (Ar-CH), 128.59 (Ar-CH), 128.4 (Ar-CH), 137.63 (CH<sub>2</sub>=CH), 137.92 (CH<sub>2</sub>=CH), 138.98 (Ar-C), 141.22 (Ar-C), 146.94 (Ar-C), 147.54 (Ar-C), 147.72 (Ar-C), 148.31 (Ar-C), 151.56 (Ar-C), 152.97 (Ar-C), 167.45 (C=O), 167.65 (C=O), 170.30 (C=O), 170.35 (C=O);  $m/z$  (EI) 440 ( $\text{M}^+$ , 100%), 381 (11), 318 (19), 296 (67), 266 (15), 175 (41), 134 (26), 84 (51), 49 (66); Accurate mass for  $\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_7$  - 440.1583, found - 440.1587.

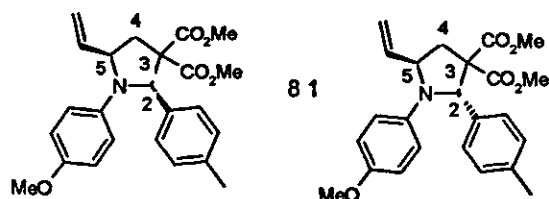
***N*-(4-Methoxy-phenyl)-2-(4-(cyano-phenyl)-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (83)**



Prepared following the general thermal procedure for compound (81), *N*-(4-methoxy-phenyl)-2-(4-cyano-phenyl)-5-vinyl pyrrolidine-3,3-dicarboxylic acid dimethyl ester (83) (0.090 g, 22%) was prepared as a yellow-brown oil using *N*-(4-methoxy-phenyl)-(4-cyano-phenyl) imine (0.240 g, 1.00 mmol);  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2952m, 2834m (CH str), 2227w (C $\equiv$ N), 1736m (C=O), 1607w, 1511m, 1344w, 1260s, 1182m, 1037m, 990w, 921w, 862w, 816m, 735m, 699w;  $\delta_{\text{H}}$  (250 MHz; CDCl<sub>3</sub>) 2.48 (1H, dd,  $J=8.0$  and  $12.0$ , C4-C(H)H), 2.53 (1H, dd,  $J=8.0$  and  $12.0$ , C4'-C'(H)H), 2.67 (1H, dd,  $J=6.0$  and  $12.0$ , C4'-C'(H)H), 3.05 (1H, dd,  $J=6.0$  and  $12.0$ , C4-C(H)H), 3.28 (3H, s, O-C'H<sub>3</sub>), 3.59 (3H, s, O-C'H<sub>3</sub>), 3.62 (3H, s, O-C'H<sub>3</sub>), 3.67 (3H, s, O-C'H<sub>3</sub>), 3.71 (3H, s, O-C'H<sub>3</sub>), 3.98 (1H, m, C5'-N-C'H), 4.62 (1H, m, C5-N-CH), 4.98-5.05 (2H, m, CH<sub>2</sub>=CH), 5.22-5.34 (3H, m, C2'-N-C'H, C'H<sub>2</sub>=CH), 5.54 (1H, m, CH<sub>2</sub>=CH), 5.80 (1H, s, C2-N-CH), 5.95 (1H, m, CH<sub>2</sub>=C'H), 6.29 (2H, d,  $J=8.0$ , 2 x Ar-CH), 6.45 (2H, d,  $J=8.0$ , 2 x Ar-C'H), 6.60 (2H, d,  $J=8.0$ , 2 x Ar-CH), 6.63 (2H, d,  $J=8.0$ , 2 x Ar-C'H), 7.21 (2H, d,  $J=8.0$ , 2 x Ar-CH), 7.40 (2H, d,  $J=8.0$ , 2 x Ar-CH), 7.45 (2H, d,  $J=8.0$ , 2 x Ar-C'H), 7.55 (2H, d,  $J=8.0$ , 2 x Ar-C'H);  $\delta_{\text{C}}$  (101 MHz; CDCl<sub>3</sub>) 32.06 (C4-CH<sub>2</sub>), 38.41 (C4'-C'H<sub>2</sub>), 52.05 (C2-CH), 52.86 (C2'-C'H), 53.54 (C5-CH), 53.84 (C5'-C'H), 55.91 (O-CH<sub>3</sub>), 55.97 (O-C'H<sub>3</sub>), 60.56 (O-CH<sub>3</sub>), 61.36 (O-C'H<sub>3</sub>), 64.75 (C3'-C'), 64.80 (C3-C), 66.73 (O-CH<sub>3</sub>), 71.43 (O-C'H<sub>3</sub>), 112.30 (C $\equiv$ N), 112.34 (C $\equiv$ N), 114.76 (Ar-C'H), 114.85 (Ar-CH), 115.90 (Ar-CH), 116.10 (Ar-C'H), 117.35 (CH<sub>2</sub>=CH), 117.45 (C'H<sub>2</sub>=CH), 118.98 (Ar-C'), 122.91 (Ar-C), 128.88 (Ar-C'H), 129.22 (Ar-CH), 132.50 (Ar-C'H), 132.88 (Ar-CH), 139.12 (Ar-C), 139.18 (CH<sub>2</sub>=CH), 139.41 (CH<sub>2</sub>=C'H), 141.66 (Ar-C'), 146.03 (Ar-C), 146.70 (Ar-C'), 153.10 (Ar-C), 153.30 (Ar-C'), 167.85 (C=O), 167.86 (C=O), 169.55 (C=O), 170.70 (C=O);  $m/z$  (EI) 420

(M<sup>+</sup>, 100%), 361 (14), 276 (63), 221 (35), 175 (33), 134 (23), 108 (16), 77 (20),  
Accurate mass for C<sub>24</sub>H<sub>24</sub>N<sub>2</sub>O<sub>5</sub> – 420.1685, found – 420.1680.

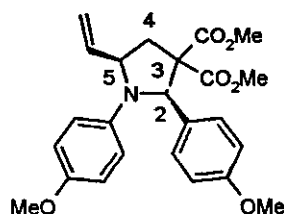
*N*-(4-Methoxy-phenyl)-2-*p*-tolyl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (84)



Prepared following the general thermal procedure for compound (81), *N*-(4-methoxy-phenyl)-2-*p*-tolyl-5-vinyl pyrrolidine-3,3-dicarboxylic acid dimethyl ester (84) (0.170 g, 42%) was prepared as a yellow-brown oil using *N*-(4-methoxy-phenyl) *p*-tolyl imine (0.230 g, 1.00 mmol);  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2953m (CH str), 1736s (C=O), 1638s, 1346w, 1243s, 1118w, 1073m, 1039m, 987w, 920m, 814s, 799s;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 2.18 (3H, s, Ar-CH<sub>3</sub>), 2.24 (3H, s, Ar-CH<sub>3</sub>'), 2.47 (1H, dd,  $J=5.8$  and 13.3, C4-CH(H)), 2.74 (1H, dd,  $J=11.3$  and 13.3, C4'-CH(H')), 3.09 (1H, dd,  $J=7.0$  and 13.3, C4-CH(H)), 3.16 (1H, dd,  $J=7.0$  and 13.3, C4'-CH(H')), 3.29 (3H, s, Ar-O-CH<sub>3</sub>), 3.31 (3H, s, Ar-O-CH<sub>3</sub>'), 3.58 (3H, s, O-CH<sub>3</sub>), 3.61 (3H, s, O-CH<sub>3</sub>'), 3.64 (3H, s, O-CH<sub>3</sub>'), 3.68 (3H, s, O-CH<sub>3</sub>'), 3.95 (1H, m, C5-N-CH), 4.61 (1H, m, C5'-N-CH'), 5.01-5.06 (2H, m, CH=CH<sub>2</sub>), 5.24 (1H, s, C2-N-CH), 5.31-5.36 (2H, m, CH=CH<sub>2</sub>'), 5.58 (1H, m, CH=CH<sub>2</sub>), 5.72 (1H, s, C2'-N-CH'), 5.98 (1H, m, CH=CH<sub>2</sub>'), 6.35 (2H, d,  $J=9.0$ , 2 x Ar-CH), 6.48 (2H, d,  $J=9.0$ , 2 x Ar-CH'), 6.58 (2H, d,  $J=9.0$ , 2 x Ar-CH), 6.60 (2H, d,  $J=9.0$ , 2 x Ar-CH'), 6.63 (2H, d,  $J=10.5$ , 2 x Ar-CH'), 6.94 (2H, d,  $J=10.5$ , 2 x Ar-CH), 7.04 (2H, d,  $J=6.0$ , 2 x Ar-CH'), 7.19 (2H, d,  $J=6.0$ , 2 x Ar-CH);  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 21.11 (Ar-CH<sub>3</sub>), 21.13 (Ar-CH<sub>3</sub>'), 36.12 (C4-CH<sub>2</sub>), 37.92 (C4'-CH<sub>2</sub>'), 52.23 (C2'-CH), 52.42 (C2-CH), 52.88 (C5-CH), 53.18 (C5'-CH), 55.35 (O-CH<sub>3</sub>), 55.65 (O-CH<sub>3</sub>'), 59.91 (O-CH<sub>3</sub>'), 60.47 (O-CH<sub>3</sub>'), 64.36 (C3'-CH), 64.47 (C3-CH), 66.45 (Ar-O-CH<sub>3</sub>), 71.05 (Ar-O-CH<sub>3</sub>'), 114.19 (Ar-CH), 114.30 (Ar-CH'), 113.93 (Ar-CH), 115.02 (Ar-CH), 115.97 (CH<sub>2</sub>=CH), 116.66 (CH<sub>2</sub>=CH'), 127.41 (Ar-CH), 127.49 (Ar-CH), 129.33 (Ar-CH), 129.53 (Ar-CH'), 135.41 (Ar-C), 137.35 (Ar-C), 137.43 (Ar-C), 137.57 (Ar-C), 138.31 (CH<sub>2</sub>=CH), 138.77 (Ar-C'), 139.66 (CH<sub>2</sub>=CH), 141.92 (Ar-C'), 150.90 (Ar-C'), 152.19 (Ar-C'), 157.82 (C=O), 167.96 (C=O), 170.87 (C=O), 170.94 (C=O);  $m/z$

(EI) 409 ( $M^+$ , 98%), 364 (17), 285 (100), 225 (31), 175 (26), 145 (39), 115 (20), 84 (28), 49 (32); Accurate mass for  $C_{24}H_{27}NO_5$  – 409.1889, found – 409.1883.

***N*,2-Bis-(4-methoxy-phenyl)-5-vinyl pyrrolidine-3,3-dicarboxylic acid dimethyl ester (85)**



***Thermal Procedure***

Prepared following the general thermal procedure for compound (81), *N*,2-bis-(4-methoxy-phenyl)-5-vinyl pyrrolidine-3,3-dicarboxylic acid dimethyl ester (85) (0.250 g, 59%) was prepared as a yellow oil using *N*,-(4-methoxy-phenyl) 4-methoxy-phenyl imine (0.240 g, 1.00 mmol) for 48 hours;  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  3022m, 2917m (CH str), 1603s (C=O), 1437m, 1186m, 1162s, 1020m, 902s, 820s, 736s, 689s;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 2.43-2.58 (2H, m, C4-CH(H), C4-CH(H)), 3.72 (3H, s, O-CH<sub>3</sub>), 3.73 (3H, s, O-CH<sub>3</sub>), 3.74 (3H, s, O-CH<sub>3</sub>), 3.75 (3H, s, O-CH<sub>3</sub>), 4.50 (1H, m, C5-N-CH), 5.05-5.12 (3H, m, CH<sub>2</sub>=CH, C2-N-CH), 5.66 (1H, m, CH<sub>2</sub>=CH), 6.75-6.83 (4H, m, 4 x Ar-CH, Ar-CH), 7.19-7.25 (4H, m, 4 x Ar-CH, Ar-CH),  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 31.29 (C4-CH<sub>2</sub>-C), 55.80 (C5-N-CH, C2-N-CH), 63.60 (O-CH<sub>3</sub>), 114.42 (Ar-CH), 117.93 (CH<sub>2</sub>=CH), 125.44 (Ar-CH), 131.24 (Ar-C), 138.06 (CH<sub>2</sub>=CH), 157.56 (C=O), 174.73 (C=O);  $m/z$  (EI) 425 ( $\text{M}^+$ , 59%), 366 (8), 281 (100), 241 (15), 175 (16), 135 (25), 71 (27); Accurate mass for  $\text{C}_{24}\text{H}_{27}\text{NO}_6$  – 425.1838, found – 425.1843.

***Microwave Procedure (General procedure)***

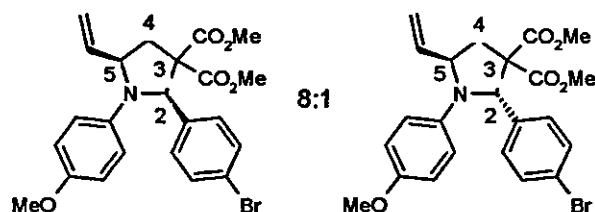
To a solution of *N*,-(4-methoxy-phenyl) 4-methoxy-phenyl imine (0.240 g, 1.00 mmol) zinc bromide (0.460 g, 2.00 mmol) and  $\text{Pd}(\text{PPh}_3)_4$  (0.110 g, 0.100 mmol) and THF (5 mL) in a 10 mL tube equipped with a magnetic stirrer bar was added 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester (62) (0.190 g, 1.00 mmol). The tube was sealed and placed in the CEM discovery microwave and was irradiated for 10 minutes at a power setting of 50 watts (250 psi maximum pressure). After this time the solvent was evaporated *in vacuo* and the residue partitioned between EtOAc (30 mL) and distilled water (30 mL). The organic layers were separated and washed

with HCl (1M 2 x 30 mL), NaHCO<sub>3</sub> (30 mL), and brine solution (2 x 30 mL) The organic layer was dried with MgSO<sub>4</sub>, filtered through a plug of cotton wool and concentrated *in vacuo* to give the crude pyrrolidine product as a dark brown heavy oil. This was then purified using column chromatography (SiO<sub>2</sub>, EtOAc:P.E. 40-60, 1:3, R<sub>f</sub> - 0.33) to yield *N*,2-bis-(4-methoxy-phenyl)-5-vinyl pyrrolidine-3,3-dicarboxylic acid dimethyl ester (**85**) (0.270 g, 63%) as a yellow oil; Data as above.

*Silica Procedure (General procedure)*

To a solution of *N*,-(4-methoxy-phenyl) 4-methoxy-phenyl imine (0.240 g, 1.00 mmol), zinc bromide (0.460 g, 2.00 mmol), palladium tetrakis(triphenyl phosphine) (0.110 g, 0.100 mmol) and chromatographic grade silica (0.100 g) in THF (10 mL) was added a 2-vinylcyclopropane-1,1-dicarboxylic acid (**62**) (0.190 g, 1.00 mmol). This mixture was stirred for 16 hours at RT, the solvent was evaporated *in vacuo* and the residue partitioned between EtOAc (30 mL) and distilled water (30 mL) The organic layer was separated and washed with aq. HCl (1M 2 x 30 mL), saturated NaHCO<sub>3</sub> solution (30 mL), and saturated brine solution (2 x 30 mL) The organic layer was dried using MgSO<sub>4</sub>, filtered and concentrated *in vacuo* to afford the crude pyrrolidine product as a dark brown heavy oil. This was then purified using column chromatography (SiO<sub>2</sub>, EtOAc:P.E. 40-60; 1:3, R<sub>f</sub> - 0.33) to yield *N*,2-bis-(4-methoxy-phenyl)-5-vinyl pyrrolidine-3,3-dicarboxylic acid dimethyl ester (**85**) (0.260 g, 62%) as a yellow oil; Data as above.

***N*-(4-Methoxy-phenyl)-2-(4-bromo-phenyl)-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (86)**



***Thermal Procedure***

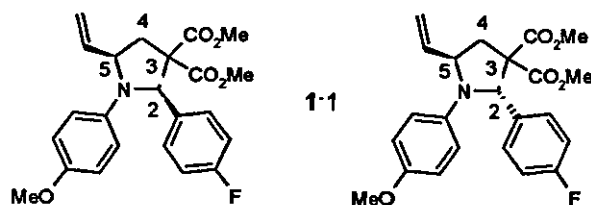
Prepared following the general thermal procedure for compound (81), *N*-(4-methoxy-phenyl)-2-(4-bromo-phenyl)-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (86) (0.113 g, 24%) was prepared as a brown oil using *N*-(4-methoxybenzene)-(4-bromo-phenyl) imine (0.290 g, 1.00 mmol);  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2101w (CH str), 1733m (C=O), 1638s, 1560w, 1510m, 1243m, 1071w, 1037w,  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 2.36 (1H, dd,  $J=4.0$  and  $12.0$ , C4-C(H)H), 2.47 (1H, dd,  $J=4.0$  and  $12.0$ , C4'-C'(H)H), 2.69 (1H, dd,  $J=8.0$  and  $12.0$ , C4'-C'(H)H), 3.15 (1H, dd,  $J=8.0$  and  $12.0$ , C4-C(H)H), 3.30 (3H, s, O-C(H)<sub>3</sub>), 3.31 (3H, s, O-CH<sub>3</sub>), 3.59 (3H, s, O-CH<sub>3</sub>), 3.62 (3H, s, O-C(H)<sub>3</sub>), 3.66 (3H, s, O-CH<sub>3</sub>), 3.69 (3H, s, O-C(H)<sub>3</sub>), 3.94 (1H, m, C5'-N-CH), 4.54 (1H, m, C5-N-CH), 4.99-5.10 (2H, m, CH<sub>2</sub>=CH), 5.21-5.34 (3H, m, C(H)=CH, C2-N-C(H)), 5.53 (1H, m, CH<sub>2</sub>=C(H)), 5.67 (1H, s, C2-N-CH), 5.94 (1H, m, CH<sub>2</sub>=C(H)), 6.33 (2H, d,  $2 \times J=9.0$ , Ar-C(H)), 6.45 (2H, d,  $2 \times J=9.0$ , Ar-CH), 6.57 (2H, d,  $2 \times J=9.0$ , Ar-CH), 6.62 (2H, d,  $J=9.0$ ,  $2 \times$  Ar-C(H)), 6.87 (2H, d,  $J=9.0$ ,  $2 \times$  Ar-CH), 7.21 (2H, d,  $J=9.0$ ,  $2 \times$  Ar-C(H)), 7.30 (2H, d,  $J=9.0$ ,  $2 \times$  Ar-CH), 7.38 (2H, d,  $J=9.0$ ,  $2 \times$  Ar-C(H));  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 36.63 (C4-CH<sub>2</sub>), 38.31 (C4'-C(H)<sub>2</sub>), 52.78 (C2'-C(H)), 52.92 (C2-CH), 53.40 (C5-CH), 53.70 (C5'-C(H)), 55.94 (O-CH<sub>3</sub>), 56.00 (O-C(H)<sub>3</sub>), 60.39 (O-CH<sub>3</sub>), 61.07 (O-C(H)<sub>3</sub>), 64.64 (C3'-C), 64.82 (C3-C), 66.51 (O-CH<sub>3</sub>), 71.18 (O-C(H)<sub>3</sub>), 114.71 (Ar-C(H)), 114.78 (Ar-CH), 115.70 (Ar-C(H)), 115.74 (Ar-CH), 116.67 (CH<sub>2</sub>=CH), 117.24 (C(H)=CH), 122.13 (Ar-C), 122.35 (Ar-C'), 129.70 (Ar-C(H)), 129.76 (Ar-CH), 131.88 (Ar-C(H)), 131.92 (Ar-CH), 138.27 (CH<sub>2</sub>=CH), 138.35 (Ar-C), 138.69 (Ar-C'), 139.73 (CH<sub>2</sub>=C(H)), 140.12 (Ar-C), 142.00 (Ar-C'), 151.61 (Ar-C), 152.96 (Ar-C'), 168.03 (C=O), 168.20 (C=O), 170.98 (C=O), 171.05 (C=O),  $m/z$  (EI) 475 ( $\text{M}^+$  -H, 100%), 473 ( $\text{M}^+$  -H, 97%), 329 (81), 318 (9), 289 (28), 238 (10), 175 (63), 134 (43), 115 (28), 77

(48), 59 (43); Accurate mass for  $C_{23}H_{24}NO_5^{79}Br$  ( $M^+ - H$ ) – 473.0838, found – 473.0839.

*Microwave Procedure*

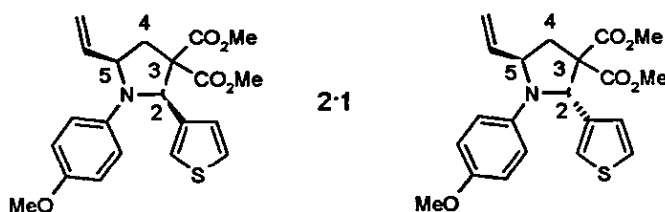
Prepared following the general microwave procedure for compound (85), *N*-(4-methoxy-phenyl)-2-(4-bromo-phenyl)-5-vinyl pyrrolidine-3,3-dicarboxylic acid dimethyl ester (86) (0.260 g, 54%) was prepared as a brown oil using *N*-(4-methoxybenzene)-(4-bromo-phenyl) imine (0.290 g, 1.00 mmol); Data as above.

***N*-(4-Methoxy-phenyl)-2-(4-fluoro-phenyl)-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (87)**



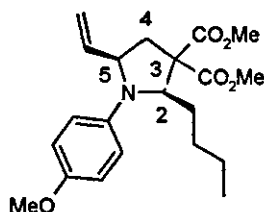
Prepared following the general thermal procedure for compound (81), *N*-(4-methoxy-phenyl)-2-(4-fluoro-phenyl)-5-vinyl pyrrolidine-3,3-dicarboxylic acid dimethyl ester (87) (0.230 g, 55%) was prepared as a yellow-brown oil using *N*-(4-methoxy-phenyl)-(4-fluoro-phenyl) imine (0.230 g, 1.00 mmol) for 48 hours,  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2955m (CH str), 1736s (C=O), 1644s, 1510s, 1340w, 1243m, 1097w, 1073w, 1040w, 988w, 920w, 816m;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 2.09 (1H, dd,  $J=6.8$  and  $13.2$ , C4-C(H)H), 2.48 (1H, dd,  $J=6.8$  and  $13.2$ , C4-C'(H)H), 2.69 (1H, dd,  $J=10.1$  and  $13.2$ , C4-C'(H)H), 2.92 (1H, dd,  $J=10.1$  and  $13.2$ , C4-C(H)H), 3.29 (3H, s, O-C'H<sub>3</sub>), 3.30 (3H, s, O-CH<sub>3</sub>), 3.57 (3H, s, O-CH<sub>3</sub>), 3.61 (3H, s, O-C'H<sub>3</sub>), 3.64 (3H, s, O-C'H<sub>3</sub>), 3.65 (3H, s, O-CH<sub>3</sub>), 3.97 (1H, m, C5-C'H), 4.66 (1H, m, C5-CH), 5.05 (1H, s, C2-C'H), 5.08-5.15 (2H, m, CH<sub>2</sub>=CH), 5.20-5.34 (2H, m, CH'<sub>2</sub>=CH), 5.60 (1H, m, CH<sub>2</sub>=C'H), 5.74 (1H, s, C2-C'H), 5.92 (1H, m, CH<sub>2</sub>=C'H), 6.34 (2H, d,  $J=9.1$ , 2 x Ar-CH'), 6.48 (2H, d,  $J=9.1$ , 2 x Ar-CH), 6.59 (2H, d,  $J=9.1$ , 2 x Ar-CH'), 6.64 (2H, d,  $J=9.1$ , 2 x Ar-CH), 6.84-7.32 (8H, m, 4 x Ar-CH, 4 x Ar-C'H);  $\delta_{\text{C}}$  (101 MHz,  $\text{CDCl}_3$ ) 35.67 (C4-CH<sub>2</sub>), 37.62 (C4-C'H<sub>2</sub>), 52.50 (C2-C'H), 52.64 (C2-CH), 53.27 (C5-CH), 53.42 (C5-C'H), 61.39 (O-CH<sub>3</sub>), 61.60 (C3-C), 61.85 (C3-C'), 62.13 (O-C'H<sub>3</sub>), 64.43 (O-CH<sub>3</sub>), 65.75 (O-C'H<sub>3</sub>), 114.31 (Ar-C'H), 114.58 (Ar-CH), 115.17 (Ar-C'H), 115.39 (Ar-CH), 116.24 (CH<sub>2</sub>=CH), 116.76 (C'H<sub>2</sub>=CH), 128.76 (Ar-CH), 129.16 (Ar-CH), 129.21 (Ar-C'H), 129.29 (Ar-C'H), 136.35 (Ar-C'), 137.45 (Ar-C), 138.03 (CH<sub>2</sub>=CH), 138.41 (Ar-C'), 139.43 (CH<sub>2</sub>=C'H), 141.75 (Ar-C), 151.15 (Ar-C), 152.50 (Ar-C'), 161.01 (Ar-C'-F), 161.23 (Ar-C-F), 163.46 (Ar-C-F), 163.68 (Ar-C'-F), 167.72 (C'=O), 167.90 (C=O), 170.69 (C'=O), 170.76 (C=O);  $m/z$  (EI) 413 ( $\text{M}^+$ , 31%), 368 (20), 269 (27), 254 (46), 184 (47), 152 (50), 123 (76), 95 (28), 84 (90), 49 (100); Accurate mass for  $\text{C}_{23}\text{H}_{24}\text{NO}_5\text{F}$  – 413.1638, found – 413.1632.

***N*-(4-Methoxy-phenyl)-2-thiophen-3-yl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (88)**



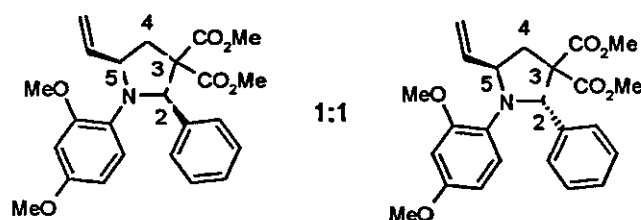
Prepared following the general thermal procedure for compound (81), *N*-(4-methoxy-phenyl)-2-thiophen-3-yl-5-vinyl pyrrolidine-3,3-dicarboxylic acid dimethyl ester (88) (0.120 g, 29%) was prepared as a yellow oil using *N*-(4-methoxy-phenyl)-(3-thiophene) imine (0.220 g, 1.00 mmol);  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2921m (CH str), 2353w (CH str), 1734s (C=O), 1612w, 1510m, 1432m, 1242s, 1038m, 930w, 816w, 704w;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 2.18 (1H, dd,  $J=5.8$  and 13.3, C4-CH(H)), 2.46 (1H, dd,  $J=5.8$  and 13.3, C4'-CH(H)), 2.69 (1H, dd,  $J=10.4$  and 13.3, C4'-CH(H')), 2.99 (1H, dd,  $J=10.4$  and 13.3, C4-CH(H')), 3.31 (3H, s, Ar-O-CH<sub>3</sub>), 3.44 (3H, s, Ar-O-CH<sub>3</sub>), 3.63 (3H, s, O-CH<sub>3</sub>), 3.55 (3H, s, O-CH<sub>3</sub>), 3.67 (3H, s, O-CH<sub>3</sub>), 3.74 (3H, s, O-CH<sub>3</sub>), 3.88 (1H, m, C5-N-CH), 4.31 (1H, m, C5'-N-CH), 4.95-5.17 (2H, m, CH=CH<sub>2</sub>), 5.33-5.29 (2H, m, CH=CH<sub>2</sub>), 5.51 (1H, s, C2-N-CH), 5.72 (1H, m, CH=CH<sub>2</sub>), 5.88 (1H, s, C2'-N-CH), 5.93 (1H, m, CH=CH<sub>2</sub>), 6.58-7.19 (14H, m, 4 x Ar-CH, 4 x Ar-CH', 3 x thiophene-CH, 3 x thiophene-CH');  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 39.37 (C4'-C(H)<sub>2</sub>), 39.68 (C4-CH<sub>2</sub>), 52.52 (C2'-C(H)), 52.90 (C2-CH), 53.12 (C5'-C(H)), 53.28 (C5-CH), 62.99 (Ar O-CH<sub>3</sub>), 64.47 (Ar O-C(H)<sub>3</sub>), 79.41 (O-C(H)<sub>3</sub>), 79.55 (O-CH<sub>3</sub>), 80.44 (O-CH<sub>3</sub>), 86.56 (O-C(H)<sub>3</sub>), 116.13 (CH<sub>2</sub>=CH), 117.82 (C(H)<sub>2</sub>=CH), 124.39 (Ar-C(H)), 124.88 (Ar-C(H)), 125.25 (Ar-CH), 123.34 (Ar-C(H)), 125.44 (Ar-C(H)), 125.46 (Ar-CH), 126.28 (Ar-CH), 126.41 (Ar-CH), 126.52 (Ar-C(H)), 126.58 (Ar-C(H)), 127.04 (Ar-C(H)), 128.31 (Ar-CH), 128.57 (Ar-CH), 128.96, (Ar-CH), 137.91 (CH<sub>2</sub>=CH), 139.48 (CH<sub>2</sub>=C(H)), 141.06 (Ar-C'), 141.38 (Ar-C'), 141.58 (Ar-C'), 167.43 (C=O), 168.67 (C=O), 170.41 (C=O), 170.69 (C=O);  $m/z$  (EI) 401 ( $\text{M}^+$ , 37%), 296 (67), 257 (41), 184 (40), 152 (72), 121 (73), 111 (100), 71 (37), 59 (63), Accurate mass for  $\text{C}_{21}\text{H}_{23}\text{NO}_5\text{S}$  - 401.1297, found - 401.1293.

***N*-(4-Methoxybenzene)-2-butyl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (89)**



Prepared following the general thermal procedure for compound (81), *N*-(4-methoxybenzene)-2-butyl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (89) (0.140 g, 34%) was prepared as a yellow-brown oil using *N*-(4-methoxybenzene)-propane imine (0.190 g, 1.00 mmol) for 48 hours;  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2953m, 2872w (CH str), 1736s (C=O), 1509s, 1239s, 1180m, 1038m, 811m, 788w;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 0.77 (3H, t,  $J=5.2$ ,  $\text{CH}_3$ ), 1.18-1.38 (6H, m,  $3 \times \text{CH}_2$ ), 2.65 (1H, dd,  $J=9.0$  and  $13.5$ , C4-CH(H)), 2.71 (1H, dd,  $J=9.0$  and  $11.0$ , C4-CH(H)), 3.63 (3H, s, Ar-OCH<sub>3</sub>), 3.73 (3H, s, O-CH<sub>3</sub>), 3.75 (3H, s, O-CH<sub>3</sub>), 3.87 (1H, m, C5-CH), 4.55 (1H, m, C2-CH), 5.22 (2H, m, vinyl CH=CH<sub>2</sub>), 5.82 (1H, m, vinyl CH=CH<sub>2</sub>), 6.65 (2H, d,  $J=8.0$ ,  $2 \times$  Ar-CH), 6.79 (2H, d,  $J=8.0$ ,  $2 \times$  Ar-CH);  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 13.97 ( $\text{CH}_3$ ), 23.11 ( $\text{CH}_2$ ), 28.62 ( $\text{CH}_2$ ), 33.39 ( $\text{CH}_2$ ), 38.27 (C4-CH<sub>2</sub>), 52.69, 52.90 (O-CH<sub>3</sub>), 55.69 (O-CH<sub>3</sub>), 60.79 (C2-CH), 62.5 (C3-C), 64.01 (C5-CH), 114.22 (Ar-CH), 114.80 (Ar-CH), 116.41 (CH=CH<sub>2</sub>), 140.49 (CH=CH<sub>2</sub>), 142.74 (Ar-C), 151.34 (Ar-C), 168.83 (C=O), 170.64 (C=O);  $m/z$  (EI) 375 ( $\text{M}^+$ , 32%), 344 (4), 318 (100), 259 (5), 200 (10), 145 (26), 134 (12), 108 (10), 85 (11), 69 (10); Accurate mass for  $\text{C}_{21}\text{H}_{29}\text{NO}_5$  – 375.2046, found – 375.2051.

***N*-(2,4-Dimethoxy-phenyl)-2-phenyl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (91)**

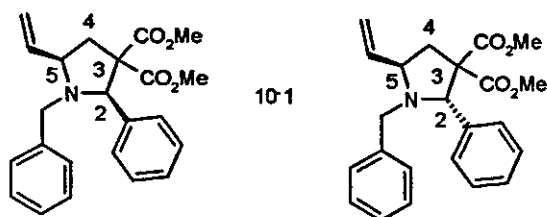


Prepared following the general thermal procedure for compound (81), *N*-(2,4-dimethoxy-phenyl)-2-phenyl-5-vinyl pyrrolidine-3,3-dicarboxylic acid dimethyl ester (91) (0.310 g, 72%) was prepared as a yellow oil using *N*-(2,4-dimethoxy-phenyl)-phenyl imine (0.240 g, 1.00 mmol) for 48 hours;  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2997m, 2950s (CH str), 1733s (C=O), 1582m, 1507s, 1436s, 1236m, 1158s, 1031s, 915s, 831m, 701m;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 2.16 (1H, dd,  $J=5.9$  and  $13.0$ , C4'-CH(H)), 2.41 (1H, dd,  $J=5.9$  and  $13.0$ , C4-CH(H)), 2.72 (1H, dd,  $J=10.8$  and  $13.1$ , C4-CH(H)), 3.03 (3H, s, O-CH<sub>3</sub>), 3.07 (1H, dd,  $J=10.8$  and  $13.1$ , C4'-CH(H')), 3.44 (3H, s, O-CH<sub>3</sub>), 3.52 (3H, s, O-CH<sub>3</sub>'), 3.57 (3H, s, O-CH<sub>3</sub>), 3.67 (3H, s, O-CH<sub>3</sub>'), 3.67 (3H, s, O-CH<sub>3</sub>'), 3.68 (3H, s, O-CH<sub>3</sub>), 3.70 (3H, s, O-CH<sub>3</sub>'), 3.70-4.10 (2H, m, C5-CH, C5'-CH'), 4.87-4.96 (2H, m, CH<sub>2</sub>=CH, CH'<sub>2</sub>=CH), 5.39 (2H, s, C2-CH, C2'-CH'), 5.45-5.60 (2H, m, CH<sub>2</sub>=CH, CH<sub>2</sub>=CH'), 5.83-5.86 (2H, m, 2 x Ar-CH'), 6.14-6.17 (2H, m, 2 x Ar-CH), 6.58 (1H, d,  $J=8.6$ , Ar-CH'), 6.86 (1H, d,  $J=8.6$ , Ar-CH), 7.01-7.17 (10H, m, 5 x Ar-CH', 5 x Ar-CH);  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 38.91 (C4-CH<sub>2</sub>), 38.95 (C4'-CH<sub>2</sub>), 52.38 (C2-CH), 52.47 (C2'-CH), 53.19 (C5-CH), 53.28 (C5'-CH), 62.47 (O-CH<sub>3</sub>), 64.27 (O-CH<sub>3</sub>'), 64.83 (C3-C), 65.23 (C3'-C'), 68.08 (O-CH<sub>3</sub>), 71.69 (O-CH<sub>3</sub>'), 100.07 (Ar O-CH<sub>3</sub>), 100.24 (Ar O-CH<sub>3</sub>'), 103.70 (Ar O-CH<sub>3</sub>), 104.06 (Ar O-CH<sub>3</sub>'), 116.48 (CH<sub>2</sub>=CH), 116.90 (CH<sub>2</sub>=CH'), 127.34 (Ar-CH), 127.51 (Ar-CH), 127.62 (Ar-CH'), 127.71 (Ar-CH), 127.99 (Ar-CH), 128.57 (Ar-CH'), 128.72 (Ar-CH), 128.90 (Ar-CH'), 128.99 (Ar-CH), 129.19 (Ar-CH'), 139.60 (Ar-C), 139.89 (CH<sub>2</sub>=CH), 140.04 (CH<sub>2</sub>=CH'), 141.29 (Ar-C'), 153.48 (C-OMe), 155.21 (C'-OMe), 157.88 (C-OMe), 158.05 (C'-OMe), 169.63 (C=O), 170.05 (C'=O), 172.12 (C=O), 172.14 (C'=O);  $m/z$  (EI) 425 ( $\text{M}^+$ , 100%),

366 (18), 281 (78), 241 (15), 205 (32), 164 (12), 105 (12), 84 (58); Accurate mass for  $C_{24}H_{28}NO_6$  – 426.1916, found – 426.1911.

### Section 3.04 – Pyrrolidines Derived from *N*-Benzyl Imines

#### *N*-Benzyl-2-phenyl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (92)



#### Thermal Procedure

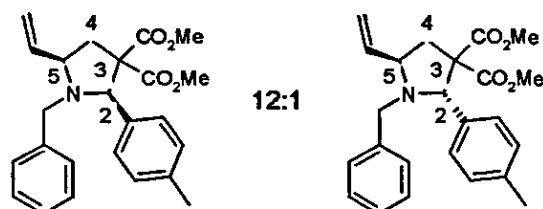
Prepared following the general thermal procedure for compound (81), *N*-benzyl-2-phenyl-5-vinyl pyrrolidine-3,3-dicarboxylic acid dimethyl ester (92) (0.350 g, 93%) was prepared as a yellow-brown oil using *N*-benzyl-phenyl imine (0.200 g, 1.00 mmol) for 48 hours;  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2951s, 2841s (CH str), 1736s (C=O), 1602m, 1585m, 1362m, 1330m, 1229s, 1064s, 1028s, 993m, 957m, 921s, 810m, 757s, 700s, 626w;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 2.13 (1H, dd,  $J=6.4$  and 13.2, C4-C(H)H), 2.21 (1H, dd,  $J=6.4$  and 13.2, C4'-C'(H)H), 2.52 (1H, dd,  $J=10.4$  and 13.2, C4-C(H)H), 2.72 (1H, dd,  $J=10.4$  and 13.2, C4'-C'(H)H), 3.05 (3H, s, O-C'H<sub>3</sub>), 3.06 (3H, s, O-CH<sub>3</sub>), 3.28 (2H, m, Ar-C'H<sub>2</sub>), 3.66 (3H, s, O-CH<sub>3</sub>), 3.69 (3H, s, O-C'H<sub>3</sub>), 3.77 (1H, m, C5'-N-C'H), 4.15 (2H, m, Ar-CH<sub>2</sub>), 4.47 (1H, m, C5-N-CH), 4.63 (1H, s, C2-N-CH), 4.95 (2H, m, CH<sub>2</sub>=CH), 5.12-5.29 (3H, m, C2'-N-C'H, C'H<sub>2</sub>=CH), 5.90 (1H, m, CH<sub>2</sub>=C'H), 6.12 (1H, m, CH<sub>2</sub>=CH), 7.05-7.38 (20H, m, 10 x Ar-CH, 10 x Ar-C'H);  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 38.34 (C4-CH<sub>2</sub>), 39.05 (C4'-C'H<sub>2</sub>), 51.15 (CH<sub>2</sub>), 51.93 (C5'-C'H), 52.12 (C5-CH), 52.76 (C2'-C'H), 52.86 (C2-CH), 53.88 (C'H<sub>2</sub>), 62.37 (C3'-C'), 64.06 (O-CH<sub>3</sub>), 64.35 (O-C'H<sub>3</sub>), 64.84 (C3-C), 69.61 (O-CH<sub>3</sub>), 70.41 (O-C'H<sub>3</sub>), 117.14 (C'H<sub>2</sub>=CH), 117.92 (CH<sub>2</sub>=CH), 126.59 (Ar-CH), 126.74 (Ar-C'H), 126.97 (Ar-C'H), 127.48 (Ar-C'H), 127.67 (Ar-CH), 127.70 (Ar-CH), 127.74 (Ar-C'H), 127.96 (Ar-CH), 128.03 (Ar-C'H), 128.37 (Ar-CH), 129.01 (Ar-C'H), 129.89 (Ar-CH), 136.53 (Ar-C'), 137.16 (CH<sub>2</sub>=CH), 138.16 (Ar-C), 139.40 (Ar-C), 139.47 (Ar-C'), 139.91 (CH<sub>2</sub>=C'H), 169.51 (C'=O), 169.70 (C=O), 171.99 (C'=O), 172.49 (C=O);  $m/z$  (EI) 379 ( $\text{M}^+$ , 13%), 320 (14), 288 (64), 159 (18), 144

(43), 104 (19), 91 (100), 65 (11); Accurate mass for  $C_{23}H_{25}NO_4$  – 379.1784, found – 379.1777.

*Microwave Procedure*

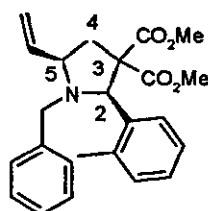
Prepared following the general microwave procedure for compound (85); *N*-benzyl-2-phenyl-5-vinyl pyrrolidine-3,3-dicarboxylic acid dimethyl ester (92) (0.320 g, 85%) was prepared as a yellow-brown oil using *N*-benzyl-phenyl imine (0.200 g, 1.00 mmol); Data as above.

***N*-Benzyl-2-*p*-tolyl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (93)**



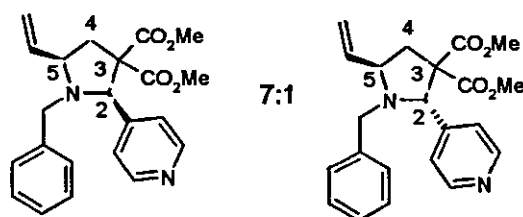
Prepared following the general thermal procedure for compound (81), *N*-benzyl-2-*p*-tolyl-5-vinyl pyrrolidine-3,3-dicarboxylic acid dimethyl ester (93) (0.230 g, 58%) was prepared as a yellow oil using *N*-benzyl-(*p*-tolyl) imine (0.210 g, 1.000 mmol) for 48 hours;  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  2951s, 2843m (CH str), 1735s (C=O), 1605m, 1331m, 1267s, 1200s, 1023m, 957m, 921m, 843m, 808m, 747m;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 2.11 (1H, dd,  $J=6.3$  and  $13.3$ , C4-CH(H)), 2.22 (3H, s, Ar-CH<sub>3</sub>), 2.62 (1H, dd,  $J=10.3$  and  $13.3$ , C4-CH(H')), 3.02 (3H, s, O-CH<sub>3</sub>), 3.12 (1H, m, C5-CH), 3.59 (3H, s, O-CH<sub>3</sub>), 3.69 (2H, s, benzyl CH<sub>2</sub>), 4.50 (1H, s, C2-CH), 5.03-5.18 (2H, m, CH=C-H<sub>2</sub>), 5.74 (1H, m, CH=CH<sub>2</sub>), 6.97-7.21 (9H, m, 9 x Ar CH);  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 21.16 (Ar-CH<sub>3</sub>), 38.24 (CH<sub>2</sub>), 38.99 (C'H<sub>2</sub>), 52.05 (C4-CH<sub>2</sub>), 51.99 (C5'-C'H), 52.18 (C5-CH), 52.73 (C2-CH), 52.87 (C2'-C'H), 53.46 (C4'-C'H<sub>2</sub>), 62.38 (O-CH<sub>3</sub>), 63.87 (C3'-C'), 64.07 (O-C'H<sub>3</sub>), 64.68 (C3-C), 69.30 (O-CH<sub>3</sub>), 70.02 (O-C'H<sub>3</sub>), 117.07 (C'H<sub>2</sub>=CH), 117.80 (CH<sub>2</sub>=CH), 116.33 (Ar-C'H), 125.98 (Ar-C'H), 126.74 (Ar-C'H), 127.68 (Ar-C'H), 128.02 (Ar-CH), 128.37 (Ar-C'H), 128.48 (Ar-CH), 128.67 (Ar-CH), 128.77 (Ar-CH), 129.95 (Ar-CH), 135.23 (Ar-C'), 136.16 (Ar-C), 138.37 (CH<sub>2</sub>=CH), 137.07 (Ar-C), 137.31 (Ar-C'), 137.41 (Ar-C'), 139.28 (Ar-C), 140.01 (CH<sub>2</sub>=C'H), 169.68 (C=O), 169.76 (C'=O), 172.02 (C=O), 172.51 (C'=O),  $m/z$  (EI) 393 ( $M^+$ , 16%), 334 (13), 302 (62), 249 (10), 208 (10), 158 (57), 118 (15), 91 (100), 43 (13); Accurate mass for  $\text{C}_{24}\text{H}_{27}\text{NO}_4$  – 393.1940, found – 393.1939

***N*-Benzyl-2-*o*-tolyl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (95)**



Prepared following the general thermal procedure for compound (81), *N*-benzyl-2-*o*-tolyl-5-vinyl pyrrolidine-3,3-dicarboxylic acid dimethyl ester (95) (0.230 g, 59%) was prepared as a yellow oil using *N*-benzyl-(2-tolyl) imine (0.210 g, 1.00 mmol) for 24 hours;  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  3027s, 2811s (CH str), 1737s (C=O), 1603m, 1330m, 1265s, 1228s, 1065s, 1009m, 992m, 955m, 912s, 755s, 726s, 700s;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 1.17 (Ar-CH<sub>3</sub>), 2.17 (1H, m, C4-CH(H)), 2.73 (1H, m, C4-CH(H)), 2.89 (3H, s, CH<sub>3</sub>-O), 3.62 (3H, s, CH<sub>3</sub>-O), 4.14-4.42 (2H, m, C2-CH, C5-CH), 5.20-5.25 (2H, m, CH<sub>2</sub>=CH), 5.72-5.91 (1H, m, CH<sub>2</sub>=CH), 6.82-7.05 (9H, m, 9 x Ar-H),  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 19.93 (Ar-CH<sub>3</sub>), 40.32 (C4-CH<sub>2</sub>), 52.09 (O-CH<sub>3</sub>), 53.30 (O-CH<sub>3</sub>), 55.18 (CH<sub>2</sub>), 64.36 (C3-C), 65.17 (C5-CH), 66.24 (C2-CH), 117.75 (CH<sub>2</sub>=CH), 125.94 (Ar CH), 127.32 (Ar CH), 127.64 (Ar CH), 128.05 (Ar CH), 129.24 (Ar CH), 130.06 (Ar CH), 130.30 (Ar CH), 137.39 (Ar C), 137.51 (Ar C), 138.66 (Ar C), 140.17 (CH<sub>2</sub>=CH), 169.61 (C=O), 172.55 (C=O);  $m/z$  (EI) 393 ( $\text{M}^+$ , 12%), 334 (18), 302 (48), 208 (9), 158 (49), 118 (12), 91 (100), 65 (10); Accurate mass for  $\text{C}_{24}\text{H}_{27}\text{NO}_4$  – 393.1940, found – 393.1932.

***N*-Benzyl-2-pyridin-4-yl-5-vinylpyrrolidine-3,3-dicarboxylic acid dimethyl ester (96)**



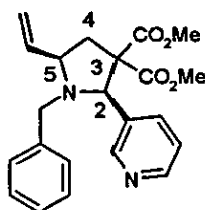
***Thermal Procedure***

Prepared following the general thermal procedure for compound (81), *N*-benzyl-2-pyridin-4-yl-5-vinyl pyrrolidine-3,3-dicarboxylic acid dimethyl ester-5-vinyl pyrrolidine (96) (0.220 g, 57%) was prepared as a yellow oil using *N*-benzyl-(pyridin-4-yl) imine (0.200 g, 1.00 mmol) for 48 hours;  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  2950m (CH str), 1734s (C=O), 1657m, 1602w, 1560w, 1264s, 1227m, 1201m, 1064m, 1027m, 921w, 807w, 750m, 699m;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 1.91 (1H, dd,  $J=6.2$  and  $12.0$ , C4-C(H)H), 2.14 (1H, dd,  $J=6.2$  and  $12.0$ , C4'-C'(H)H), 2.45 (1H, dd,  $J=8.0$  and  $12.0$ , C4-C(H)H), 2.64 (1H, dd,  $J=8.0$  and  $12.0$ , C4'-C'(H)H), 2.98 (3H, s, O-C'H<sub>3</sub>), 3.00 (3H, s, O-CH<sub>3</sub>), 3.20-3.30 (2H, m, Ar-C'H<sub>2</sub>), 3.59 (3H, s, O-CH<sub>3</sub>), 3.62 (3H, s, O-C'H<sub>3</sub>), 3.70 (1H, m, C5'-N-C'H), 3.96-3.90 (2H, m, CH<sub>2</sub>), 4.41 (1H, m, C5-N-CH), 4.56 (1H, s, C2'-N-C'H), 4.92-4.98 (2H, m, CH<sub>2</sub>=CH), 5.06-5.22 (3H, m, C2-N-C'H, C'H<sub>2</sub>=CH), 5.73 (1H, m, CH<sub>2</sub>=C'H), 6.03 (1H, m, CH<sub>2</sub>=CH), 6.99-7.34 (18H, m, 9 x Ar-CH, 9 x Ar-C'H);  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 38.02 (C4'-C'H<sub>2</sub>), 39.10 (C4-CH<sub>2</sub>), 50.91 (C5'-C'H), 51.14 (C5-CH), 51.74 (C2-CH), 51.95 (C2'-C'H), 52.40 (CH<sub>2</sub>), 52.84 (C'H<sub>2</sub>), 62.13 (C3-C), 63.03 (C3'-C'), 63.31 (O-C'H<sub>3</sub>), 65.42 (O-CH<sub>3</sub>), 68.92 (O-C'H<sub>3</sub>), 69.38 (O-CH<sub>3</sub>), 116.12 (CH<sub>2</sub>=CH), 116.66 (C'H<sub>2</sub>=CH), 125.95 (Ar-C'H), 126.64 (Ar-CH), 126.68 (Ar-CH), 126.79 (Ar-CH), 126.85 (Ar-C'H), 126.94 (Ar-C'H), 127.01 (Ar-CH), 127.07 (Ar-C'H), 127.84 (Ar-CH), 128.35 (Ar-C'H), 135.49 (Ar-C'), 138.44 (CH<sub>2</sub>=C'H), 138.88 (CH<sub>2</sub>=CH), 141.93 (Ar-C'), 168.49 (C'=O), 169.81 (C=O), 170.12 (C=O), 170.97 (C'=O);  $m/z$  (EI) 379 ( $\text{M}^+ - \text{H}$ , 9%), 320 (10), 288 (46), 236 (13), 159 (16), 144 (33), 121 (24), 105 (28), 91 (100), 77 (19), Accurate mass for  $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_4$  - 379.1657, found - 379.1657.

***Microwave Procedure***

Prepared following the general microwave procedure for compound (85), *N*-benzyl-2-pyridin-4-yl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (96) (0.380 g, 86%) was prepared as a yellow oil using *N*-benzyl-(4-pyridine) imine (0.200 g, 1.00 mmol); Data as above.

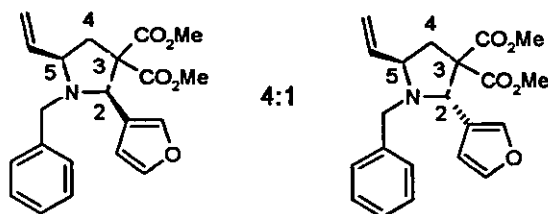
***N*-Benzyl-2-pyridin-3-yl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (97)**



***Microwave Procedure***

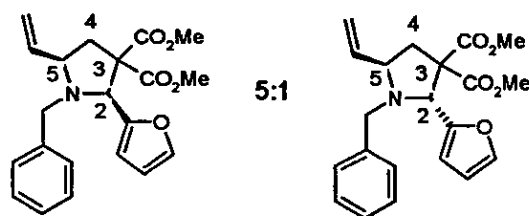
Prepared following the general microwave procedure for compound (85), *N*-benzyl-2-pyridin-3-yl)-5-vinyl pyrrolidine-3,3-dicarboxylic acid dimethyl ester (97) (0.310 g, 82%) was prepared as a yellow-brown oil using *N*-benzyl-(pyridin-3-yl) imine (0.200 g, 1.00 mmol);  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  3027w, 2951m (CH str), 2842w, 1731s (C=O), 1434s, 1199s, 1136m, 1067m, 1026m, 913m, 732m, 700m, 646w;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 2.22 (1H, dd,  $J=5.6$  and  $13.2$ , C4-CH(H)), 2.62 (1H, dd,  $J=10.8$  and  $13.2$ , C4-CH(H)), 3.04 (2H, s, Ar-CH<sub>2</sub>-N), 3.16 (1H, m, C5-N-CH), 3.67 (3H, s, O-CH<sub>3</sub>), 3.68 (3H, s, O-CH<sub>3</sub>), 4.60 (1H, s, C2-N-CH), 5.13-5.27 (2H, m, CH<sub>2</sub>=CH), 5.27 (1H, m, CH<sub>2</sub>=CH), 6.93-7.04 (5H, m, 5 x Ar-CH), 7.19 (1H, s, Ar-CH pyridine), 7.57 (1H, m, Ar-CH pyridine), 8.31 (2H, m, 2 x Ar-CH pyridine);  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 25.98 (C4-CH<sub>2</sub>), 52.51 (C5-CH-vinyl), 53.43 (C2-CH-Ar), 65.34 (O-CH<sub>3</sub>), 68.33 (N-CH<sub>2</sub>), 68.77 (O-CH<sub>3</sub>), 118.12 (CH<sub>2</sub>=CH), 127.22 (Ar-CH), 128.18 (Ar-CH), 130.09 (Ar-CH), 132.42 (Ar-CH pyridine), 136.67 (Ar-C), 137.00 (Ar-CH pyridine), 139.71 (CH<sub>2</sub>=CH), 148.83 (Ar-CH=N), 150.62 (Ar-CH=N), 169.26 (C=O), 171.94 (C=O);  $m/z$  (EI) 379 ( $\text{M}^+ - \text{H}$ , 6%), 321 (24), 289 (82), 229 (7), 159 (17), 145 (39), 105 (19), 91 (100); Accurate mass for  $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_4$  – 379.1657, found – 379.1666.

***N*-Benzyl-2-furan-3-yl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (99)**



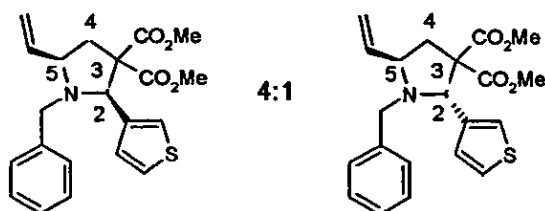
Prepared following the general thermal procedure for compound (81), *N*-benzyl-2-furan-3-yl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (99) (0.250 g, 69%) was prepared as a yellow oil using *N*-benzyl 3-furan-3-yl imine (0.190 g, 1.00 mmol) for 24 hours;  $\nu_{\max}$ (film)/cm<sup>-1</sup> 2928s (CH str), 2861m, 1740s (C=O), 1642m, 1478m, 1260m, 1142m, 1063m, 999m, 952w, 901w, 829w, 781w;  $\delta_{\text{H}}$  (250 MHz; CDCl<sub>3</sub>) 2.13 (1H, dd, *J*=6.4 and 13.2, C4-CH(H)), 2.45 (1H, dd, *J*=6.4 and 13.2, C4'-CH(H)), 2.61 (1H, dd, *J*=10.4 and 13.2, C4'-CH(H')), 2.92 (1H, dd, *J*=10.4 and 13.2, C4-CH(H)), 3.35 (2H, s, Ar-CH<sub>2</sub>'), 3.38 (2H, s, Ar-CH<sub>2</sub>), 3.70 (3H, s, O-CH<sub>3</sub>), 3.74 (3H, s, O-CH<sub>3</sub>'), 3.75 (3H, s, O-CH<sub>3</sub>'), 3.83 (3H, s, O-CH<sub>3</sub>), 4.29 (1H, m, C5'-N-CH'), 4.88 (1H, m, C5-N-CH), 5.00-5.19 (4H, m, CH=CH<sub>2</sub>, CH=CH<sub>2</sub>), 5.50 (1H, s, C2'-N-CH'), 5.57 (1H, s, C2-N-CH), 5.78 (1H, m, CH=CH<sub>2</sub>), 5.95 (1H, m, CH'=CH<sub>2</sub>), 6.28-6.39 (4H, m, 2 x Ar-CH-O, 2 x Ar-CH'-O), 7.19-7.68 (12H, m, 6 x Ar-CH, 6 x Ar-CH');  $\delta_{\text{C}}$  (101 MHz; CDCl<sub>3</sub>) 39.84 (C4'-C'H<sub>2</sub>), 39.93 (C4-CH<sub>2</sub>), 49.94 (CH<sub>2</sub>), 52.40 (C5'-C'H), 52.53 (C5-CH), 52.80 (C2-CH), 52.97 (C2'-C'H), 53.17 (CH<sub>2</sub>'), 65.19 (C3'-C'), 65.28 (C3-C), 77.61 (O-CH<sub>3</sub>), 78.04 (O-C'H<sub>3</sub>), 79.14 (O-C'H<sub>3</sub>), 79.28 (O-CH<sub>3</sub>), 108.77 (furan CH), 108.77 (furan CH), 109.14 (furan C'H), 109.24 (furan C'H), 116.02 (C'H<sub>2</sub>=CH), 117.58 (CH<sub>2</sub>=CH), 122.75 (Ar-C'), 122.81 (Ar-C), 123.23 (Ar-C'H), 125.63 (Ar-C'H), 125.76 (Ar-C'H), 126.70 (Ar-C'H), 127.23 (Ar-C'H), 128.72 (Ar-C'H), 133.38 (Ar-CH), 136.65 (Ar-CH), 138.09 (Ar-CH), 140.51 (Ar-CH), 140.75 (CH<sub>2</sub>=C'H), 142.71 (CH<sub>2</sub>=CH), 144.57 (Ar-C), 146.87 (Ar-C'), 169.07 (C'=O), 169.17 (C=O), 170.16 (C=O), 170.86 (C'=O); *m/z* (EI) 369 (M<sup>+</sup>, 23%), 310 (12), 278 (62), 225 (19), 184 (10), 159 (13), 134 (49), 91 (100), 65 (14); Accurate mass for - C<sub>21</sub>H<sub>23</sub>NO<sub>5</sub> - 369.1576, found - 369.1571.

***N*-Benzyl-2-furan-2-yl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (100)**



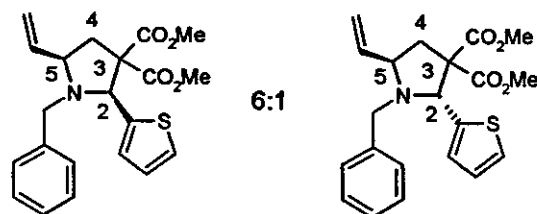
Prepared following the general thermal procedure for compound (81), *N*-benzyl-2-furan-2-yl-5-vinyl pyrrolidine-3,3-dicarboxylic acid dimethyl ester (100) (0.110 g, 30%) was prepared as a yellow oil using *N*-benzyl furan-2-yl imine (0.190 g, 1.00 mmol) for 48 hours;  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2951w (CH str), 1735s (C=O), 1455m, 1433m, 1265m, 1205m, 1144m, 1064m, 1010m, 923w, 884w, 764w, 698w;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 2.15 (1H, dd,  $J=6.1$  and  $13.2$ , C4'-CH(H)), 2.35 (1H, dd,  $J=10.5$  and  $13.2$ , C4'-CH(H)), 2.66 (1H, dd,  $J=6.1$  and  $13.2$ , C4-CH(H)), 3.11 (2H, s, CH<sub>2</sub>), 3.21 (1H, dd,  $J=10.5$  and  $13.2$ , C4-CH(H)), 3.31 (3H, s, O-CH<sub>3</sub>), 3.31 (3H, s, O-CH<sub>3</sub>), 3.32 (3H, s, O-CH<sub>3</sub>), 3.60 (1H, m, C5'-N-CH), 3.62 (3H, s, O-CH<sub>3</sub>), 3.69 (3H, s, O-CH<sub>3</sub>), 3.73 (1H, m, C5-N-CH), 4.62 (1H, s, C2-N-CH), 4.79 (1H, s, C2'-N-CH), 5.00-5.19 (2H, m, CH=CH<sub>2</sub>), 5.66 (1H, m, CH=CH<sub>2</sub>), 5.76 (1H, m, CH=CH<sub>2</sub>), 6.13-6.21 (2H, m, CH=CH<sub>2</sub>), 7.06-7.30 (16H, m, 8 x Ar-CH, 8 x Ar-CH);  $\delta_{\text{C}}$  (101 MHz,  $\text{CDCl}_3$ ) 37.26 (C4'-C(H<sub>2</sub>)), 38.60 (C4-CH<sub>2</sub>), 51.38 (C(H<sub>2</sub>)), 52.58 (C5'-C(H)), 52.63 (C5-CH), 52.93 (C2-CH), 52.96 (C2'-C(H)), 54.55 (CH<sub>2</sub>), 62.09 (O-C(H<sub>3</sub>)), 62.53 (C3'-C), 62.84 (O-CH<sub>3</sub>), 64.22 (O-C(H<sub>3</sub>)), 64.47 (O-CH<sub>3</sub>), 108.95 (furan CH), 109.87 (furan C(H)), 110.21 (furan C(H)), 110.50 (furan CH), 116.72 (C(H<sub>2</sub>)=CH), 117.39 (CH<sub>2</sub>=CH), 126.70 (Ar-C(H)), 126.79 (Ar-C(H)), 127.78 (Ar-CH), 128.02 (Ar-C(H)), 128.25 (Ar-CH), 129.60 (Ar-CH), 139.35 (Ar-C), 139.72 (Ar-C), 140.18 (furan CH), 140.50 (furan C(H)), 141.93 (CH<sub>2</sub>=C(H)), 142.48 (CH<sub>2</sub>=CH), 151.65 (Ar-C), 153.11 (Ar-C), 168.66 (C=O), 169.17 (C=O), 170.97 (C=O), 171.43 (C=O),  $m/z$  (EI) 369 ( $\text{M}^+$ , 20%), 310 (10), 278 (78), 225 (18), 134 (72), 94 (11), 91 (100), 59 (6), Accurate mass for  $\text{C}_{21}\text{H}_{23}\text{NO}_5$  - 369.1576, found - 369.1580.

***N*-Benzyl-2-thiophen-3-yl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (101)**



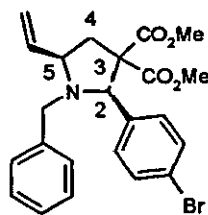
Prepared following the general thermal procedure for compound (81), *N*-benzyl-2-thiophen-3-yl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (101) (0.240 g, 62%) was prepared as a brown oil using *N*-benzyl thiophen-3-yl imine (0.200 g, 1.00 mmol) for 48 hours;  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2949m (CH str), 2358w, 1732s (C=O), 1433m, 1266s, 1200m, 1166m, 1076m, 991w, 955w, 923w, 690m;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 2.14 (1H, dd,  $J=6.4$  and  $13.3$ , C4-CH'(H)), 2.19 (1H, dd,  $J=6.4$  and  $13.3$ , C4-CH(H)), 2.42 (1H, dd,  $J=10.5$  and  $13.3$ , C4-CH(H)), 2.64 (1H, dd,  $J=10.5$  and  $13.3$ , C4-CH(H')), 3.13 (3H, s, O-CH<sub>3</sub>'), 3.18 (3H, s, O-CH<sub>3</sub>), 3.62 (3H, s, O-CH<sub>3</sub>'), 3.68 (3H, s, O-CH<sub>3</sub>), 3.69 (2H, s, benzyl CH<sub>2</sub>'), 3.70 (2H, s, benzyl CH<sub>2</sub>), 3.73 (1H, m, C5-CH'), 3.82 (1H, m, C5-CH), 4.60 (1H, s, C2-CH'), 4.96 (1H, s, C2-CH), 5.03-5.06 (2H, m, CH=CH<sub>2</sub>'), 5.29-5.38 (2H, m, CH=CH<sub>2</sub>), 5.76 (1H, m, CH'=CH<sub>2</sub>), 6.00 (1H, m, CH=CH<sub>2</sub>), 6.95-7.17 (16H, m, 8 x Ar CH', 8 x Ar CH);  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 37.79 (C4-CH<sub>2</sub>), 38.78 (C4'-CH<sub>2</sub>), 51.11 (CH<sub>2</sub>), 52.21 (C'H), 52.40 (C5-CH), 52.76 (C5'-CH), 52.90 (C2-CH), 54.14 (C2'-CH<sub>2</sub>), 62.99 (C3-C), 63.47 (O-CH<sub>3</sub>), 63.90 (O-CH<sub>3</sub>), 64.48 (C3'-C'), 64.80 (O-C'H<sub>3</sub>), 66.51 (O-C'H<sub>3</sub>), 117.13 (C'H<sub>2</sub>=CH), 117.48 (CH<sub>2</sub>=CH), 123.48 (Ar-C'H), 124.11 (Ar-C'H), 124.45 (Ar-C'H), 124.93 (Ar-C'H), 126.43 (Ar-CH), 126.76 (Ar-C'H), 127.70 (Ar-CH), 127.99 (Ar-C'H), 129.06 (Ar-CH), 128.10 (Ar-C'H), 129.28 (Ar-CH), 129.78 (Ar-CH), 136.68 (Ar-C'), 138.48 (Ar-C), 138.52 (CH<sub>2</sub>=C'H), 139.24 (Ar-C'), 139.88 (CH<sub>2</sub>=CH), 141.03 (Ar-C'), 169.47 (C'=O), 169.64 (C'=O), 171.89 (C=O);  $m/z$  (EI) 385 ( $M^+$ , 13%), 326 (7), 294 (28), 150 (31), 110 (9), 91 (100), 65 (16), 59 (9); Accurate mass for  $\text{C}_{21}\text{H}_{23}\text{NO}_4\text{S}$  – 385.1347, found – 385.1344.

***N*-Benzyl-2-thiophen-2-yl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (102)**



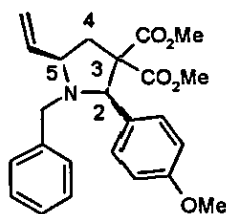
Prepared following the general thermal procedure for compound (81), *N*-benzyl-2-thiophen-2-yl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (102) (0.130 g, 34%) was prepared as a brown oil using *N*-benzyl thiophen-2-yl imine (0.200 g, 1.00 mmol) for 48 hours;  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2949w (CH str), 2355w, 1733s (C=O), 1433m, 1265m, 1231m, 1197m, 1136m, 1064m, 923m, 883m, 698m, 667m;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 2.16 (1H, dd,  $J=5.9$  and 13.2, C4-CH(H)), 2.31 (1H, dd, 10.9 and 13.2, C4-CH(H)), 2.64 (1H, dd,  $J=5.9$  and 13.2, C4-CH(H')), 2.98 (1H, dd, 10.9 and 13.2, C4-CH(H')), 3.11 (1H, m, C5-CH'), 3.22 (3H, s, O-CH<sub>3</sub>), 3.24 (3H, s, O-CH<sub>3</sub>), 3.44 (1H, m, C5-CH), 3.63 (3H, s, O-CH<sub>3</sub>), 3.69 (3H, s, O-CH<sub>3</sub>), 3.71 (2H, s, CH<sub>2</sub>), 3.81 (2H, s, CH<sub>2</sub>), 4.91 (1H, s, C2-CH'), 5.01-5.16 (5H, m, C2-CH, CH=C-H', CH=CH<sub>2</sub>), 5.64-5.77 (2H, m, CH'=CH<sub>2</sub>, CH=CH<sub>2</sub>), 6.78-6.80 (6H, m, 3 x Ar CH' (thiophene), 3 x Ar CH (thiophene)), 7.12 (10H, m, 5 x Ar CH' (benzyl), 5 x Ar CH (benzyl)),  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 36.95 (CH<sub>2</sub>), 38.41 (C'H<sub>2</sub>), 50.97 (C4-CH<sub>2</sub>), 52.37 (C4'-C'H), 52.57 (C5'-CH), 52.97 (C5'-C'H), 53.05 (C2-CH), 54.72 (C2'-C'H<sub>2</sub>), 62.87 (O-CH<sub>3</sub>), 64.22 (C3'-C'), 64.29 (C3-C), 64.48 (O-C'H<sub>3</sub>), 64.67 (O-CH<sub>3</sub>), 65.70 (O-C'H<sub>3</sub>), 117.11 (C'H<sub>2</sub>=CH), 117.36 (CH<sub>2</sub>=CH), 125.07 (Ar-C'H), 125.44 (Ar-C'H), 125.48 (Ar-C'H), 126.27 (Ar-CH), 126.32 (Ar-CH), 126.73 (Ar-CH), 126.87 (Ar-C'H), 127.75 (Ar-C'H), 128.03 (Ar-CH), 128.38 (Ar-CH), 129.91 (Ar-CH), 136.83 (Ar-C'), 138.97 (Ar-C'), 139.10 (CH<sub>2</sub>=CH), 139.63 (CH<sub>2</sub>=C'H), 145.52 (Ar-C), 168.82 (C=O), 168.95 (C'=O), 171.41 (C=O), 171.61 (C'=O),  $m/z$  (EI) 385 ( $\text{M}^+$ , 35%), 326 (18), 294 (69), 241 (14), 159 (26), 150 (62), 110 (12), 91 (100), 65 (11); Accurate mass for  $\text{C}_{21}\text{H}_{23}\text{NO}_4\text{S}$  – 385.1347, found – 385.1353

***N*-Benzyl-2-(4-bromo-phenyl)-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (103)**



Prepared following the general thermal procedure for compound (81), *N*-benzyl-2-(4-bromo-benzene)-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (103) (0.310 g, 68%) was prepared as a yellow oil using *N*-benzyl-(4-bromo-phenyl) imine (0.290 g, 1.00 mmol) for 24 hours,  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2950s, 2842m (CH str), 1732s (C=O), 1201s, 1070s, 1010s, 922m, 845m, 739s, 700m;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 2.13 (1H, dd,  $J=6.3$  and  $13.3$ , C4-CH(CH)), 2.60 (1H, dd,  $J=10.6$  and  $13.3$ , C4-CH(CH)), 3.04 (2H s, benzyl CH<sub>2</sub>), 3.10-3.17 (1H, m, C5-CH), 3.62 (3H, s, O-CH<sub>3</sub>), 3.68 (3H, s, O-CH<sub>3</sub>), 4.49 (1H, m, C2-CH), 5.07-5.22 (2H, m, CH<sub>2</sub>=CH), 5.76 (1H, m, CH<sub>2</sub>=CH), 6.93-7.33 (7H, m, 7 x Ar-CH), 7.59-7.41 (2H, m, 4 x Ar-CH),  $\delta_{\text{C}}$  (101 MHz,  $\text{CDCl}_3$ ) 38.30 (C4-CH<sub>2</sub>), 38.87 (C4-C'H<sub>2</sub>), 51.15 (benzyl CH<sub>2</sub>), 52.08 (C5-C'H), 52.28 (C5-CH), 52.87 (C2-C'H), 52.95 (C2-CH), 54.05 (benzyl C'H<sub>2</sub>), 62.30 (O-CH<sub>3</sub>), 63.95 (C3-C), 64.39 (O-C'H<sub>3</sub>), 64.70 (C3-C'), 69.06 (O-CH<sub>3</sub>), 69.81 (O-C'H<sub>3</sub>), 117.44 (C'H<sub>2</sub>=CH), 118.22 (CH<sub>2</sub>=CH), 121.29 (C'-Br), 121.67 (C-Br), 126.73 (Ar-CH), 126.89 (Ar-C'H), 127.76 (Ar-CH), 128.31 (Ar-CH), 128.45 (Ar-C'H), 129.68 (Ar-C'H), 129.84 (Ar-C'H), 130.77 (Ar-CH), 130.98 (Ar-C'H), 131.10 (Ar-CH), 132.17 (Ar-C), 132.46 (Ar-C'), 136.30 (Ar-C), 136.78 (CH<sub>2</sub>=CH), 138.72 (Ar-C'), 139.62 (CH<sub>2</sub>=C'H), 169.25 (C'=O), 171.77 (C'=O);  $m/z$  (EI) 459 ( $\text{M}^+$ , 16%), 457 ( $\text{M}^+$ , 16%), 398 (15), 366 (81), 302 (22), 222 (47), 195 (41), 159 (64), 106 (42), 92 (100), 65 (32); Accurate mass for  $\text{C}_{23}\text{H}_{24}\text{NO}_4^{79}\text{Br}$  – 457.0888, found – 457.0890

***N*-Benzyl-2-(4-methoxy-phenyl)-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (104)**



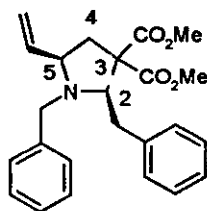
***Thermal Procedure***

Prepared following the general thermal procedure for compound (81), *N*-benzyl-2-(4-methoxy-phenyl)-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (104) (0.320 g, 79%) was prepared as a yellow-brown oil using *N*-benzyl-(4-methoxybenzene) imine (0.230 g, 1.00 mmol) for 48 hours;  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2950m, 2836w (CH str), 1731s (C=O), 1510s, 1432m, 1265s, 1199s, 1171s, 1033m, 923w, 845w, 745w, 701m,  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 2.12 (1H, dd,  $J=6.4$  and  $13.2$ , C4-CH(H)), 2.61 (1H, dd,  $J=9.0$  and  $13.2$ , C4-CH(H)), 3.04 (3H, s, Ar-O-CH<sub>3</sub>), 3.25 (2H, m, Ar-CH<sub>2</sub>-N), 3.55 (1H, m, C2-N-CH), 3.66 (3H, s, O-CH<sub>3</sub>), 3.72 (3H, s, O-CH<sub>3</sub>), 3.78 (1H, m, C5-N-CH), 5.04-5.19 (2H, m, CH<sub>2</sub>=CH), 5.78 (1H, m, CH<sub>2</sub>=CH), 6.74 (2H, d,  $J=8.8$ , 2 x Ar-CH), 6.98 (2H, d,  $J=8.0$ , 2 x Ar-CH), 7.08-7.25 (5H, m, 5 x Ar-CH);  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 39.31 (C4-CH<sub>2</sub>), 53.10 (C2-CH), 53.94 (Ar-CH<sub>2</sub>-N), 55.58 (C5-CH), 64.52 (O-CH<sub>3</sub>), 70.20 (O-CH<sub>3</sub>), 113.52 (Ar-O-CH<sub>3</sub>), 117.46 (CH<sub>2</sub>=CH), 127.11 (Ar-CH), 127.89 (Ar-CH), 128.40 (Ar-CH), 128.73 (Ar-CH), 130.32 (Ar-CH), 131.66 (Ar-C), 136.85 (Ar-C), 140.37 (CH<sub>2</sub>=CH), 159.36 (Ar-C-OMe), 170.07 (C=O), 172.42 (C=O);  $m/z$  (EI) 409 ( $\text{M}^+$ , 17%), 350 (16), 318 (53), 265 (21), 175 (100), 159 (41), 134 (19), 91 (80); Accurate mass for  $\text{C}_{24}\text{H}_{27}\text{NO}_5$  – 409.1889, found – 409.1892.

***Microwave Procedure***

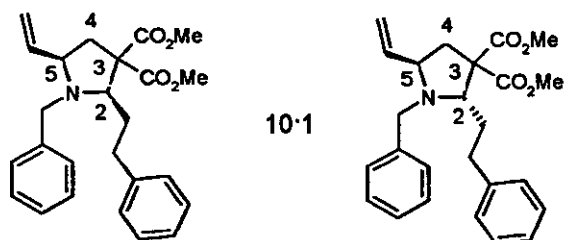
Prepared following the general microwave procedure for compound (85), *N*-benzyl-2-(4-methoxy-phenyl)-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (104) (0.360 g, 89%) was prepared as a yellow-brown oil using *N*-benzyl-(4-methoxy-phenyl) imine (0.230 g, 1.00 mmol); Data as above.

***N*,2-Dibenzyl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (105)**



Prepared following the general thermal procedure for compound (81), *N*,2-dibenzyl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (105) (0.270 g, 69%) was prepared as a yellow oil using *N*-benzyl-benzyl imine (0.210 g, 1.00 mmol) for 48 hours;  $\nu_{\text{max}}$ (film)/cm<sup>-1</sup> 2954m, 2852m (CH str), 1732s (C=O), 1667s, 1644m, 1335m, 1264s, 1229s, 1076w, 920m, 873w, 753m, 699s;  $\delta_{\text{H}}$ (250 MHz; CDCl<sub>3</sub>) 2.14 (1H, dd, *J*=6.4 and 13.2, C4'-C'(H)H), 2.67 (1H, dd, *J*=10.8 and 13.2, C4'-C'(H)H), 2.99 (2H, s, benzyl CH<sub>2</sub>), 3.61 (3H, s, CH<sub>3</sub>-O), 3.67 (3H, s, CH<sub>3</sub>-O), 3.69 (2H, m, CH<sub>2</sub>), 4.55 (1H, m, C2-CH), 4.92 (1H, m, C5-CH), 5.04-5.08 (2H, m, CH<sub>2</sub>=CH), 5.85 (1H, m, CH<sub>2</sub>=CH), 6.81-7.89 (10H, m, 10 x Ar-H);  $\delta_{\text{C}}$  (101 MHz; CDCl<sub>3</sub>) 31.87 (CH<sub>2</sub>), 39.43 (C4-CH<sub>2</sub>), 52.32 (O-CH<sub>3</sub>), 52.98 (O-CH<sub>3</sub>), 53.15 (C5-CH), 54.25 (N-Bn CH<sub>2</sub>), 64.43 (C2-CH), 64.72 (C3-C), 117.52 (CH<sub>2</sub>=CH), 127.84 (Ar CH), 128.54 (Ar CH), 128.75 (Ar CH), 129.25 (Ar CH), 129.36 (Ar CH), 136.90 (Ar C), 139.84 (Ar-C), 140.29 (CH<sub>2</sub>=CH), 169.89 (C=O), 172.37 (C=O); *m/z* (EI) 393 (M<sup>+</sup>, 1%), 379 (16), 320 (22), 288 (81), 236 (12), 207 (83), 144 (63), 105 (100), 77 (98), 51 (24), Accurate mass for C<sub>24</sub>H<sub>27</sub>NO<sub>4</sub> – 393.1940, found – 393.1949.

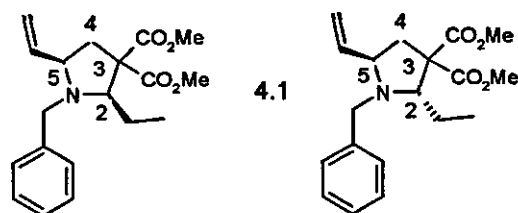
***N*-Benzyl-2-phenylethyl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (106)**



Prepared following the general thermal procedure for compound (81), *N*-benzyl-2-phenylethyl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (106) (0.180 g, 43%) was prepared as a brown oil using *N*-benzyl-(phenyl-ethyl) imine (0.220 g, 1.00 mmol) for 48 hours;  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2952m (CH str), 2361w, 1732s (C=O), 1651m, 1435s, 1267m, 1158m, 1096m, 1027w, 998w, 747m, 696s;  $\delta_{\text{H}}$  (250 MHz,  $\text{CDCl}_3$ ) 1.26-1.33 (2H, m, Ar-CH<sub>2</sub>-CH<sub>2</sub>), 1.34-1.39 (2H, m, Ar-CH<sub>2</sub>-CH<sub>2</sub>), 1.98 (1H, dd, *J*=6.5 and 13.1, C4-CH(H)), 2.12 (1H, dd, *J*=11.1 and 13.1, C4-CH(H)), 2.39 (1H, dd, *J*=6.5 and 13.1, C4-CH'(H)), 2.62 (2H, m, Ar-CH<sub>2</sub>-CH<sub>2</sub>), 2.79 (1H, m, C2-CH), 2.94 (1H, dd, *J*=11.1 and 13.1, C4-CH(H')), 3.47 (2H, s, benzyl CH<sub>2</sub>), 3.58 (2H, m, Ar-CH<sub>2</sub>-CH<sub>2</sub>), 3.60 (3H, s, O-CH<sub>3</sub>), 3.63 (2H, s, benzyl CH<sub>2</sub>), 3.66 (3H, s, O-CH<sub>3</sub>), 3.68 (1H, m, C2-CH'), 3.75 (3H, s, O-CH<sub>3</sub>), 3.78 (3H, s, O-CH<sub>3</sub>), 4.00 (1H, m, C5-CH'), 4.29 (1H, m, C5-N-CH), 4.92-5.07 (2H, m, CH=CH<sub>2</sub>), 5.09-5.25 (2H, m, CH=CH<sub>2</sub>), 5.62 (1H, m, CH'=CH<sub>2</sub>), 5.75 (1H, m, CH=CH<sub>2</sub>), 7.01-7.22 (20H, m, 10 x Ar CH', 10 x Ar CH);  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 29.68 (Ar-CH<sub>2</sub>-CH<sub>2</sub>), 31.07 (Ar-CH<sub>2</sub>-CH<sub>2</sub>), 32.05 (Ar-CH<sub>2</sub>-C'H<sub>2</sub>), 34.46 (C4-CH<sub>2</sub>), 36.09 (Ar-C'H<sub>2</sub>-CH<sub>2</sub>), 39.27 (C4-C'H<sub>2</sub>), 50.85 (benzyl CH<sub>2</sub>), 52.52 (C5-C'H), 52.73 (C5-CH), 52.75 (C2-CH), 53.02 (C2-C'H), 58.05 (benzyl C'H<sub>2</sub>), 62.78 (O-CH<sub>3</sub>), 63.13 (C3-C'), 64.03 (O-CH<sub>3</sub>), 66.27 (O-C'H<sub>3</sub>), 66.51 (O-C'H<sub>3</sub>), 116.23 (C'H<sub>2</sub>=CH), 117.42 (CH<sub>2</sub>=CH), 125.92 (Ar-CH), 126.43 (Ar-CH), 127.00 (Ar-CH), 128.12 (Ar-CH), 128.26 (Ar-C'H), 128.36 (Ar-C'H), 128.45 (Ar-C'H), 128.50 (Ar-CH), 128.64 (Ar-C'H), 128.90 (Ar-C'H), 129.21 (Ar-C'H), 129.25 (Ar-CH), 137.54 (Ar-C), 139.11 (Ar-C), 139.88 (Ar-C'), 140.53 (CH<sub>2</sub>=C'H), 142.21 (CH<sub>2</sub>=CH), 142.69 (Ar-C'), 169.83 (C=O), 170.17 (C=O), 172.12 (C=O), 172.13 (C=O), *m/z* (EI) 407

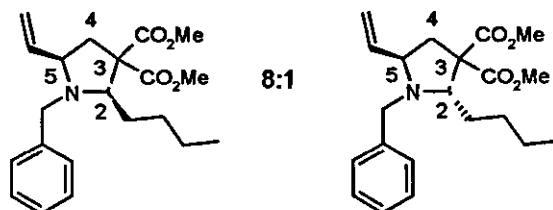
(M<sup>+</sup>, 2%), 344 (10), 302 (61), 200 (38), 168 (84), 153 (99), 121 (86), 91 (100), 71 (73), 59 (53); Accurate mass for – C<sub>25</sub>H<sub>29</sub>NO<sub>4</sub> – 407.2096, found – 407.2106

***N*-Benzyl-2-ethyl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (107)**



Prepared following the general thermal procedure for compound (81), *N*-benzyl-2-ethyl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (107) (0.180 g, 53%) was prepared as a yellow oil using *N*-benzyl-ethyl imine (0.150 g, 1.00 mmol) for 48 hours;  $\nu_{\text{max}}$ (film)/ $\text{cm}^{-1}$  2951m, 2840w (CH str), 1734s (C=O), 1433m, 1262s, 1196m, 1136m, 1070m, 990w, 955w, 920w, 748w;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 0.62 (3H, t,  $J=7.4$ ,  $\text{CH}_2\text{-CH}_3$ ), 0.72 (3H, t,  $J=7.4$ ,  $\text{CH}_2\text{-CH}_3$ ), 1.05 (1H, m,  $\text{CH}'(\text{H})\text{-CH}_3$ ), 1.17 (1H, m,  $\text{CH}'(\text{H})\text{-CH}_3$ ), 1.50 (1H, m,  $\text{CH}(\text{H})\text{-CH}_3$ ), 1.75 (1H, m,  $\text{CH}(\text{H})\text{-CH}_3$ ), 2.24 (1H, dd,  $J=6.0$  and 13.1,  $\text{C4-CH}(\text{H})$ ), 2.36 (1H, dd,  $J=11.1$  and 13.1,  $\text{C4-CH}'(\text{H})$ ), 2.51 (1H, dd,  $J=11.1$  and 13.1,  $\text{C4-CH}(\text{H})$ ), 2.65 (1H, dd,  $J=6.0$  and 13.1,  $\text{C4-CH}(\text{H})$ ), 2.98 (1H, m,  $\text{C5-CH}'$ ), 3.53 (1H, t,  $J=12.1$ ,  $\text{C2-CH}'$ ), 3.55 (3H, s,  $\text{O-CH}_3$ ), 3.59 (2H, s, benzyl  $\text{CH}_2$ ), 3.61 (3H, s,  $\text{O-CH}_3$ ), 3.66 (3H, s,  $\text{O-CH}_3$ ), 3.68 (2H, s, benzyl  $\text{CH}_2$ ), 3.73 (3H, s,  $\text{O-CH}_3$ ), 3.96 (1H, m,  $\text{C5-CH}$ ), 4.87-5.02 (2H, m,  $\text{CH=CH}_2$ ), 5.13-5.20 (2H, m,  $\text{CH=CH}_2$ ), 5.59 (1H, m,  $\text{CH}'=\text{CH}_2$ ), 5.66 (1H, m,  $\text{CH}=\text{CH}_2$ ), 7.09-7.24 (10H, m, 5 x Ar  $\text{CH}'$ , 5 x Ar  $\text{CH}$ );  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 10.11 ( $\text{CH}_2\text{-C}'\text{H}_3$ ), 13.87 ( $\text{CH}_2\text{-CH}_3$ ), 21.07 ( $\text{CH}_2\text{-CH}_3$ ), 26.41 ( $\text{CH}_2\text{-CH}_3$ ), 37.34 ( $\text{C4-CH}_2$ ), 39.21 ( $\text{C4'-C}'\text{H}_2$ ), 52.26 ( $\text{C5-CH}$ ), 52.49 ( $\text{C5'-C}'\text{H}$ ), 52.79 ( $\text{C2'-CH}$ ), 52.92 ( $\text{C2'-C}'\text{H}$ ), 55.47 ( $\text{CH}_2$ ), 58.10 ( $\text{C}'\text{H}_2$ ), 62.84 ( $\text{C3'-C}'$ ), 64.00 ( $\text{C3-C}$ ), 65.16 ( $\text{O-CH}_3$ ), 66.26 ( $\text{O-CH}_3$ ), 68.02 ( $\text{O-C}'\text{H}_3$ ), 70.31 ( $\text{O-C}'\text{H}_3$ ), 115.91 ( $\text{C}'\text{H}_2=\text{CH}$ ), 116.50 ( $\text{CH}_2=\text{CH}$ ), 126.78 (Ar- $\text{C}'\text{H}$ ), 127.73 (Ar- $\text{C}'\text{H}$ ), 128.03 (Ar- $\text{C}'\text{H}$ ), 128.57 (Ar- $\text{CH}$ ), 129.44 (Ar- $\text{CH}$ ), 129.91 (Ar- $\text{CH}$ ), 138.47 (Ar- $\text{C}$ ), 139.90 (Ar- $\text{C}'$ ), 140.12 ( $\text{CH}_2=\text{CH}$ ), 140.65 ( $\text{CH}_2=\text{C}'\text{H}$ ), 169.89 ( $\text{C=O}$ ), 170.13 ( $\text{C}'=\text{O}$ ), 172.19 ( $\text{C}'=\text{O}$ ), 172.32 ( $\text{C=O}$ );  $m/z$  (EI) 331 ( $\text{M}^+$ , 2%), 302 (88), 272 (6), 240 (10), 145 (7), 91 (100), 65 (7), 55 (3); Accurate mass for  $\text{C}_{19}\text{H}_{25}\text{NO}_4$  – 331.1783, found – 331.1789

***N*-Benzyl-2-butyl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (108)**



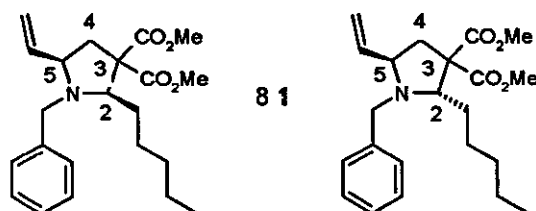
***Thermal Procedure***

Prepared following the general thermal procedure for compound (81), *N*-benzyl-2-butyl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (108) (0.240 g, 68%) was prepared as a yellow oil using *N*-benzyl-butyl imine (0.180 g, 1.00 mmol) for 48 hours;  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  2953s, 2867m (CH str), 1734s (C=O), 1641w, 1453s, 1267s, 1197s, 1137s, 1076m, 990m, 921m, 749m;  $\delta_{\text{H}}(250 \text{ MHz}; \text{CDCl}_3)$  0.64 (3H, t,  $J=7.5$ , aliphatic  $\text{CH}_3$ ), 0.72 (3H, t,  $J=7.5$ , aliphatic  $\text{CH}_3$ ), 0.96-1.18 (12H, m, 3 x aliphatic  $\text{CH}_2$ , 3 x aliphatic  $\text{CH}_2$ ), 2.24 (1H, dd,  $J=6.0$  and 13.1, C4-CH(H)), 2.35 (1H, dd,  $J=11.1$  and 13.1, C4-CH(H)), 2.68 (1H, dd,  $J=6.0$  and 13.1, C4-CH(H)), 2.82 (1H, dd,  $J=11.1$  and 13.1, C4-CH(H)), 2.96 (1H, m, C5-CH), 3.30 (1H, m, C5-N-CH), 3.57 (1H, m, C2-CH), 3.58 (2H, s, benzyl  $\text{CH}_2$ ), 3.60 (3H, s, O-CH<sub>3</sub>), 3.63 (3H, s, O-CH<sub>3</sub>), 3.66 (3H, s, O-CH<sub>3</sub>), 3.67 (3H, s, O-CH<sub>3</sub>), 3.68 (2H, s, benzyl  $\text{CH}_2$ ), 3.75 (1H, m, C2-N-CH), 4.87-5.02 (2H, m, CH=CH<sub>2</sub>), 5.08-5.23 (2H, m, CH=CH<sub>2</sub>), 5.59 (1H, m, CH=CH<sub>2</sub>), 5.77 (1H, m, CH=CH<sub>2</sub>), 7.12-7.23 (10H, m, 5 x Ar CH, 5 x Ar CH);  $\delta_{\text{C}}(101 \text{ MHz}; \text{CDCl}_3)$  13.92 (C'H<sub>3</sub>), 15.68 (CH<sub>3</sub>), 22.91 (C'H<sub>2</sub>), 24.02 (CH<sub>2</sub>), 27.78 (C'H<sub>2</sub>), 29.65 (CH<sub>2</sub>), 30.27 (CH<sub>2</sub>), 33.53 (C'H<sub>2</sub>), 37.24 (C4-CH<sub>2</sub>), 39.17 (C4'-C'H<sub>2</sub>), 50.63 (benzyl CH<sub>2</sub>), 52.35 (C5'-C'H), 52.43 (C5-CH), 52.63 (C2-CH), 52.78 (C2'-C'H), 57.96 (benzyl C'H<sub>2</sub>), 62.87 (C3-C), 62.94 (C3'-C'), 63.51 (O-CH<sub>3</sub>), 64.24 (O-CH<sub>3</sub>), 66.21 (O-C'H<sub>3</sub>), 66.89 (O-C'H<sub>3</sub>), 115.94 (C'H<sub>2</sub>=CH), 116.47 (CH<sub>2</sub>=CH), 126.64 (Ar-C'H), 126.78 (Ar-C'H), 127.89 (Ar-CH), 128.00 (Ar-C'H), 128.30 (Ar-CH), 129.47 (Ar-CH), 139.53 (Ar-C), 139.79 (Ar-C'), 140.16 (CH<sub>2</sub>=CH), 140.66 (CH<sub>2</sub>=C'H), 169.90 (C'=O), 172.04 (C=O), 172.18 (C'=O),  $m/z$  (EI) 359 ( $\text{M}^+$ , 2%), 328 (4), 303 (100), 268 (7), 174 (3), 145 (7), 124 (5), 91 (81), 65 (5), 41 (5); Accurate mass for  $\text{C}_{21}\text{H}_{29}\text{NO}_4$  - 359.2096, found - 359.2099.

*Silica Procedure*

Formed following the general silica enhanced procedure for compound (85), *N*-benzyl-2-butyl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (108) (0.270 g, 75%) was prepared as a yellow oil using *N*-benzyl-butyl imine (0.180 g, 1.00 mmol); Data as above

***N*-Benzyl-2-hexyl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (109)**



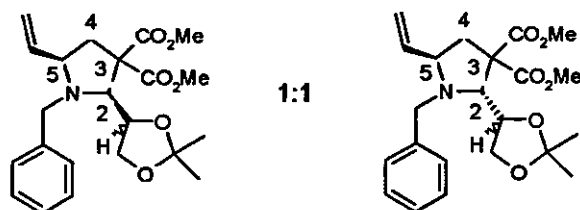
***Thermal Procedure***

Prepared following the general thermal procedure for compound (81), *N*-benzyl-2-hexyl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (109) (0.280 g, 76%) was prepared as a yellow oil using *N*-benzyl-hexyl imine (0.190 g, 1.00 mmol) for 48 hours;  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  2912s, 2857s (CH str), 1753s (C=O), 1720s, 1434s, 1335w, 1222s, 1195s, 1136m, 1075m;  $\delta_{\text{H}}(250 \text{ MHz}; \text{CDCl}_3)$  0.76-1.71 (24H, m, 4  $\times$   $\text{CH}_2$ , 1  $\times$   $\text{CH}_3$  alkyl chain', 4  $\times$   $\text{CH}_2$ , 1  $\times$   $\text{CH}_3$  alkyl chain), 1.99 (1H, dd,  $J=8.0$  and 13.0, C4-C(H)H), 2.35 (1H, dd,  $J=8.0$  and 13.0, C4'-C'(H)H), 2.86 (1H, dd,  $J=11.5$  and 13.0, C4-C(H)H), 3.04 (1H, dd,  $J=11.5$  and 13.0, C4'-C'(H)H), 3.63 (3H, s, O-CH<sub>3</sub>), 3.68 (3H, s, O-C'H<sub>3</sub>), 3.74 (3H, s, O-C'H<sub>3</sub>), 3.76 (3H, s, O-CH<sub>3</sub>), 3.80 (2H, m, C5-CH, C5'-C'H), 3.82 (2H, m, CH<sub>2</sub>), 4.29 (2H, m, C'H<sub>2</sub>), 4.62 (1H, s, C2-CH), 4.94-5.11 (3H, m, CH<sub>2</sub>=CH, C2'-C'H), 5.07-5.31 (1H, m, C'H<sub>2</sub>=CH), 5.64 (1H, m, CH<sub>2</sub>=C'H), 5.92 (1H, m, CH<sub>2</sub>=CH), 6.96-7.49 (10H, m, Ar-CH, Ar-C'H);  $\delta_{\text{C}}(101 \text{ MHz}; \text{CDCl}_3)$  14.40 (C'H<sub>3</sub>), 15.01 (CH<sub>3</sub>), 21.17 (CH<sub>2</sub>), 22.70 (C'H<sub>2</sub>), 22.79 (CH<sub>2</sub>), 24.22 (C'H<sub>2</sub>), 25.67 (CH<sub>2</sub>), 28.30 (C'H<sub>2</sub>), 28.83 (CH<sub>2</sub>), 30.16 (C'H<sub>2</sub>), 31.69 (CH<sub>2</sub>), 32.11 (C'H<sub>2</sub>), 32.44 (CH<sub>2</sub>), 34.27 (C'H<sub>2</sub>), 39.56 (CH<sub>2</sub> benzyl), 41.26 (C'H<sub>2</sub>), 51.06 (C4-CH<sub>2</sub>), 52.55 (C5'-C'H), 52.65 (C5-CH), 52.78 (C2-CH), 53.23 (C2'-C'H), 58.45 (C4'-C'H<sub>2</sub>), 63.32 (C3-C), 64.71 (C3'-C'), 66.64 (O-C'H<sub>3</sub>), 66.92 (O-CH<sub>3</sub>), 67.13 (O-CH<sub>3</sub>), 67.38 (O-C'H<sub>3</sub>), 116.20 (C'H<sub>2</sub>=CH), 116.78 (CH<sub>2</sub>=CH), 127.13 (Ar-CH), 128.03 (Ar-C'H), 128.25 (Ar-C'H), 128.36 (Ar-CH), 129.84 (Ar-C'H), 130.25 (Ar-CH), 139.94 (Ar-C), 140.25 (Ar-C'), 140.56 (CH<sub>2</sub>=CH), 141.09 (CH<sub>2</sub>=C'H), 170.26 (C'=O), 170.51 (C=O), 172.42 (C=O), 172.56 (C'=O);  $m/z$  (EI) 387 ( $M^+$ , 8%), 342 (23), 328 (34), 303 (100), 282 (36), 138 (26), 91 (97), 65 (20). Accurate mass for C<sub>22</sub>H<sub>31</sub>NO<sub>4</sub> - 387.2409 found - 387.2401.

*Microwave Procedure*

Prepared following the general microwave procedure for compound (85), *N*-benzyl-2-hexyl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (109) (0.270 g, 72%) was prepared as a yellow oil using *N*-benzyl-hexyl imine (0.190 g, 1.00 mmol), Data as above

***N*-Benzyl-2-(2,2-dimethyl-[1,3]dioxolan-4-yl)-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (112)**

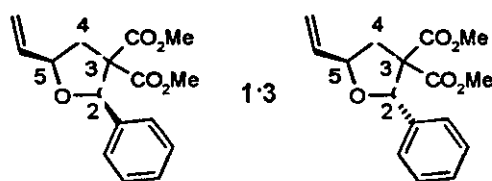


Prepared following the general thermal procedure for compound (81), *N*-benzyl-2-(2,2-dimethyl-[1,3]dioxolan-4-yl)-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (112) (0.170 g, 42%) was prepared as a brown oil using *N*-benzyl-(2,2-dimethyl-[1,3]dioxolan-4-yl) imine (0.220 g, 1.00 mmol) for 48 hours,  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  3027m, 2952m (CH str), 1734s (C=O), 1643m, 1453m, 1370m, 1266s, 1154m, 1066m, 990w, 921w, 845w, 755w,  $\delta_{\text{H}}$  (250 MHz,  $\text{CDCl}_3$ ) 1.07-1.20 (6H, m,  $\text{C}(\text{CH}_3)\text{CH}_3$ ,  $\text{C}(\text{CH}_3)\text{CH}'_3$ ), 1.25-1.32 (6H, m,  $\text{C}(\text{CH}_3)\text{CH}_3$ ,  $\text{C}(\text{CH}_3)\text{CH}'_3$ ), 2.12 (1H, dd,  $J=6.4$  and  $12.8$ , C4- $\text{CH}(\text{H})$ ), 2.30 (1H, dd,  $J=6.4$  and  $12.8$ , C4- $\text{CH}'(\text{H})$ ), 2.39 (2H, s, benzyl  $\text{CH}_2$ ), 2.53 (1H, dd,  $J=11.2$  and  $12.8$ , C4- $\text{CH}(\text{H}')$ ), 2.76 (1H, dd,  $J=11.2$  and  $12.8$ , C4- $\text{CH}(\text{H})$ ), 2.96-3.04 (2H, m, diol  $\text{CH}_2\text{-CH}$ ), 3.31-3.35 (2H, m, diol  $\text{CH}_2\text{-CH}$ ), 3.39 (2H, s, benzyl  $\text{CH}_2$ ), 3.42 (2H, m, diol  $\text{CH}_2\text{-CH}'$ ), 3.48 (2H, m, diol  $\text{CH}_2\text{-CH}$ ), 3.57 (3H, s, O- $\text{CH}_3$ ), 3.71 (3H, s, O- $\text{CH}_3$ ), 3.72 (3H, s, O- $\text{CH}_3$ ), 3.80 (3H, s, O- $\text{CH}_3$ ), 3.84 (1H, m, C5- $\text{CH}'$ ), 3.86 (1H, m, C5- $\text{CH}$ ), 3.92 (1H, m, C2- $\text{CH}'$ ), 4.63 (1H, m, C2- $\text{CH}$ ), 4.80-5.02 (2H, m,  $\text{CH}=\text{CH}_2$ ), 5.05-5.19 (2H, m,  $\text{CH}=\text{CH}_2$ ), 5.50 (1H, m,  $\text{CH}'=\text{CH}_2$ ), 5.75 (1H, m,  $\text{CH}=\text{CH}_2$ ), 7.13-7.23 (10H, m, 5 x Ar  $\text{CH}'$ , 5 x Ar  $\text{CH}$ );  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 24.49 ( $\text{CH}_3$ ), 24.71 ( $\text{C}'\text{H}_3$ ), 25.61 ( $\text{CH}_3$ ), 25.62 ( $\text{C}'\text{H}_3$ ), 37.77 (C4'- $\text{C}'\text{H}_2$ ), 38.59 (C4- $\text{CH}_2$ ), 51.41 (C5'- $\text{C}'\text{H}$ ), 51.44 (C5- $\text{CH}$ ), 52.04 (C2- $\text{CH}$ ), 52.11 (C2'- $\text{C}'\text{H}$ ), 58.05 (benzyl  $\text{CH}_2$ ), 59.04 (benzyl  $\text{C}'\text{H}_2$ ), 61.04 (diol  $\text{CH}_2$ ), 61.65 (O- $\text{CH}_3$ ), 64.86 (O- $\text{CH}_3$ ), 65.02 (C3'- $\text{C}'$ ), 65.38 (diol  $\text{C}'\text{H}_2$ ), 65.93 (C3- $\text{C}$ ), 66.55 (O- $\text{C}'\text{H}_3$ ), 67.95 (O- $\text{C}'\text{H}_3$ ), 75.76 (diol  $\text{CH}$ ), 76.13 (diol  $\text{C}'\text{H}$ ), 107.28 (diol  $\text{C}$ ), 107.94 (diol  $\text{C}'$ ), 114.35 ( $\text{C}'\text{H}_2=\text{CH}$ ), 114.52 ( $\text{CH}_2=\text{CH}$ ), 126.24 (Ar- $\text{CH}$ ), 126.64 (Ar- $\text{C}'\text{H}$ ), 126.87 (Ar- $\text{C}'\text{H}$ ), 127.02 (Ar- $\text{C}'\text{H}$ ), 128.68 (Ar- $\text{CH}$ ), 128.86 (Ar- $\text{CH}$ ), 138.24 (Ar- $\text{C}'$ ), 138.44 (Ar- $\text{C}$ ), 139.27 ( $\text{CH}_2=\text{C}'\text{H}$ ), 139.42 ( $\text{CH}_2=\text{CH}$ ), 167.35 (C=O), 167.66 (C=O), 170.60 (C=O),

170 63 ( $\underline{\text{C}}=\text{O}$ ),  $m/z$  (EI) 403 ( $\text{M}^+$ , 1%), 388 (21), 314 (18), 303 (100), 242 (5), 212 (7), 153 (7), 101 (27), 91 (99), 65 (15); Accurate mass for  $\text{C}_{22}\text{H}_{29}\text{NO}_6$  – 403.1924, found – 403.1923.

### Section 3.05 – Tetrahydrofurans Formed

#### 2-Phenyl-5-vinyl dihydro-furan-3,3-dicarboxylic acid dimethyl ester (239)

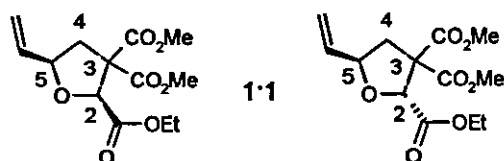


#### General Procedure

To a solution of benzaldehyde (0.110 g, 1.00 mmol), zinc bromide (0.460 g, 2.00 mmol) and  $\text{Pd}(\text{PPh}_3)_4$  (0.110 g, 0.100 mmol) in THF (10 mL) was added a 2-vinylcyclopropane-1,1-dicarboxylic acid (**62**) (0.190 g, 1.00 mmol). This mixture was stirred for 48 h at 35 °C, the solvent was evaporated *in vacuo* and the residue partitioned between EtOAc (30 mL) and distilled water (30 mL). The organic layer was separated and washed with aq. HCl (1M 2 x 30 mL), saturated  $\text{NaHCO}_3$  solution (30 mL), and saturated brine solution (2 x 30 mL). The organic layer was dried using  $\text{MgSO}_4$ , filtered and concentrated *in vacuo* to afford the crude pyrrolidine product as a dark brown heavy oil. This was then purified using column chromatography ( $\text{SiO}_2$ , EtOAc:P.E. 40-60, 1:4,  $R_f$  - 0.35) to yield 2-phenyl-5-vinyl-dihydro-furan-3,3-dicarboxylic acid dimethyl ester (**240**) (0.21 g, 72%) as a yellow oil;  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  2951m (CH str), 1732s (C=O), 1433m, 1271s, 1206s, 1051m, 928m, 752m, 700m;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 2.21 (1H, dd,  $J=6.0$  and 13.3, C4-CH(H)), 2.51 (1H, dd,  $J=6.0$  and 13.3, C4'-CH(H)), 2.77 (1H, dd,  $J=10.3$  and 13.3, C4'-CH(H')), 3.03 (1H, dd,  $J=10.3$  and 13.3, C4-CH(H')), 3.11 (3H, s, O-CH<sub>3</sub>'), 3.16 (3H, s, O-CH<sub>3</sub>), 3.76 (3H, s, O-CH<sub>3</sub>'), 3.81 (3H, s, O-CH<sub>3</sub>'), 4.41 (1H, m, C5'-CH'), 4.88 (1H, m, C5-CH), 5.19-5.29 (1H, m, CH<sub>2</sub>=CH), 5.36-5.43 (1H, m, CH<sub>2</sub>=CH), 5.69 (1H, s, C2'-CH'), 5.79 (1H, s, C2-CH), 5.89 (1H, m, CH<sub>2</sub>=CH'), 6.10 (1H, m, CH<sub>2</sub>=CH), 7.25-7.30 (5H, m, 5 x Ar-CH), 7.39-7.41 (5H, m, 5 x Ar-CH'),  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 40.35 (C4'-C'H<sub>2</sub>), 40.52 (C4-CH<sub>2</sub>), 52.18 (C5'-C'H), 52.18 (C5-CH), 52.83 (C2'-C'H), 52.98 (C2-CH), 65.71 (C3-C), 66.19 (C3'-C'), 79.24 (O-C'H<sub>3</sub>), 79.96 (O-CH<sub>3</sub>), 83.49 (O-CH<sub>3</sub>), 84.22 (O-C'H<sub>3</sub>), 116.12 (CH<sub>2</sub>=CH), 117.71 (C'H<sub>2</sub>=CH), 126.51 (Ar-CH), 126.96 (Ar-CH), 127.81 (Ar-C'H), 127.87 (Ar-C'H), 128.00 (Ar-CH), 128.13

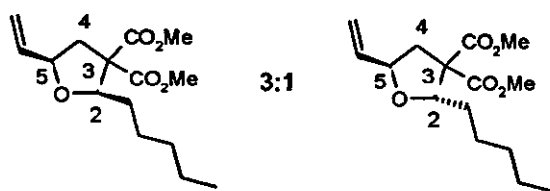
(Ar-C'H), 136.46 (CH<sub>2</sub>=C'H), 137.77 (CH<sub>2</sub>=CH), 138.14 (Ar-C'), 138.26 (Ar-C), 168.97 (C'=O), 169.13 (C=O), 170.41 (C=O), 171.22 (C'=O); *m/z* (EI) 290 (M<sup>+</sup>, 10%), 236 (68), 230 (17), 184 (55), 152 (74), 124 (55), 115 (42), 105 (100), 77 (42), 59 (35); Accurate mass for C<sub>16</sub>H<sub>18</sub>O<sub>5</sub> – 290.1154, found – 290.1150.

**5-Vinyl-dihydro-furan-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (241)**



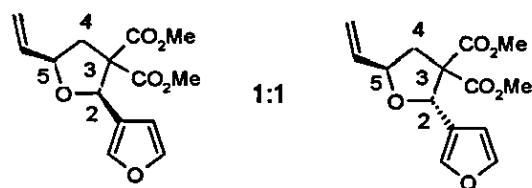
Prepared following the general thermal procedure for compound (240), 5-vinyl-dihydro-furan-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (242) (0.290 g, 96%) was prepared as a yellow oil using ethyl glyoxalate (0.100 g, 1.00 mmol) for 16 hours,  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2957m, 2906m, 2341w (CH str), 1740s (C=O), 1646w, 1436s, 1395m, 1373m, 1205s, 1115m, 1070m, 1025m, 934m, 848w, 784w, 755w;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 1.11-1.13 (3H, m, O-CH<sub>2</sub>-CH<sub>3</sub>), 1.14-1.15 (3H, m, O-CH<sub>2</sub>-CH<sub>3</sub>), 2.20 (1H, dd, J=6.8 and 13.2, C4-C(H)H), 2.48 (1H, dd, J=6.8 and 13.2, C4'-C'(H)H), 2.55 (1H, dd, J=7.6 and 13.2, C4'-C'(H)H), 2.82 (1H, dd, J=7.6 and 13.2, C4-C(H)H), 3.37 (2H, m, O-CH<sub>2</sub>-CH<sub>3</sub>), 3.58 (3H, s, O-CH<sub>3</sub>), 3.59 (3H, s, O-CH<sub>3</sub>), 3.65 (3H, s, O-CH<sub>3</sub>), 3.69 (3H, s, O-CH<sub>3</sub>), 4.01-4.07 (2H, m, O-CH<sub>2</sub>-CH<sub>3</sub>), 4.40 (1H, m, C5'-O-C'H), 4.86 (1H, m, C5-O-CH), 4.88 (1H, s, C2-O-CH), 4.99-5.07 (3H, m, C'H<sub>2</sub>=CH, C2'-O-C'H), 5.13-5.18 (2H, m, CH<sub>2</sub>=CH), 5.62 (1H, m, CH<sub>2</sub>=C'H), 5.67 (1H, m, CH<sub>2</sub>=CH);  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 14.36 (O-CH<sub>2</sub>-CH<sub>3</sub>), 14.39 (O-CH<sub>2</sub>-CH<sub>3</sub>), 39.48 (C4'-CH<sub>2</sub>), 39.94 (C4-CH<sub>2</sub>), 53.44 (C5'-CH), 53.50 (C5-CH), 53.71 (C2-CH), 53.87 (C2'-CH), 61.79 (O-CH<sub>2</sub>-CH<sub>3</sub>), 61.83 (O-CH<sub>2</sub>-CH<sub>3</sub>), 64.45 (C3'-CH), 64.80 (C3-CH), 80.93 (O-CH<sub>3</sub>), 81.35 (O-CH<sub>3</sub>), 81.42 (O-CH<sub>3</sub>), 81.64 (O-CH<sub>3</sub>), 117.19 (C'H<sub>2</sub>=CH), 118.30 (CH<sub>2</sub>=CH), 137.26 (CH<sub>2</sub>=CH), 137.30 (CH<sub>2</sub>=C'H), 168.22 (C=O), 168.70 (C'=O), 169.80 (C=O), 169.82 (C'=O), 170.06 (C=O), 170.14 (C'=O),  $m/z$  (EI) 286 ( $\text{M}^+$ , 1%), 227 (18), 181 (20), 153 (100), 145 (11), 121 (58), 84 (37), 59 (32), 49 (32), Accurate mass for  $\text{C}_{13}\text{H}_{18}\text{O}_7$  - 286.1053, found - 286.1048.

**2-Pentyl-5-vinyl-dihydro-furan-3,3-dicarboxylic acid dimethyl ester (243)**



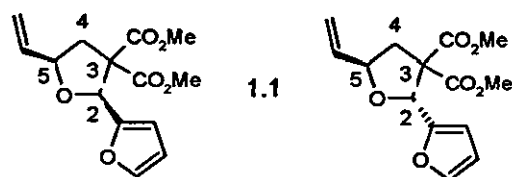
Prepared following the general thermal procedure for compound (240), 2-pentyl-5-vinyl-dihydro-furan-3,3-dicarboxylic acid dimethyl ester (244) (0.210 g, 72%) was prepared as a yellow oil using hexanal (0.100 g, 1.00 mmol) for 48 hours;  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  2953m (CH str), 2859m, 1736s (C=O), 1434m, 1264s, 1204m, 1159m, 1076m, 1026m, 925w, 811w, 677w;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 0.79-1.52 (22H, m, 11 x  $\text{CH}$  alkane chain, 11 x  $\text{CH}'$  alkane chain'), 2.01 (1H, dd,  $J=6.5$  and  $13.2$ , C4-CH(H)), 2.36-2.44 (2H, m, C4'-CH(H'), C4'-CH(H)), 2.79 (1H, dd,  $J=6.5$  and  $13.2$ , C4-CH(H)), 3.66 (3H, s, O-CH<sub>3</sub>), 3.67 (3H, s, O-CH<sub>3</sub>'), 3.67 (3H, s, O-CH<sub>3</sub>), 3.69 (3H, s, O-CH<sub>3</sub>'), 4.17-4.27 (4H, m, CH=CH<sub>2</sub>, C5-CH, C2-CH), 4.38 (1H, m, C2'-CH'), 4.63 (1H, m, C5'-CH'), 5.04-5.23 (2H, m, CH=CH<sub>2</sub>), 5.77 (1H, m, CH=CH<sub>2</sub>), 5.88 (1H, m, CH=CH<sub>2</sub>);  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 13.86 (CH<sub>3</sub>), 13.98 (C'H<sub>3</sub>), 22.27 (C'H<sub>2</sub>), 22.38 (C'H<sub>2</sub>), 26.41 (C'H<sub>2</sub>), 26.51 (CH<sub>2</sub>), 28.24 (C'H<sub>2</sub>), 29.54 (CH<sub>2</sub>), 30.29 (CH<sub>2</sub>), 30.59 (CH<sub>2</sub>), 31.48 (C4-CH<sub>2</sub>), 40.20 (C4'-C'H<sub>2</sub>), 45.09 (C5'-C'H), 52.46 (C5-CH), 52.61 (C2'-C'H), 52.70 (C2-CH), 63.44 (C3-C), 63.50 (C3'-C'), 78.12 (O-CH<sub>3</sub>), 78.86 (O-C'H<sub>3</sub>), 81.97 (O-CH<sub>3</sub>), 82.86 (O-C'H<sub>3</sub>), 115.40 (CH<sub>2</sub>=CH), 117.17 (C'H<sub>2</sub>=CH), 137.46 (CH<sub>2</sub>=C'H), 138.51 (CH<sub>2</sub>=CH), 169.72 (C=O), 169.94 (C'=O), 170.37 (C=O), 170.97 (C'=O);  $m/z$  (EI) 284 ( $M^+$ , 8%), 225 (29), 215 (65), 183 (52), 174 (76), 153 (100), 132 (42), 121 (59), 99 (27), 59 (37), Accurate mass for  $\text{C}_{15}\text{H}_{24}\text{O}_5$  – 284.1623, found – 284.1621.

**5-Vinyl-4,5-dihydro-[2,3']bifuranyl-3,3-dicarboxylic acid dimethyl ester (245)**



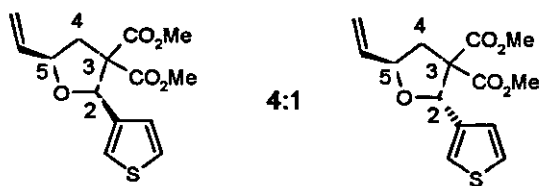
Prepared following the general thermal procedure for compound (240), 5-vinyl-4,5-dihydro-[2,3']bifuranyl-3,3-dicarboxylic acid dimethyl ester (246) (0.150 g, 54%) was prepared as a yellow oil using 3-furaldehyde (0.100 g, 1.00 mmol) for 48 hours,  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2921m (CH str), 2849m, 1733s (C=O), 1653m, 1436m, 1261m, 1159m, 1068m, 1018m, 920w, 873w, 700w;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 2.16 (1H, dd,  $J=6.4$  and 13.2, C4'-CH(H)), 2.42 (1H, dd,  $J=10.2$  and 13.2, C4-CH(H)), 2.54 (1H, dd,  $J=10.2$  and 13.2, C4'-CH(H)), 2.90 (1H, dd,  $J=6.4$  and 13.2, C4-CH(H)), 3.09 (1H, m, C5'-O-CH), 3.29 (3H, s, O-CH<sub>3</sub>), 3.31 (3H, s, O-CH<sub>3</sub>), 3.49 (1H, m, C5-O-CH), 3.63 (3H, s, O-CH<sub>3</sub>), 3.70 (3H, s, O-CH<sub>3</sub>), 4.44 (1H, s, C2'-CH), 4.77 (1H, s, C2-CH), 5.02-5.31 (4H, m, CH=CH<sub>2</sub>, CH=CH<sub>2</sub>), 5.69 (1H, m, CH=CH<sub>2</sub>), 5.95 (1H, m, CH=CH<sub>2</sub>), 7.05-7.28 (6H, m, 3 x Ar-CH, 3 x Ar-CH);  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 49.94 (C4'-C'H<sub>2</sub>), 51.19 (C5-CH), 51.46 (C2-CH), 51.74 (C5'-C'H), 51.88 (C2'-C'H), 53.17 (C4-CH<sub>2</sub>), 59.51 (O-CH<sub>3</sub>), 61.84 (O-C'H<sub>3</sub>), 62.18 (O-C'H<sub>3</sub>), 62.26 (C3-C), 62.47 (C3'-C), 63.53 (O-CH<sub>3</sub>), 116.01 (C'H<sub>2</sub>=CH), 116.14 (CH<sub>2</sub>=CH), 123.23 (Ar-C), 125.63 (Ar-C'H), 125.76 (Ar-C'H), 126.70 (Ar-CH), 127.04 (Ar-C'H), 127.23 (Ar-CH), 128.72 (Ar-CH), 135.92 (Ar-C), 138.22 (CH<sub>2</sub>=CH), 138.83 (CH<sub>2</sub>=C'H), 168.18 (C'=O), 168.69 (C=O), 170.47 (C'=O), 170.79 (C=O);  $m/z$  (EI) 280 ( $M^+$ , 64%), 194 (14), 184 (34), 152 (69), 124 (61), 108 (58), 95 (100), 71 (62), 59 (85), 41 (38); Accurate mass for  $\text{C}_{14}\text{H}_{16}\text{O}_6$  - 280.0947, found - 280.0948.

**5-Vinyl-4,5-dihydro-[2,2']bifuranyl-3,3-dicarboxylic acid dimethyl ester (246)**



Prepared following the general thermal procedure for compound (240), 5-vinyl-4,5-dihydro-[2,2']bifuran-3,3-dicarboxylic acid dimethyl ester (247) (0.080g, 27%) was prepared as a yellow oil using 2-furaldehyde (0.100 g, 1.00 mmol) for 48 hours,  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2952m (CH str), 1733s (C=O), 1501w, 1434m, 1273s, 1160m, 1048m, 1019m, 930w, 874w, 795w,  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 2.13 (1H, dd,  $J=6.4$  and 13.3, C2-CH(H)), 2.47 (1H, dd,  $J=6.4$  and 13.3, C4'-CH'(H)), 2.61 (1H, dd,  $J=10.0$  and 13.4, C4'-CH(H')), 2.89 (1H, dd,  $J=10.0$  and 13.4, C4-CH(H)), 3.35 (3H, s, O-CH<sub>3</sub>), 3.40 (3H, s, O-CH<sub>3</sub>), 3.70 (3H, s, O-CH<sub>3</sub>), 3.73 (3H, s, O-CH<sub>3</sub>), 4.27 (1H, m, C5-CH), 4.89 (1H, m, C5'-CH'), 5.15-5.30 (4H, m, CH=CH<sub>2</sub>, CH=CH<sub>2</sub>), 5.49 (1H, s, C2'-CH'), 5.61 (1H, s, C2-CH), 5.79 (1H, m, CH=CH<sub>2</sub>), 5.95 (1H, m, CH=CH<sub>2</sub>), 6.28-6.30 (2H, m, Ar-O-CH, Ar-O-CH'), 7.19-7.37 (4H, m, 2 x Ar-CH, 2 x Ar-CH');  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 38.66 (C4-CH<sub>2</sub>), 39.92 (C4'-CH<sub>2</sub>), 52.35 (C5-CH), 52.40 (C5'-CH), 52.79 (C2'-CH), 52.96 (C2-CH), 65.18 (C3-C), 65.27 (C3'-C), 77.61 (O-CH<sub>3</sub>), 78.03 (O-CH<sub>3</sub>), 79.13 (O-CH<sub>3</sub>), 79.28 (O-CH<sub>3</sub>), 116.01 (C'H<sub>2</sub>=CH), 117.78 (CH<sub>2</sub>=CH), 122.75 (Ar-C'), 122.81 (Ar-C), 136.65 (CH<sub>2</sub>=C'H), 138.09 (CH<sub>2</sub>=CH), 139.53 (Ar-C'H), 140.50 (Ar-C'H), 140.75 (Ar-CH), 141.67 (Ar-C'H), 142.46 (Ar-CH), 142.71 (Ar-CH), 169.07 (C'=O), 169.17 (C=O), 170.16 (C=O), 170.85 (C'=O);  $m/z$  (EI) 280 ( $\text{M}^+$ , 100%), 194 (16), 184 (39), 152 (77), 124 (58), 108 (59), 95 (82), 71 (44), 59 (47); Accurate mass for  $\text{C}_{14}\text{H}_{16}\text{O}_6$  – 280.0947, found – 280.0947.

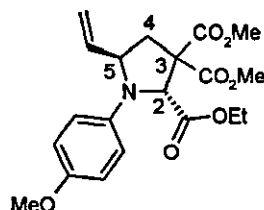
**2-Thiophen-3-yl-5-vinyl-dihydro-furan-3,3-dicarboxylic acid dimethyl ester (247)**



Prepared following the general thermal procedure for compound (240), 2-thiophen-3-yl-5-vinyl-dihydro-furan-3,3-dicarboxylic acid dimethyl ester (248) (0.150 g, 49%) was prepared as a yellow oil using thiophene-3-carboxaldehyde (0.110 g, 1.00 mmol) for 48 hours;  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  2950m (CH str), 1731s (C=O), 1434s, 1271s, 1205s, 1135m, 1050s, 928m, 868w, 815w, 784m;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 2.13 (1H, dd,  $J=6.4$  and 13.6, C4-CH(H)), 2.44 (1H, dd,  $J=6.4$  and 13.6, C4'-CH(H)), 2.65 (1H, dd,  $J=10.0$  and 13.6, C4'-CH(H')), 2.93 (1H, dd,  $J=10.0$  and 13.6, C4-CH(H)), 3.19 (3H, s, O-CH<sub>3</sub>), 3.23 (3H, s, O-CH<sub>3</sub>), 3.70 (3H, s, O-CH<sub>3</sub>), 3.73 (3H, s, O-CH<sub>3</sub>), 4.31 (1H, m, C5'-CH'), 4.92 (1H, m, C5-CH), 5.17-5.33 (4H, m, CH=CH', CH=CH<sub>2</sub>), 5.64 (1H, s, C2'-CH'), 5.72 (1H, s, C2-CH), 5.87 (1H, m, CH=CH<sub>2</sub>), 5.99 (1H, m, CH'=CH<sub>2</sub>), 6.99-7.23 (6H, m, 3 x Ar-CH, 3 x Ar-CH'),  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 38.80 (C4'-C'H<sub>2</sub>), 40.19 (C4-CH<sub>2</sub>), 52.39 (C5'-C'H), 52.48 (C5-CH), 52.80 (C2-CH), 52.95 (C2'-C'H), 56.39 (C3-C), 63.99 (C3'-C'), 79.18 (O-C'H<sub>3</sub>), 79.51 (O-CH<sub>3</sub>), 80.54 (O-CH<sub>3</sub>), 81.07 (O-C'H<sub>3</sub>), 116.02 (CH<sub>2</sub>=CH), 117.59 (C'H<sub>2</sub>=CH), 122.70 (Ar-C'H), 123.40 (Ar-C'H), 124.47 (Ar-C'H), 124.96 (Ar-CH), 125.02 (Ar-CH), 126.53 (Ar-CH), 127.93 (CH<sub>2</sub>=C'H), 136.62 (Ar-C'), 138.13 (CH<sub>2</sub>=CH), 138.94 (Ar-C), 169.04 (C'=O), 169.16 (C=O), 170.24 (C=O), 171.00 (C'=O),  $m/z$  (EI) 296 ( $\text{M}^+$ , 100%), 276 (10), 210 (22), 184 (32), 152 (74), 124 (70), 111 (84), 93 (23), 71 (46), 59 (43); Accurate mass for  $\text{C}_{14}\text{H}_{16}\text{O}_5\text{S}$  – 296.0718, found – 296.0719.

### Section 3.06 – Pyrrolidines Derived from Ethyl Carbonate Imines

#### *N*-(4-Methoxy-phenyl)-5-vinyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (122)



#### Thermal Procedure

Prepared following the general thermal procedure for compound (81), *N*-(4-Methoxy-phenyl)-5-vinyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (122) (0.380 g, 97%) was prepared as a orange-brown crystalline solid using *N*-(4-methoxybenzene)-ethyl ester imine (0.210 g, 1.00 mmol) for 16 hours,  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2954m, 2836w (CH str), 1741s (C=O), 1513s, 1354m, 1257s, 1178s, 1072m, 1036m, 994w, 973w, 931w, 865w, 816w, 783m;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 0.76-1.25 (3H, m, O-CH<sub>2</sub>-CH<sub>3</sub>), 2.44 (1H, dd,  $J=1.2$  and  $13.2$ , C4-CH(H)), 3.12 (1H, dd,  $J=9.6$  and  $12.8$ , C4-CH(H)), 3.62 (3H, s, O-CH<sub>3</sub>), 3.63 (3H, s, O-CH<sub>3</sub>), 3.64 (3H, s, O-CH<sub>3</sub>), 3.89-4.03 (3H, m, O-CH<sub>2</sub>-CH<sub>3</sub>), 4.37 (1H, m, C5-CH), 4.35-5.18 (2H, m, CH<sub>2</sub>=CH), 5.21 (1H, s, C2-CH), 5.61 (1H, m, CH<sub>2</sub>=CH), 6.51 (2H, d,  $J=9.0$ , 2 x Ar CH), 6.67 (2H, d,  $J=9.0$ , 2 x Ar CH);  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 14.42 (O-CH<sub>2</sub>-CH<sub>3</sub>), 37.55 (C4-CH<sub>2</sub>), 53.50 (C5-CH), 53.55 (C2-CH), 55.88 (O-CH<sub>3</sub>), 60.25 (O-CH<sub>3</sub>), 61.62 (O-CH<sub>2</sub>-CH<sub>3</sub>), 62.01 (C3-C), 67.26 (O-CH<sub>3</sub>), 114.85 (Ar-CH), 115.39 (Ar-CH), 115.69 (CH<sub>2</sub>=CH), 139.15 (CH<sub>2</sub>=CH), 139.82 (Ar-C), 152.48 (Ar-C), 168.42 (C=O), 169.86 (C=O), 171.13 (C=O);  $m/z$  (EI) 391 ( $M^+$ , 93%), 332 (31), 318 (100), 259 (43), 200 (29), 134 (49), 108 (23), 84 (53), 49 (62), Accurate mass for  $\text{C}_{20}\text{H}_{25}\text{NO}_7$  – 391.1631, found – 391.1633.

#### Microwave Procedure

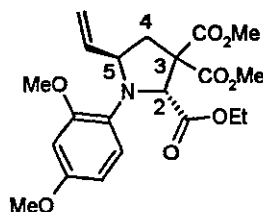
Prepared following the general microwave procedure for compound (85), *N*-(4-methoxy-phenyl)-5-vinyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-

dimethyl ester (**122**) (0.360 g, 91%) was prepared as a orange-brown crystalline solid using *N*-(4-methoxybenzene)-ethyl ester imine (0.210 g, 1.00 mmol), Data as above

#### *Silica Procedure*

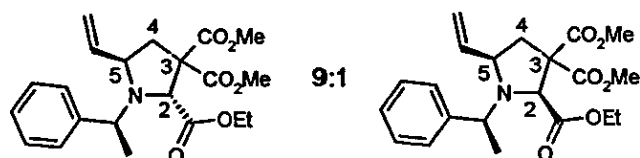
Formed following the general silica enhanced procedure for compound (**85**), *N*-(4-methoxy-phenyl)-5-vinyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (**122**) (0.340 g, 94%) was prepared as a yellow-brown oil crystalline solid using *N*-(4-methoxybenzene)-ethyl ester imine (0.210 g, 1.00 mmol) for 45 minutes; Data as above.

***N*-(2,4-Dimethoxy-phenyl)-5-vinyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (123)**



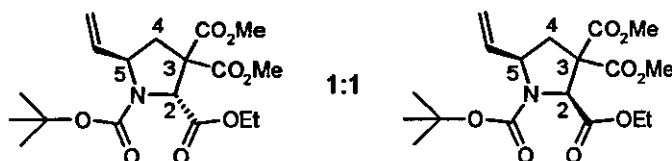
Prepared following the general thermal procedure for compound (81), *N*-(2,4-dimethoxy-phenyl)-5-vinyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (123) (0.410 g, 94%) was prepared as a brown oil using *N*-(2,4-dimethoxybenzene)-ethyl ester imine (0.240 g, 1.00 mmol) for 48 hours;  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2955s, 2838m, 2365w (CH str), 1740s (C=O), 1611s, 1586m, 1508s, 1437s, 1208s, 1159s, 1031s, 926m, 834m, 731m;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 0.89 (3H, t,  $J=7.1$ , O-CH<sub>2</sub>CH<sub>3</sub>), 2.37 (1H, dd,  $J=5.5$  and 13.3, C4-C(H)H), 3.00 (1H, dd,  $J=8.9$  and 13.3, C4-C(H)H), 3.62 (3H, s, O-CH<sub>3</sub>), 3.65 (3H, s, O-CH<sub>3</sub>), 3.73 (3H, s, O-CH<sub>3</sub>), 3.76 (3H, s, O-CH<sub>3</sub>), 3.79 (2H, m, O-CH<sub>2</sub>CH<sub>3</sub>), 4.90 (1H, m, C5-CH), 4.93-5.12 (2H, m, CH<sub>2</sub>=CH), 5.42 (1H, s, C2-CH), 5.52 (1H, m, CH<sub>2</sub>=CH), 6.27 (1H, dd,  $J=2.7$  and 8.7, Ar-H), 6.34 (1H, d,  $J=2.7$ , Ar-H), 6.71 (1H, d,  $J=8.8$ , Ar-H);  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 13.96 (O-CH<sub>2</sub>-CH<sub>3</sub>), 37.18 (C4-CH<sub>2</sub>), 52.64 (C5-CH), 53.20 (C2-CH), 55.01 (O-CH<sub>3</sub>), 55.66 (O-CH<sub>3</sub>), 60.28 (O-CH<sub>2</sub>-CH<sub>3</sub>), 60.62 (O-CH<sub>3</sub>), 61.64 (C3-C), 67.70 (O-CH<sub>3</sub>), 99.90 (Ar-CH), 103.39 (Ar-CH), 116.71 (CH<sub>2</sub>=CH), 124.61 (Ar-CH), 127.24 (Ar-C), 139.26 (CH<sub>2</sub>=CH), 153.73 (Ar-C), 156.02 (Ar-C), 169.02 (C=O), 170.09 (C=O), 170.11 (C=O),  $m/z$  (EI) 421 ( $M^+$ , 16%), 362 (6), 348 (100), 213 (14), 153 (41), 138 (29), 121 (15), 84 (16), 59 (13); Accurate mass for  $\text{C}_{21}\text{H}_{27}\text{NO}_8$  – 421.1737, found – 421.1730.

***N*-(1-Phenyl-ethyl)-5-vinyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (139)**



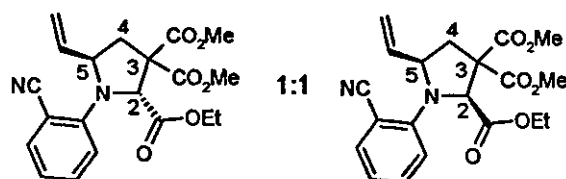
Prepared following the general thermal procedure for compound (81), *N*-(1-phenyl-ethyl)-5-vinyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (139) (0.070 g, 18%) was prepared as a yellow-brown oil using *N*-(1-phenyl ethyl)-ethyl ester imine (0.210 g, 1.00 mmol) for 48 hours;  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2979m, 2955m (CH str), 1963w, 1738s (C=O), 1643w, 1602w, 1453s, 1372m, 1266s, 1236s, 1196m, 1095m, 1074m, 1029m, 962m, 838w, 765w;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 1.21 (3H, m, C'H<sub>3</sub>), 1.26 (3H, m, CH<sub>3</sub>), 2.31 (1H, dd,  $J=6.0$  and 12.8, C4-C(H)H), 2.46 (1H, dd,  $J=6.0$  and 12.8, C4'-C'(H)H), 2.48 (1H, dd,  $J=9.8$  and 12.8, C4'-C'(H)H), 2.90 (1H, dd,  $J=9.8$  and 12.8, C4-C(H)H), 3.42 (1H, m, C5'-C'H), 3.52 (3H, s, O-C'H<sub>3</sub>), 3.54 (3H, s, O-CH<sub>3</sub>), 3.55 (3H, s, O-C'H<sub>3</sub>), 3.57 (3H, s, O-C'H<sub>3</sub>), 3.66 (2H, m, O-C'H<sub>2</sub>-CH<sub>3</sub>), 3.69 (1H, m, C'H), 3.96 (2H, m, O-CH<sub>2</sub>-CH<sub>3</sub>), 4.23 (1H, s, C2-CH), 4.27 (1H, s, C2'-C'H), 4.52 (1H, m, C'H), 4.56-4.78 (2H, m, CH<sub>2</sub>=CH), 4.96-5.08 (2H, m, C'H<sub>2</sub>=CH), 5.45 (1H, m, CH<sub>2</sub>=CH), 5.76 (1H, m, CH<sub>2</sub>=C'H), 7.14-7.23 (10H, m, 5 x Ar-CH, 5 x Ar-C'H);  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 15.04 (C'H<sub>3</sub>), 17.68 (CH<sub>3</sub>), 22.25 (O-CH<sub>2</sub>-C'H<sub>3</sub>), 24.23 (O-CH<sub>2</sub>-CH<sub>3</sub>), 39.42 (C4'-C'H<sub>2</sub>), 44.51 (C4-C'H<sub>2</sub>), 53.11 (C5'-C'H), 53.15 (C5-CH), 53.59 (C2-CH), 53.66 (C2'-C'H), 55.46 (CH), 56.52 (C'H), 60.96 (O-C'H<sub>2</sub>-CH<sub>3</sub>), 61.19 (O-CH<sub>2</sub>-CH<sub>3</sub>), 62.87 (C3'-C'), 63.00 (C3-C), 63.68 (O-CH<sub>3</sub>), 63.99 (O-C'H<sub>3</sub>), 65.18 (O-CH<sub>3</sub>), 67.42 (O-C'H<sub>3</sub>), 116.26 (C'H<sub>2</sub>=CH), 116.87 (CH<sub>2</sub>=CH), 127.22 (Ar-CH), 127.37 (Ar-C'H), 127.83 (Ar-C'H), 128.11 (Ar-CH), 128.18 (Ar-C'H), 128.50 (Ar-CH), 141.29 (CH<sub>2</sub>=CH), 141.99 (CH<sub>2</sub>=C'H), 143.31 (Ar-C), 143.55 (Ar-C'), 169.01 (C=O), 169.08 (C'=O), 170.41 (C=O), 170.72 (C'=O), 172.93 (C=O), 173.38 (C'=O);  $m/z$  (EI) 389 ( $\text{M}^+$ , 1%), 316 (64), 212 (56), 153 (8), 105 (100), 91 (10), 77 (9); Accurate mass for  $\text{C}_{21}\text{H}_{27}\text{NO}_6$  – 389.1838, found – 389.1841.

**5-Vinyl-pyrrolidine-1,2,3,3-tetracarboxylic acid *N*-*tert*-butyl ester 2-ethyl ester 3,3-dimethyl ester (126)**



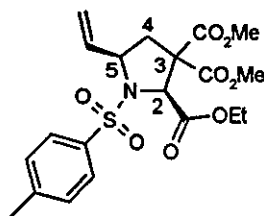
Prepared following the general thermal procedure for compound (81), 5-vinyl-pyrrolidine-1,2,3,3-tetracarboxylic acid *N*-*tert*-butyl ester 2-ethyl ester 3,3-dimethyl ester (126) (0.180 g, 47%) was prepared as a yellow oil using *N*-*tert*-butyl ester ethyl ester imine (0.200 g, 1.00 mmol) for 48 hours;  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  3369s, 2978s (CH str), 1745s (C=O), 1682s, 1509s, 1367s, 1245s, 1212s, 1154s, 1060s, 1025s, 985m,  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 1.25 (6H, m, O-CH<sub>2</sub>-CH<sub>3</sub>, O-CH<sub>2</sub>-CH<sub>3</sub>), 1.40 (18H, m, 9 x C(CH<sub>3</sub>)<sub>3</sub>, 9 x C(CH<sub>3</sub>)<sub>3</sub>), 2.29 (1H, dd, *J*=6.4 and 13.2, C4CH(H)), 2.49-2.72 (2H, m, C4'-CH'(H), C4'-CH(H')), 2.99 (1H, dd, *J*=10.0 and 13.2, C4-CH(H)), 3.68 (3H, s, O-CH<sub>3</sub>), 3.70 (3H, s, O-CH<sub>3</sub>), 3.71 (3H, s, O-CH<sub>3</sub>), 3.75 (3H, s, O-CH<sub>3</sub>), 4.08-4.33 (4H m, O-CH<sub>2</sub>-CH<sub>3</sub>, O-CH<sub>2</sub>-CH<sub>3</sub>), 4.45 (1H, m, C5-CH), 4.83 (1H, m, C5'-CH'), 5.01 (1H, s, C2-CH), 5.20 (2H, m, CH=CH<sub>2</sub>), 5.27 (1H, s, C2'-N-CH'), 5.34-5.50 (2H, m, CH=CH<sub>2</sub>), 5.74 (1H, m, CH=CH<sub>2</sub>), 5.97 (1H, m, CH'=CH<sub>2</sub>);  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 13.99 (O-CH<sub>2</sub>-C(H)<sub>3</sub>), 14.97 (O-CH<sub>2</sub>-C(H)<sub>3</sub>), 28.19 (C(CH<sub>3</sub>)<sub>3</sub>), 39.10 (C4'-C(H)<sub>2</sub>), 39.54 (C4-CH<sub>2</sub>), 52.50 (C5-CH), 52.99 (C2-CH), 53.05 (C5'-C(H)), 53.43 (C2'-C(H)), 61.39 (O-CH<sub>2</sub>-CH<sub>3</sub>), 62.13 (O-CH<sub>2</sub>-CH<sub>3</sub>), 64.08 (C3-C), 64.43 (C3'-C'), 80.36 (C(CH<sub>3</sub>)<sub>3</sub>), 80.52 (O-CH<sub>3</sub>), 80.98 (O-C(H)<sub>3</sub>), 81.01 (O-C(H)<sub>3</sub>), 81.27 (O-CH<sub>3</sub>), 88.90 (C'(CH<sub>3</sub>)<sub>3</sub>), 117.80 (CH<sub>2</sub>=CH), 118.61 (C'H<sub>2</sub>=CH), 132.92 (CH<sub>2</sub>=CH), 136.93 (CH<sub>2</sub>=C(H)), 167.71 (C=O), 167.80 (C'=O), 168.29 (C=O), 168.48 (C'=O), 169.41 (C'=O), 169.65 (C'=O), 169.73 (C=O), 169.93 (C=O), *m/z* (EI) 385 (*M*<sup>+</sup>, 1%), 284 (10), 213 (21), 189 (25), 153 (33), 133 (33), 89 (30), 57 (100), 41 (20); Accurate mass for C<sub>18</sub>H<sub>27</sub>NO<sub>4</sub> – 385.1736, found – 385.1747.

***N*-(2-Cyano-phenyl)-5-vinyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (127)**



Prepared following the general thermal procedure for compound (81), *N*-(2-cyano-phenyl)-5-vinyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (127) (0.230 g, 58%) was prepared as a yellow oil using *N*-(2-cyano-phenyl)-ethyl ester imine (0.200 g, 1.00 mmol) for 48 hours;  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2983w (CH str), 2342m (C $\equiv$ N), 1740s (C=O), 1629m, 1604m, 1577m, 1371w, 1314m, 1282s, 1231m, 1088, 1020m, 848w, 752m, 668w;  $\delta_{\text{H}}$  (250 MHz; CDCl<sub>3</sub>) 1.17-1.22 (6H, m, O-CH<sub>2</sub>-C'H<sub>3</sub>, O-CH<sub>2</sub>-CH<sub>3</sub>), 2.34 (1H, dd, *J*=6.8 and 13.2, C4'-C'(H)H), 2.55 (1H, dd, *J*=6.8 and 13.2, C4-C(H)H), 2.67 (1H, dd, *J*=10.0 and 13.2, C4'-C'(H)H), 2.78 (1H, dd, *J*=10.0 and 13.2, C4-C(H)H), 3.66 (3H, s, O-C'H<sub>3</sub>), 3.68 (3H, s, O-C'H<sub>3</sub>), 3.72 (3H, s, O-CH<sub>3</sub>), 3.76 (3H, s, O-CH<sub>3</sub>), 4.15 (1H, m, C5'-C'H), 4.08-4.16 (2H, m, O-C'H<sub>2</sub>-CH<sub>3</sub>), 4.21-4.26 (2H, m, O-CH<sub>2</sub>-CH<sub>3</sub>), 4.76 (1H, m, C5-CH), 4.96 (1H, s, C2-CH), 5.07-5.14 (3H, m, CH<sub>2</sub>=CH, C2'-C'H), 5.20-5.26 (2H, m, C'H<sub>2</sub>=CH), 5.71 (1H, m, CH<sub>2</sub>=C'H), 5.92 (1H, m, CH<sub>2</sub>=CH), 6.65-6.81 (4H, m, 4 x Ar-CH), 7.20-7.41 (4H, m, 4 x Ar-C'H);  $\delta_{\text{C}}$  (101 MHz; CDCl<sub>3</sub>) 12.99 (O-CH<sub>2</sub>-CH<sub>3</sub>), 13.05 (O-CH<sub>2</sub>-C'H<sub>3</sub>), 38.17 (C4-C'H<sub>2</sub>), 38.61 (C4-CH<sub>2</sub>), 52.06 (C5'-C'H), 52.13 (C5-CH), 52.34 (C2-CH), 52.49 (C2'-C'H), 60.47 (O-CH<sub>2</sub>-CH<sub>3</sub>), 62.06 (O-C'H<sub>2</sub>-CH<sub>3</sub>), 63.30 (C3'-C'), 65.86 (C3-C), 111.38 (C $\equiv$ N), 114.15 (C $\equiv$ N), 115.84 (Ar-C'-C $\equiv$ N), 116.02 (Ar-C-C $\equiv$ N), 116.98 (C'H<sub>2</sub>=CH), 117.25 (C'H<sub>2</sub>=CH), 118.11 (Ar-CH), 127.55 (Ar-C'H), 131.34 (Ar-CH), 132.08 (Ar-C'H), 132.98 (Ar-CH), 133.35 (Ar-C'H), 135.93 (CH<sub>2</sub>=C'H), 135.96 (CH<sub>2</sub>=CH), 145.93 (Ar-C), 167.39 (C'=O), 168.49 (C'=O), 168.78 (C'=O); *m/z* (EI) 286 (M<sup>+</sup>, 6%), 227 (63), 213 (25), 181 (62), 153 (100), 118 (99), 91 (78), 59 (99); Accurate mass for C<sub>20</sub>H<sub>22</sub>N<sub>2</sub>O<sub>6</sub> – 386.1478, found – 386.1487.

***N*-(Toluene-4-sulfonyl)-5-vinyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (128)**



***Thermal Procedure***

Prepared following the general thermal procedure for compound (81), *N*-(toluene-4-sulfonyl)-5-vinyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (128) (0.250 g, 56%) was prepared as a white crystalline solid using *N*-tosyl-ethyl ester imine (0.260 g, 1.00 mmol) for 96 hours;  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  2955m (CH str), 1742s (C=O), 1436s, 1350s, 1267s, 1166s, 1093s, 1028m, 931m, 815m, 664s,  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 1.15 (3H, t,  $J=7.3$ , O-CH<sub>2</sub>-CH<sub>3</sub>), 2.34 (3H, s, Ar-CH<sub>3</sub>), 2.54 (1H, dd,  $J=10.0$  and 13.2, C4-CH(H)), 2.67 (1H, dd,  $J=6.8$  and 13.2, C4-CH(H)), 3.61 (3H, s, O-CH<sub>3</sub>), 3.64 (3H, s, O-CH<sub>3</sub>), 4.05-4.15 (2H, m, O-CH<sub>2</sub>-CH<sub>3</sub>), 4.14 (1H, m, C5-CH), 5.00-5.17 (3H, m, C2-CH, CH<sub>2</sub>=CH), 5.74 (1H, m, CH<sub>2</sub>=CH), 7.21 (2H, d,  $2 \times J=8.3$ , Ar-CH), 7.63 (2H, d,  $J=8.3$ ,  $2 \times$  Ar-CH);  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 14.27 (O-CH<sub>2</sub>-CH<sub>3</sub>), 21.88 (Ar-CH<sub>3</sub>), 39.02 (C4-CH<sub>2</sub>), 53.56 (C5-CH), 53.97 (C2-CH), 62.32 (O-CH<sub>2</sub>-CH<sub>3</sub>), 62.40 (C3-C), 62.48, 65.59 (O-CH<sub>3</sub>), 117.86 (CH<sub>2</sub>=CH), 128.22 (Ar-CH), 129.66 (Ar-CH), 136.92 (Ar-C), 138.12 (CH<sub>2</sub>=CH), 143.93 (Ar-C), 167.51 (C=O), 168.67 (C=O), 169.78 (C=O);  $m/z$  (EI) 440 ( $M^+ + H$ , 29%), 366 (100), 155 (25), 109 (20), 91 (55), 81 (43), 69 (61), 43 (65), Accurate mass for  $\text{C}_{20}\text{H}_{25}\text{NO}_8\text{S}$  – 439.1301, found – 439.1304.

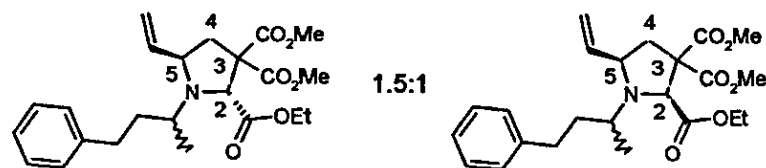
***Microwave Procedure***

Prepared following the general microwave procedure for compound (81), *N*-(toluene-4-sulfonyl)-5-vinyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (128) (0.330 g, 74%) was prepared as a white crystalline solid using *N*-tosyl-ethyl ester imine (0.260 g, 1.00 mmol); Data as above.

### *Silica Procedure*

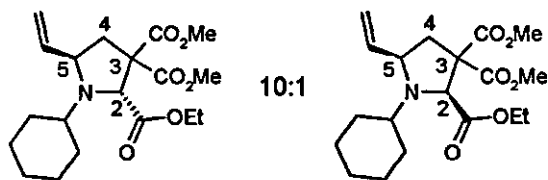
Prepared following the general silica enhanced procedure for compound (85), *N*-(toluene-4-sulfonyl)-2-ethyl ester-3,3-dicarboxylic acid dimethyl ester-5-vinyl pyrrolidine (128) (0.260 g, 57%) was prepared as a white crystalline solid using *N*-tosyl-ethyl ester imine (0.26 g, 1.00 mmol); Data as above.

***N*-(1-Methyl-3-phenyl-propyl)-5-vinyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (130)**



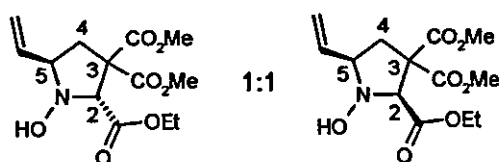
Prepared following the general thermal procedure for compound (81), *N*-(1-methyl-3-phenyl propyl)-5-vinyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (130) (0.180 g, 44%) was prepared as a yellow oil using *N*-(1-methyl-3-phenyl propyl)-ethyl ester imine (0.220 g, 1.00 mmol) for 48 hours;  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2954m (CH str), 1736s (C=O), 1654m, 1436m, 1271s, 1156m, 1060w, 1028w, 975w, 929w, 748m;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 1.10-1.24 (6H, m, O-CH<sub>2</sub>-CH<sub>3</sub>, O-CH<sub>2</sub>-CH<sub>3</sub>), 1.45-1.49 (2H, m, CH<sub>2</sub>), 1.64 (1H, m, CH(H)), 1.73 (1H, m, CH(H)), 2.39 (1H, dd,  $J=6.8$  and  $13.6$ , C4-CH(H)), 2.39-2.56 (2H, m, C4'-CH(H), C4'-CH(H')), 2.83 (1H, dd,  $J=6.8$  and  $13.6$ , C4-CH(H')), 3.32 (1H, m, C5-CH), 3.44 (1H, m, C5'-CH'), 3.59 (3H, s, O-CH<sub>3</sub>), 3.60 (3H, s, O-CH<sub>3</sub>), 3.66 (3H, s, O-CH<sub>3</sub>), 3.69 (3H, s, O-CH<sub>3</sub>), 3.98-4.07 (4H, m, O-CH<sub>2</sub>-CH<sub>3</sub>, O-CH<sub>2</sub>-CH<sub>3</sub>), 4.25 (1H, s, C2'-CH), 4.31 (1H, s, C2-CH), 4.89-5.06 (2H, m, CH=CH<sub>2</sub>), 5.07-5.28 (2H, m, CH=CH<sub>2</sub>), 5.66 (1H, m, CH=CH<sub>2</sub>), 5.93 (1H, m, CH=CH<sub>2</sub>), 7.04-7.18 (10H, m, 5 x Ar-CH, 5 x Ar-CH');  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 13.79 (O-CH<sub>2</sub>-CH<sub>3</sub>), 13.97 (O-CH<sub>2</sub>-CH<sub>3</sub>), 14.07 (CH-CH<sub>3</sub>), 14.64 (CH-CH<sub>3</sub>), 17.69 (CH-CH<sub>3</sub>), 32.45 (C4-CH<sub>2</sub>), 32.79 (C4'-CH<sub>2</sub>), 32.89 (CH<sub>2</sub>), 37.63 (C'H<sub>2</sub>), 38.53 (O-CH<sub>2</sub>-CH<sub>3</sub>), 39.33 (O-CH<sub>2</sub>-CH<sub>3</sub>), 53.28 (C5'-CH), 52.78 (C5-CH), 53.28 (C2'-CH), 53.87 (C2-CH), 60.84 (CH<sub>2</sub>), 60.88 (C'H<sub>2</sub>), 61.56 (O-CH<sub>3</sub>), 62.54 (O-CH<sub>3</sub>), 63.17 (C3'-CH), 63.43 (C3-CH), 63.83 (O-CH<sub>3</sub>), 67.19 (O-CH<sub>3</sub>), 115.93 (C'H<sub>2</sub>=CH), 116.72 (CH<sub>2</sub>=CH), 125.50 (Ar-CH), 125.60 (Ar-CH), 128.26 (Ar-CH), 128.29 (Ar-CH), 128.37 (Ar-CH), 128.45 (Ar-CH), 140.98 (Ar-CH), 141.53 (CH<sub>2</sub>=CH), 142.63 (CH<sub>2</sub>=CH), 142.71 (Ar-CH), 168.79 (C=O), 168.85 (C=O), 170.08 (C=O), 170.34 (C=O), 172.98 (C=O), 173.26 (C=O);  $m/z$  (EI) 417 ( $\text{M}^+$ , 2%), 344 (100), 312 (41), 284 (4), 212 (16), 153 (6), 91 (41), 49 (121); Accurate mass for  $\text{C}_{23}\text{H}_{31}\text{NO}_6$  - 417.2151, found - 417.2158.

***N*-Cyclohexyl-5-vinyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (131)**



Prepared following the general thermal procedure for compound (81), *N*-cyclohexyl-5-vinyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (131) (0.160 g, 42%) was prepared as a yellow oil using *N*-cyclohexyl-ethyl ester imine (0.180 g, 1.00 mmol) for 48 hours;  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  2929s, 2854m (CH str), 1740s (C=O), 1654w, 1436m, 1370m, 1263s, 1201m, 1201m, 1182m, 1070m, 1030m, 891w,  $\delta_{\text{H}}$  (250 MHz,  $\text{CDCl}_3$ ) 1.01-1.66 (26H, m, O-CH<sub>2</sub>-C'H<sub>3</sub>, O-CH<sub>2</sub>-CH<sub>3</sub>, 5 x CH<sub>2</sub>', 5 x CH<sub>2</sub>), 2.40-2.51 (3H, m, C4-C'(H)H, C4-C'(H)H, C4-C(H)H), 2.92 (1H, dd, J=6.4 and 13.2, C4-C(H)H), 3.40-3.48 (2H, m, O-C'H<sub>2</sub>-CH<sub>3</sub>), 3.59 (3H, s, O-C'H<sub>3</sub>), 3.60 (3H, s, O-CH<sub>3</sub>), 3.67 (3H, s, O-CH<sub>3</sub>), 3.71 (3H, s, O-C'H<sub>3</sub>), 3.82-3.95 (2H, m, O-CH<sub>2</sub>-CH<sub>3</sub>), 4.03 (1H, m, C5'-C'H), 4.08 (1H, m, C5-CH), 4.32 (1H, s, C2'-C'H), 4.46 (1H, s, C2-CH), 4.92-5.09 (4H, m, C'H<sub>2</sub>=CH, CH<sub>2</sub>=CH), 5.32 (1H, m, CH<sub>2</sub>=CH), 5.66 (1H, m, CH<sub>2</sub>=C'H);  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 14.40 (O-CH<sub>2</sub>-C'H<sub>3</sub>), 14.50 (O-CH<sub>2</sub>-CH<sub>3</sub>), 25.86 (C'H<sub>2</sub>), 25.99 (CH<sub>2</sub>), 26.21 (C'H<sub>2</sub>), 26.50 (CH<sub>2</sub>), 26.60 (CH<sub>2</sub>), 27.78 (C'H<sub>2</sub>), 29.62 (C'H<sub>2</sub>), 32.66 (CH<sub>2</sub>), 33.36 (C'H<sub>2</sub>), 37.89 (CH<sub>2</sub>), 53.13 (C4-CH<sub>2</sub>), 53.16 (C4'-C'H<sub>2</sub>), 53.53 (C5-CH), 53.63 (C5'-C'H), 56.62 (C2-CH), 57.83 (C2'-C'H), 60.92 (O-CH<sub>2</sub>-CH<sub>3</sub>), 60.94 (O-C'H<sub>2</sub>-CH<sub>3</sub>), 61.17 (O-CH<sub>3</sub>), 62.42 (C3-C), 62.62 (C3'-C'), 63.17 (O-C'H<sub>3</sub>), 65.65 (O-CH<sub>3</sub>), 66.24 (O-C'H<sub>3</sub>), 115.25 (CH<sub>2</sub>=CH), 116.26 (C'H<sub>2</sub>=CH), 141.79 (CH<sub>2</sub>=CH), 143.07 (CH<sub>2</sub>=C'H), 169.23 (C'=O), 169.41 (C=O), 170.48 (C=O), 170.61 (C'=O), 172.92 (C=O), 173.74 (C'=O),  $m/z$  (EI) 367 ( $\text{M}^+$ , 1%), 308 (4), 294 (100), 212 (20), 153 (4), 84 (6). Accurate mass for  $\text{C}_{19}\text{H}_{29}\text{NO}_6$  – 367.1995, found – 367.2003.

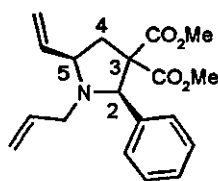
***N*-Hydroxy-5-vinyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (132)**



Prepared following the general thermal procedure for compound (81), *N*-hydroxy-5-vinyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (132) (0.170 g, 55%) was prepared as a yellow oil using *N*-hydroxy-ethyl ester imide (0.120 g, 1.00 mmol) for 48 hours;  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  3373br m (H-O), 2959m (CH str), 1748s (C=O), 1437m, 1371m, 1261s, 1205s, 1033s, 856w;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 1.20 (3H, t,  $J=7.2$ , O-CH<sub>2</sub>-CH<sub>3</sub> ester), 1.25 (3H, t,  $J=7.2$ , O-CH<sub>2</sub>-C'<sub>3</sub>H<sub>3</sub> ester), 2.26 (1H, dd,  $J=6.8$  and 13.2, C4-C(H)H), 2.52 (1H, dd,  $J=9.6$  and 13.2, C4'-C(H)H), 2.65 (1H, dd,  $J=6.8$  and 13.2, C4'-C'(H)H), 2.88 (1H, dd,  $J=9.6$  and 13.2, C4'-C'(H)H), 3.65 (3H, s, O-CH<sub>3</sub>), 3.67 (3H, s, O-C'<sub>3</sub>H<sub>3</sub>), 3.72 (3H, s, O-CH<sub>3</sub>), 3.76 (3H, s, O-C'<sub>3</sub>H<sub>3</sub>), 4.09-4.16 (4H, m, O-CH<sub>2</sub>-CH<sub>3</sub>, O-CH<sub>2</sub>-CH<sub>3</sub>), 4.45 (1H, m, C5-CH'), 4.82 (1H, m, C5-CH), 4.95 (1H, s, C2-CH'), 5.06-5.10 (2H, m, CH<sub>2</sub>=CH), 5.11 (1H, s, C2-CH), 5.19-5.25 (2H, m, C'H<sub>2</sub>=CH), 5.72 (1H, m, CH<sub>2</sub>=CH), 5.86 (1H, m, CH<sub>2</sub>=C'H), 10.32 (2H, s, H'O-N, HO-N);  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 14.28 (O-CH<sub>2</sub>-CH<sub>3</sub>), 14.35 (O-CH<sub>2</sub>-C'<sub>3</sub>H<sub>3</sub>), 39.47 (C4-CH<sub>2</sub>), 39.94 (C4'-C'H<sub>2</sub>), 53.18 (C5-CH), 53.51 (C5'-C'H), 53.77 (C2-CH), 53.92 (C2'-C'H), 61.95 (O-CH<sub>2</sub>), 62.17 (O-C'H<sub>2</sub>), 64.44 (C3-C), 64.73 (C3'-C'), 77.89 (O-CH<sub>3</sub>), 80.94 (O-C'H<sub>3</sub>), 81.29 (O-CH<sub>3</sub>), 81.40 (O-C'H<sub>3</sub>), 117.27 (CH<sub>2</sub>=CH), 118.38 (C'H<sub>2</sub>=CH), 137.11 (CH<sub>2</sub>=C'H), 142.31 (CH<sub>2</sub>=CH), 162.51 (C'=O), 162.86 (C=O), 168.31 (C=O), 168.77 (C'=O), 169.85 (C=O), 170.26 (C'=O);  $m/z$  (EI) 301 ( $M^+$ , 1%), 287 (26), 227 (99), 195 (99), 167 (92), 159 (100), 139 (76), 122 (99), 85 (51), 79 (99).

### Section 3.07 – Pyrrolidines Derived from *N*-Olefin Imines

#### *N*-Allyl-2-phenyl-5-vinyl pyrrolidine-3,3-dicarboxylic acid dimethyl ester (161)



#### Thermal Procedure

Prepared following the general thermal procedure for compound (81), *N*-allyl-2-phenyl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (161) (0.270 g, 81%) was prepared as a yellow-brown oil using *N*-allyl-phenyl imine (0.150 g, 1.00 mmol) for 48 hours,  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  2950m (CH str), 2812w, 1731s (C=O), 1454s, 1434s, 1265s, 1197s, 1138s, 1063s, 920s, 753m, 701s;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 1.18 (2H, m, N-CH(H), N-CH(H)), 2.18 (2H, dd,  $J=6$  and 13.2, C4-CH(H)), 2.63 (2H, dd,  $J=10.8$  and 13.2 C4-CH(H)), 3.08 (3H, s, O-CH<sub>3</sub>), 3.13 (1H, m, C5-CH), 3.18 (1H, m, C2-CH), 3.69 (3H, s, O-CH<sub>3</sub>), 4.88-4.95 (2H, m, vinyl CH<sub>2</sub>=CH), 5.09-5.20 (2H, m, allyl CH<sub>2</sub>=CH), 5.67 (1H, m, vinyl CH<sub>2</sub>=CH), 5.73 (1H, m, allyl CH<sub>2</sub>=CH), 7.14-7.31 (5H, m, 5 x Ar-CH);  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 39.40 (C4-CH<sub>2</sub>), 52.30 (O-CH<sub>3</sub>), 52.69 (N-CH<sub>2</sub>), 53.24 (O-CH<sub>3</sub>), 64.30 (C5-CH), 64.63 (C3-C), 70.34 (C2-CH), 117.81 (vinyl CH<sub>2</sub>=CH), 118.20 (allyl CH<sub>2</sub>=CH), 127.90 (Ar-CH), 128.05 (Ar-CH), 129.16 (Ar-CH), 133.86 (vinyl CH<sub>2</sub>=CH), 139.96 (allyl CH<sub>2</sub>=CH), 140.35 (Ar-C), 169.75 (C=O), 172.51 (C=O);  $m/z$  (EI) 329 ( $\text{M}^+$ , 16%), 288 (89), 270 (72), 252 (17), 210 (18), 185 (21), 144 (100), 109 (56), 91 (20); Accurate mass for  $\text{C}_{19}\text{H}_{23}\text{NO}_4$  – 329.1627, found – 329.1629.

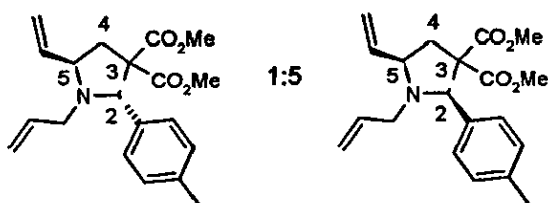
#### Microwave Procedure

Prepared following the general microwave procedure for compound (85), *N*-allyl-2-phenyl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (161) (0.230 g, 71%) was prepared as a yellow-brown oil using *N*-allyl-phenyl imine (0.150 g, 1.00 mmol); Data as above

### *Silica Procedure*

Prepared following the general silica enhanced procedure for compound (85), *N*-allyl-2-phenyl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (161) (0.260 g, 79%) was prepared as a yellow-brown oil using *N*-allyl-phenyl imine (0.150 g, 1.00 mmol), Data as above.

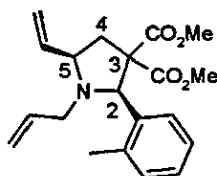
***N*-Allyl-2-*p*-tolyl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (174)**



Prepared following the general thermal procedure for compound (81), *N*-allyl-2-*p*-tolyl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (174) (0.190 g, 54%) was prepared as a yellow oil using *N*-allyl-(4-methyl phenyl) imine (0.160 g, 1.00 mmol) for 48 hours;  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2950m (CH str), 2812m, 1733s (C=O), 1511m, 1433s, 1267s, 1187s, 1137m, 1065m, 993m, 920m, 838w, 799w;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 2.17 (1H, dd,  $J=6.0$  and  $13.2$ , C4-CH(H')), 2.22 (3H, s, Ar-CHH'<sub>3</sub>), 2.30 (3H, s, Ar-CHH'<sub>3</sub>), 2.41 (1H, dd,  $J=6.0$  and  $13.2$ , C4-CH(H)), 2.60 (1H, dd,  $J=10.8$  and  $13.2$ , C4-CH'H'), 2.67 (1H, dd,  $J=10.8$  and  $13.2$ , C4-CH(H)), 3.03 (3H, s, O-CH'H'<sub>3</sub>), 3.07 (3H, s, O-CHH'<sub>3</sub>), 3.13 (2H, m, N-CH'H'<sub>2</sub>), 3.43 (2H, m, N-CHH'<sub>2</sub>), 3.68 (3H, s, O-CH'H'<sub>3</sub>), 3.72 (3H, s, O-CHH'<sub>3</sub>), 4.31 (1H, s, C5-CH), 4.35 (1H, m, C5-CH'), 4.64 (1H, s, C2-CH'), 4.85 (1H, s, C2-CH), 4.92-4.94 (2H, m, allyl CH=CH'H'<sub>2</sub>), 4.97-4.99 (2H, m, allyl CH=CHH'<sub>2</sub>), 5.08-5.21 (2H, m, vinyl CH=CH'H'<sub>2</sub>), 5.31-5.38 (2H, m, vinyl CH=CHH'<sub>2</sub>), 5.65 (1H, m, allyl CH'H'=CHH'<sub>2</sub>), 5.78 (1H, m, vinyl CH'H'=CHH'<sub>2</sub>), 5.83 (1H, m, allyl CH=CHH'<sub>2</sub>), 6.00 (1H, m, vinyl CH=CHH'<sub>2</sub>), 6.98 (2H, d,  $J=7.6$ , 2 x Ar-CH), 7.00 (2H, d,  $J=7.6$ , 2 x Ar-CH'), 7.17 (2H, d,  $J=7.6$ , 2 x Ar-CH), 7.18 (2H, d,  $J=7.6$ , 2 x Ar-CH');  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 21.11 (Ar-C'H'<sub>3</sub>), 21.24 (Ar-CHH'<sub>3</sub>), 29.69 (C4-CHH'<sub>2</sub>), 38.22 (C4-CH'H'<sub>2</sub>), 49.93 (N-CHH'<sub>2</sub>), 51.91 (C2-CH'), 52.15 (C5-CH), 52.23 (N-CH'H'<sub>2</sub>), 52.80 (C2-CH), 52.91 (C2-CH'), 55.89 (C3-C), 62.95 (O-CHH'<sub>3</sub>), 64.17 (C3-C'), 69.32 (O-CHH'<sub>3</sub>), 79.12 (O-CH'H'<sub>3</sub>), 84.17 (O-CH'H'<sub>3</sub>), 117.30 (allyl CH'H'=CH), 117.53 (allyl CH=CH), 117.54 (vinyl CH=CH), 117.74 (vinyl CH=CH), 126.86 (Ar-CH), 128.36 (Ar-CH), 128.37 (Ar-CH'), 128.55 (Ar-CH'), 133.54 (allyl CH=CH'), 133.56 (allyl CH=CH), 133.55 (allyl CH=CH), 136.57 (Ar-C), 136.84 (Ar-C'), 137.03 (Ar-C), 137.71 (Ar-C'), 141.91 (vinyl CH=CH), 141.94 (vinyl CH=CH), 169.00 (C=O), 169.44 (C'=O), 171.24 (C=O), 172.16 (C'=O);  $m/z$  (EI) 343 ( $\text{M}^+$ , 18%), 302 (65), 284 (56), 252 (25), 184 (23), 158 (100).

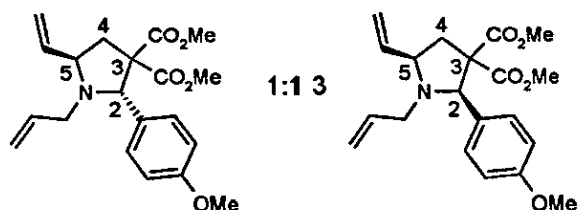
118 (32), 109 (55), 91 (24), 59 (21); Accurate mass for  $\text{C}_{20}\text{H}_{25}\text{NO}_4$  – 343.1783, found – 343.1783.

***N*-Allyl-2-*o*-tolyl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (175)**



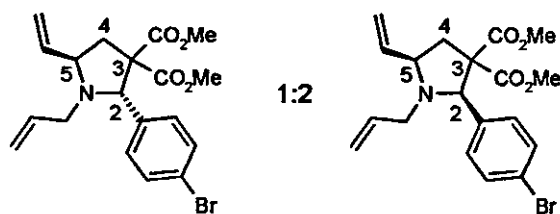
Prepared following the general thermal procedure for compound (81), *N*-allyl-2-*o*-tolyl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (175) (0.250 g, 72%) was prepared as a yellow oil using *N*-allyl-(2-methyl phenyl) imine (0.160 g, 1.00 mmol) for 48 hours;  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2949w (CH str), 1732s (C=O), 1434s, 1267m, 1096m, 1026w, 997w, 920w, 746m, 694s;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 2.15 (1H, dd,  $J=4.8$  and 13.2, C4-CH(H)), 2.24 (3H, s, Ar-CH<sub>3</sub>), 2.73 (1H, dd,  $J=12.8$  and 13.2, C4-CH(H)), 2.93 (3H, s, O-CH<sub>3</sub>), 3.08 (2H, d,  $J=6.8$ , N-CH<sub>2</sub>), 3.17 (1H, m, C5-CH), 3.70 (3H, s, O-CH<sub>3</sub>), 4.87-4.98 (2H, m, vinyl CH=CH<sub>2</sub>), 5.02 (1H, s, C2-CH), 5.10-5.22 (2H, m, allyl CH=CH<sub>2</sub>), 5.62 (1H, m, vinyl CH=CH<sub>2</sub>), 5.71 (1H, m, allyl CH=CH<sub>2</sub>), 6.94-7.46 (4H, m, 4 x Ar-CH);  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 19.66 (Ar-CH<sub>3</sub>), 39.79 (C4-CH<sub>2</sub>), 51.73 (C5-CH), 52.97 (C2-CH), 53.25 (N-CH<sub>2</sub>), 63.99 (O-CH<sub>3</sub>), 65.05 (O-CH<sub>3</sub>), 117.11 (vinyl CH<sub>2</sub>=CH), 117.60 (allyl CH<sub>2</sub>=CH), 125.42 (Ar-CH), 127.01 (Ar-CH), 128.83 (Ar-CH), 129.35 (Ar-CH), 134.41 (vinyl CH<sub>2</sub>=CH), 136.99 (Ar-C), 138.89 (Ar-C), 139.47 (allyl CH<sub>2</sub>=CH), 169.19 (C=O), 172.30 (C=O);  $m/z$  (EI) 343 ( $\text{M}^+$ , 24%), 284 (70), 252 (44), 198 (20), 184 (13), 158 (100), 118 (29), 109 (63), 94 (14), 41 (20); Accurate mass for  $\text{C}_{20}\text{H}_{25}\text{NO}_4$  – 343.1783, found – 343.1788

***N*-Allyl-2-(4-methoxy-phenyl)-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (178)**



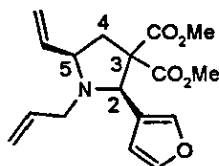
Prepared following the general thermal procedure for compound (81), *N*-allyl-2-(4-methoxy-phenyl)-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (178) (0.180 g, 51%) was prepared as a yellow oil using *N*-allyl-(4-methoxy-phenyl) imine (0.180 g, 1.00 mmol) for 48 hours;  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2950m (CH str), 1731s (C=O), 1664m, 1510m, 1434s, 1250, 1178m, 1096m, 997w, 930w, 837w, 747m;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 1.35 (2H, m, N-CH<sub>2</sub>), 1.73 (2H, m, N-CH<sub>2</sub>'), 1.99 (1H, dd,  $J=2.16$  and 8.8, C4-CH(H)), 2.43 (2H, m, C4'-CH(H'), C4'-CH'(H)), 2.79 (1H, dd,  $J=6.4$  and 8.8, C4-CH(H)), 3.66 (3H, s, O-CH<sub>3</sub>), 3.68 (3H, s, O-CH<sub>3</sub>'), 3.69 (3H, s, O-CH<sub>3</sub>), 3.71 (3H, s, O-CH<sub>3</sub>), 3.71 (3H, s, O-CH<sub>3</sub>'), 3.72 (3H, s, O-CH<sub>3</sub>'), 3.73 (1H, s, C2-CH), 3.76 (1H, s, C2'-CH'), 4.18 (1H, m, C5'-CH'), 4.29 (1H, m, C5-CH), 4.67 (1H, m, allyl CH=CH<sub>2</sub>), 5.05-5.23 (8H, m, vinyl CH=CH<sub>2</sub>, CH=CH<sub>2</sub>', allyl CH=C-H<sub>2</sub>, CH=CH<sub>2</sub>'), 5.50 (1H, m, allyl CH'=CH<sub>2</sub>), 5.75 (1H, m, vinyl CH=CH<sub>2</sub>), 5.86 (1H, m, vinyl CH'=CH<sub>2</sub>), 7.19-7.35 (4H, m, 2 x Ar-CH, 2 x Ar-CH'), 7.48-7.53 (4H, m, 2 x Ar-CH, 2 x Ar-CH');  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 28.50 (C4-CH<sub>2</sub>), 30.15 (C4'-C'H<sub>2</sub>), 52.66 (C5-CH), 52.77 (C5'-C'H), 55.28 (C2'-C'H), 55.62 (C2-CH), 61.23 (C3-C), 62.52 (C3'-C'), 63.42 (N-C'H<sub>2</sub>), 63.46 (N-CH<sub>2</sub>), 78.48 (O-CH<sub>3</sub>), 79.04 (O-C'H<sub>3</sub>), 81.97 (O-CH<sub>3</sub>), 82.72 (O-C'H<sub>3</sub>), 114.40 (allyl C'H<sub>2</sub>=CH), 117.51 (allyl CH<sub>2</sub>=CH), 118.45 (vinyl C'H<sub>2</sub>=CH), 118.10 (vinyl CH<sub>2</sub>=CH), 128.54 (Ar-C'H), 128.64 (Ar-C'H), 130.47 (Ar-C'H), 130.50 (Ar-C), 132.12 (Ar-C'), 132.53 (Ar-C), 133.94 (Ar-C'), 134.06 (Ar-CH), 134.71 (Ar-CH), 134.82 (Ar-C'H), 135.04 (Ar-CH), 137.13 (Ar-CH), 169.59 (C=O), 169.82 (C'=O), 170.19 (C=O), 170.86 (C'=O),  $m/z$  (EI) 359 ( $M^+$ , 1%), 277 (91), 200 (39), 168 (66), 153 (50), 121 (62), 108 (30), 71 (100), 59 (43), 41 (58); Accurate mass for  $\text{C}_{20}\text{H}_{25}\text{NO}_5$  – 359.1732, found – 359.1740.

***N*-Allyl-2-(4-bromo-phenyl)-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (179)**



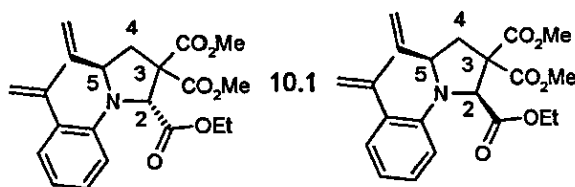
Prepared following the general thermal procedure for compound (81), *N*-allyl-2-(4-bromo-phenyl)-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (179) (0.240 g, 58%) was prepared as a yellow oil using *N*-allyl-(4-bromo-phenyl) imine (0.220 g, 1.00 mmol) for 48 hours;  $\nu_{\max}$ (film)/cm<sup>-1</sup> 2950m (CH str), 2812m, 1733s (C=O), 1485m, 1433m, 1270s, 1200s, 1137m, 1010m, 921m, 843m, 802m, 712w;  $\delta_{\text{H}}$  (250 MHz; CDCl<sub>3</sub>) 2.10 (1H, dd, *J*=5.9 and 13.2, C4-CH(H)), 2.17 (1H, dd, *J*=5.9 and 13.2, C4-CH'(H)), 2.46 (1H, dd, *J*=9.0 and 13.2, C4-CH(H')), 2.57 (2H, m, N-CH<sub>2</sub>'), 2.91 (1H, dd, *J*=9.0 and 13.2, C4-CH(H)), 3.09 (3H, s, O-CH<sub>3</sub>'), 3.15 (3H, s, O-CH<sub>3</sub>), 3.45 (2H, m, N-CH<sub>2</sub>), 3.68 (3H, s, O-CH<sub>3</sub>'), 3.72 (3H, s, O-CH<sub>3</sub>), 4.05 (1H, m, C5-CH), 4.38 (1H, m, C5-CH'), 4.63 (1H, s, C2-CH'), 4.87 (1H, s, C2-CH), 4.87-4.93 (2H, m, vinyl CH=CH<sub>2</sub>'), 5.09-5.14 (2H, m, allyl CH=CH<sub>2</sub>'), 5.15-5.19 (4H, m, allyl CH=CH<sub>2</sub>, vinyl CH=CH<sub>2</sub>), 5.62 (1H, m, allyl CH'=CH<sub>2</sub>), 5.67 (1H, m, allyl CH=CH<sub>2</sub>), 5.86 (1H, m, vinyl CH=CH<sub>2</sub>), 6.00 (1H, m, vinyl CH'=CH<sub>2</sub>), 7.18-7.36 (8H, m, 4 x Ar CH', 4 x Ar CH);  $\delta_{\text{C}}$  (101 MHz; CDCl<sub>3</sub>) 38.87 (N-CH<sub>2</sub>'), 40.32 (N-CH<sub>2</sub>'), 45.02 (C4-CH<sub>2</sub>'), 52.07 (C4'-CH<sub>2</sub>'), 52.30 (C5'-CH), 52.41 (C5-CH), 52.94 (C2-CH), 53.02 (C2'-CH), 55.70 (C3-C), 55.97 (C3'-C'), 79.31 (O-CH<sub>3</sub>'), 80.00 (O-CH<sub>3</sub>'), 82.81 (O-CH<sub>3</sub>), 83.55 (O-CH<sub>3</sub>'), 116.29 (allyl CH<sub>2</sub>=CH), 117.62 (allyl CH=CH<sub>2</sub>'), 117.84 (vinyl CH<sub>2</sub>=CH), 118.03 (vinyl CH=CH<sub>2</sub>'), 121.38 (Ar-C'), 122.06 (Ar-C), 128.31 (Ar-CH), 128.68 (Ar-CH'), 130.52 (Ar-CH), 130.80 (Ar-CH), 130.92 (Ar-C'), 130.95 (Ar-C), 132.44 (allyl CH<sub>2</sub>=CH), 133.31 (allyl CH<sub>2</sub>=CH'), 136.78 (vinyl CH<sub>2</sub>=CH), 137.31 (vinyl CH<sub>2</sub>=CH'), 168.81 (C=O), 169.12 (C'=O), 170.99 (C=O), 171.87 (C'=O); *m/z* (EI) 409 (M<sup>+</sup>, 5%), 407 (M<sup>+</sup>, 6%), 368 (35), 316 (19), 224 (33), 184 (50), 152 (52), 109 (87), 71 (77), 59 (77), 41 (100); Accurate mass for - C<sub>19</sub>H<sub>22</sub><sup>79</sup>BrNO<sub>4</sub> - 407.0732, found - 407.0731.

***N*-Allyl-2-furan-3-yl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (181)**



Prepared following the general thermal procedure for compound (81), *N*-allyl-2-furan-3-yl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (181) (0.160 g, 49%) was prepared as a yellow oil using *N*-allyl-2-furan-3-yl imine (0.140 g, 1.00 mmol) for 48 hours;  $\nu_{\text{max}}$ (film)/ $\text{cm}^{-1}$  2951m (CH str), 1732s (C=O), 1434s, 1269m, 1162m, 1095m, 1025m, 997w, 872w, 797w, 694m;  $\delta_{\text{H}}$  (250 MHz,  $\text{CDCl}_3$ ) 1.70 (2H, m, N-CH<sub>2</sub>), 2.44 (1H, dd,  $J=8.8$  and 16.0, C4-CH(H)), 2.75 (1H, dd,  $J=6.8$  and 16.0, C4-CH(H)), 3.67 (3H, s, O-CH<sub>3</sub>), 3.68 (3H, s, O-CH<sub>3</sub>), 4.16-4.32 (2H, m, allyl CH=CH<sub>2</sub>), 4.66 (1H, m, C5-CH), 5.10-5.23 (3H, m, vinyl CH=CH<sub>2</sub>, C2-CH), 5.57 (1H, m, allyl CH=CH<sub>2</sub>), 5.86 (1H, m, vinyl CH=CH<sub>2</sub>), 7.19-7.54 (3H, m, 3 x Ar-CH),  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 28.42 (N-CH<sub>2</sub>), 30.15 (C4-CH<sub>2</sub>), 52.66 (C5-CH), 52.86 (C2-CH), 63.42 (C3-C), 79.05 (O-CH<sub>3</sub>), 82.72 (O-CH<sub>3</sub>), 117.52 (vinyl CH<sub>2</sub>=CH), 118.05 (allyl CH<sub>2</sub>=CH), 128.54 (Ar-CH), 130.49 (Ar-CH), 132.53 (Ar-C), 134.06 (Ar-CH), 134.80 (vinyl CH<sub>2</sub>=CH), 135.10 (allyl CH<sub>2</sub>=CH), 169.82 (C=O), 170.86 (C=O),  $m/z$  (EI) 319 (M<sup>+</sup>, 3%), 277 (71), 261 (60), 183 (100), 153 (22), 121 (18), 108 (36), 71 (27), 59 (15); Accurate mass for C<sub>17</sub>H<sub>21</sub>NO<sub>5</sub> – 319.1419, found – 319.1414

***N*-(2-Isopropenyl-phenyl)-5-vinyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (162)**



**Thermal Procedure**

Prepared following the general thermal procedure for compound (81), *N*-(2-isopropenyl-phenyl)-5-vinyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (162) (0.230 g, 58%) was prepared as a yellow oil using *N*-(2-isopropenyl-phenyl)-ethyl ester imine (0.220 g, 1.00 mmol) for 48 hours;  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2930m (CH str), 2851w, 1740s (C=O), 1434m, 1269s, 1232s, 1114m, 1070m, 1024m, 967w, 848w, 755w;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 1.14-1.22 (6H, m, O-CH<sub>2</sub>-CH<sub>3</sub>), 1.96 (3H, s, Ar-C-CH<sub>3</sub>), 1.99 (3H, s, Ar-C-CH<sub>3</sub>), 2.28 (1H, dd,  $J=6.8$  and  $13.2$ , C4'-CH(H)), 2.55 (1H, dd,  $J=7.5$  and  $13.2$ , C4-CH(H)), 2.62 (1H, dd,  $J=6.8$  and  $13.2$ , C4-CH(H)), 2.89 (1H, dd,  $J=7.5$  and  $13.2$ , C4'-CH(H)), 3.65 (3H, s, O-CH<sub>3</sub>), 3.70 (3H, s, O-CH<sub>3</sub>), 3.72 (3H, s, O-CH<sub>3</sub>), 3.75 (3H, s, O-CH<sub>3</sub>), 4.08-4.14 (4H, m, O-CH<sub>2</sub>-CH<sub>3</sub>, O-CH<sub>2</sub>-CH<sub>3</sub>), 4.41 (1H, m, C5-CH), 4.82 (1H, m, C5'-CH), 4.95 (1H, s, C2-CH), 5.06-5.21 (5H, m, C=CH<sub>2</sub>, C=CH<sub>2</sub>, C2'-N-CH), 5.24-5.25 (4H, m, CH=CH<sub>2</sub>, CH=CH<sub>2</sub>), 5.72 (1H, m, vinyl CH=CH<sub>2</sub>), 5.91 (1H, m, vinyl CH=CH<sub>2</sub>), 6.63-6.65 (2H, m, Ar CH', Ar CH), 6.96-6.71 (2H, m, Ar CH', Ar CH), 7.30-7.32 (2H, m, Ar CH', Ar CH), 7.62-7.64 (2H, m, Ar CH', Ar CH);  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 14.07 (O-CH<sub>2</sub>-C'H<sub>3</sub>), 14.20 (O-CH<sub>2</sub>-CH<sub>3</sub>), 23.89 (Ar-C-C'H<sub>3</sub>), 24.07 (Ar-C-CH<sub>3</sub>), 39.15 (C4'-C'H<sub>2</sub>), 39.61 (C4-CH<sub>2</sub>), 53.11 (C5-CH), 53.18 (C5'-C'H), 53.38 (C2-CH), 53.54 (C5'-C'H), 61.47 (O-C'H<sub>2</sub>-CH<sub>3</sub>), 61.51 (O-CH<sub>2</sub>-CH<sub>3</sub>), 64.12 (C3-C), 64.46 (C3'-C'), 80.59 (O-CH<sub>3</sub>), 81.02 (O-C'H<sub>3</sub>), 81.09 (O-C'H<sub>3</sub>), 81.30 (O-CH<sub>3</sub>), 116.66 (CH<sub>2</sub>=C), 116.90 (C'H<sub>2</sub>=C), 118.02 (CH<sub>2</sub>=CH), 118.11 (C'H<sub>2</sub>=CH), 127.78 (Ar-C'H), 127.88 (Ar-C'H), 127.93 (Ar-CH), 128.16 (Ar-CH), 134.81 (Ar-C'H), 134.08 (Ar-C'H), 135.08 (Ar-CH), 135.14 (Ar-CH), 136.90 (CH<sub>2</sub>=C'H), 136.94 (CH<sub>2</sub>=CH), 142.84 (Ar-C'), 143.42 (Ar-C'), 167.89 (C=O), 168.37 (C=O), 169.47 (C=O), 169.49 (C'=O), 169.72 (C'=O), 169.81

(C=O);  $m/z$  (EI) 401 (M<sup>+</sup>, 3%), 213 (12), 153 (18), 144 (61), 132 (100), 121 (11), 117 (9), 59 (9); Accurate mass for C<sub>22</sub>H<sub>27</sub>NO<sub>6</sub> – 401.1838, found – 401.1833.

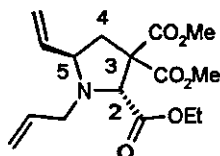
#### *Microwave Procedure*

Prepared following the general microwave procedure for compound (85), *N*-(2-isopropenyl-phenyl)-5-vinyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (162) (0.350 g, 88%) was prepared as a yellow oil using *N*-(2-isopropenyl-phenyl)-ethyl ester imine (0.220 g, 1.00 mmol); Data as above.

#### *Silica Procedure*

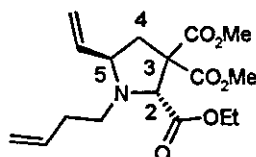
Prepared following the general silica enhanced procedure for compound (85), *N*-(2-isopropenyl-phenyl)-5-vinyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (162) (0.230 g, 58%) was prepared as a yellow oil using *N*-(2-isopropenyl-phenyl)-ethyl ester imine (0.220 g, 1.00 mmol); Data as above.

***N*-Allyl-5-vinyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (183)**



Prepared following the general thermal procedure for compound (81), *N*-allyl-5-vinyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (183) (0.200 g, 61%) was prepared as a yellow oil using *N*-allyl-ethyl carbonate imine (0.140 g, 1.00 mmol) for 48 hours,  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2954m (CH str), 1740s (C=O), 1434m, 1371w, 1267s, 1203s, 1114m, 1070m, 932w, 848w, 752w;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 1.18 (3H, t,  $J=7.4$ ,  $\text{CH}_2\text{-CH}_3$  ester), 2.55 (1H, dd  $J=6.8$  and  $12.8$ , C4-C(H)H), 2.91 (1H, dd  $J=10.0$  and  $12.8$ , C4-C(H)H), 3.65 (3H, s, O-CH<sub>3</sub>), 3.76 (3H, s, O-CH<sub>3</sub>), 4.05-4.15 (2H, m, O-CH<sub>2</sub>-CH<sub>3</sub>), 4.43 (1H, m, C5-CH), 4.82 (1H, m, C2-CH), 5.06-5.13 (2H, m, CH<sub>2</sub>=CH vinyl), 5.20-5.26 (2H, m, CH<sub>2</sub>=CH allyl), 5.71 (1H, m, CH<sub>2</sub>=CH vinyl), 5.91 (1H, m, CH<sub>2</sub>=CH allyl);  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 14.53 (O-CH<sub>2</sub>-CH<sub>3</sub>), 39.47 (C4-CH<sub>2</sub>), 39.94 (CH<sub>2</sub> allyl), 53.43 (C2-CH-ester), 53.88 (C5-CH), 61.83 (O-CH<sub>2</sub>), 64.78 (C3-C), 80.92 (O-CH<sub>3</sub>), 81.34 (O-CH<sub>3</sub>), 81.41 (vinyl CH<sub>2</sub>=CH), 81.63 (allyl CH<sub>2</sub>=CH), 117.20 (vinyl CH<sub>2</sub>=CH), 118.33 (allyl CH<sub>2</sub>=CH), 168.21 (C=O), 168.69 (C=O), 170.05 (C=O);  $m/z$  (EI) 325 ( $\text{M}^+$  +H, 4%), 295 (7), 252 (38), 227 (36), 213 (100), 195 (18), 181 (35), 121 (98), 94 (33), 65 (33), (59), Accurate mass for  $\text{C}_{16}\text{H}_{23}\text{NO}_6$  – 326.1603, found – 326.1597.

***N*-But-4-enyl-5-vinyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (184)**



***Thermal Procedure***

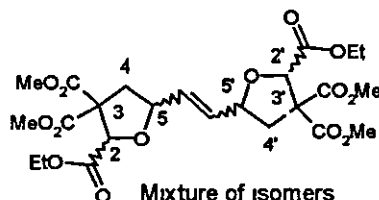
Prepared following the general thermal procedure for compound (81), *N*-but-4-enyl-5-vinyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (184) (0.280 g, 82%) was prepared as a yellow-brown oil using *N*-but-4-enyl-ethyl ester imine (0.160 g, 1.00 mmol) for 48 hours;  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2955m (CH str), 1737s (C=O), 1434s, 1270s, 1154m, 1070s, 1025s, 933m;  $\delta_{\text{H}}(250 \text{ MHz}; \text{CDCl}_3)$  1.07 (3H, t,  $J=4.7$  CH<sub>2</sub>-CH<sub>3</sub> ester), 2.13 (1H, dd,  $J=6.8$  and  $12.8$ , C4-C(H)H), 2.41 (1H, dd,  $J=1.6$  and  $10.0$ , CH<sub>2</sub>=CH-C(H)H), 2.49 (1H, dd,  $J=1.6$  and  $7.0$ , CH<sub>2</sub>=CH-C(H)H), 2.77 (1H, dd,  $J=7.6$  and  $13.2$ , C4-C(H)H), 3.51-3.53, (2H, d,  $J=5.0$ , N-CH<sub>2</sub>), 3.59 (3H, s, O-CH<sub>3</sub>), 3.63 (3H, s, O-CH<sub>3</sub>), 3.96-4.01 (2H, m, O-CH<sub>2</sub>-CH<sub>3</sub>), 4.27 (1H, s, N-CH), 4.63 (1H, m, C5-CH), 4.93-5.00 (2H, m, CH<sub>2</sub>=CH vinyl), 5.06-5.12 (2H, m, CH<sub>2</sub>=CH butyl), 5.59 (1H, m, CH<sub>2</sub>=CH vinyl), 5.78 (1H, m, CH<sub>2</sub>=CH butyl),  $\delta_{\text{C}}$  (101 MHz; CDCl<sub>3</sub>) 14.39 (O-CH<sub>2</sub>-CH<sub>3</sub>), 39.46 (N-CH<sub>2</sub>-CH<sub>2</sub>), 39.92 (C4-CH<sub>2</sub>), 53.44 (C5-CH), 53.71 (C2-CH), 61.77 (N-CH<sub>2</sub>-CH<sub>2</sub>), 61.81 (O-CH<sub>2</sub>-CH<sub>3</sub>), 64.76 (C3-C), 80.91 (CH<sub>2</sub>=CH vinyl), 81.32 (CH<sub>2</sub>=CH butyl), 81.39 (O-CH<sub>3</sub>), 81.61 (O-CH<sub>3</sub>), 117.18 (CH<sub>2</sub>=CH vinyl), 118.31 (CH<sub>2</sub>=CH butyl), 168.20 (C=O), 168.67 (C=O), 169.79 (C=O);  $m/z$  (EI) 339 (M<sup>+</sup>, 1%), 227 (48), 213 (100), 181 (50), 153 (99), 145 (33), 121 (99), 94 (44), 65 (45), 59 (99); Accurate mass for C<sub>17</sub>H<sub>25</sub>NO<sub>6</sub> – 339.1126, found – 339.1097.

***Silica Procedure***

Prepared following the general silica enhanced procedure for compound (85), *N*-but-3-enyl-5-vinyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (184) (0.280 g, 81%) was prepared as a yellow-brown oil using yellow-brown oil using *N*-but-3-enyl-ethyl ester imine (0.160 g, 1.00 mmol); Data as above.

### Section 3.08 – Ring Closing / Cross Coupling Products

#### 2-Ethyl-3,3-dimethyl-5-((E)-2-{5'-[ethyloxycarbonyl]-3',3'-di[(methoxy)carbonyl] THF-2-yl}eth-1-enyl)tetrahydrofuran-2',3',3'-tri-carboxylate (192)

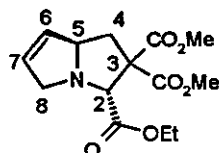


#### General Procedure

To a solution of de-gassed DCM (100 mL) and 2-Ethyl carbonylate-5-(vinyl-THF)-3,3-dicarboxylic acid dimethyl ester (**242**) (0.570 g, 2.00 mmol) in a 250 mL round bottomed flask was added the Grubbs first generation catalyst (0.100 g, 0.100 mmol). The solution was stirred positive under nitrogen at RT for 16 hours. After this time the reaction was then filtered through a plug of cotton wool and then concentrated *in vacuo* to afford the crude product as a brown heavy oil. This mixture was then purified using column chromatography (SiO<sub>2</sub>, EtOAc P.E. 40-60; 1:2, R<sub>f</sub> - 0.30) to afford 2-ethyl-3,3-dimethyl-5-((E)-2-{5'-[ethyloxycarbonyl]-3',3'-di[(methoxy)carbonyl] tetrahydrofuran-2-yl}eth-1-enyl) tetrahydrofuran-2',3',3'-tricarboxylate (**192**) (0.170 g, 31%) as a brown oil;  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2955m, 2357m (CH str), 1736s (C=O), 1436m, 1267s, 1232s, 1172m, 1068m;  $\delta_{\text{H}}$  (250 MHz; CDCl<sub>3</sub>) 1.03-1.10 (12H, m, 2x O-CH<sub>2</sub>-CH<sub>3</sub>, 2x O-CH<sub>2</sub>-CH<sub>3</sub>'), 2.09 (2H, m, C4-CH<sub>2</sub>), 2.37 (2H, m, C4'-CH<sub>2</sub>'), 2.48 (2H, m, C4''-CH<sub>2</sub>'), 2.73 (2H, m, C4'''-CH<sub>2</sub>'), 3.50 (3H, s, O-CH<sub>3</sub>), 3.50 (3H, s, O-CH<sub>3</sub>'), 3.51 (3H, s, O-CH<sub>3</sub>'), 3.51 (3H, s, O-CH<sub>3</sub>'), 3.57 (3H, s, O-CH<sub>3</sub>'), 3.60 (3H, s, O-CH<sub>3</sub>'), 3.60 (3H, s, O-CH<sub>3</sub>'), 3.60 (3H, s, O-CH<sub>3</sub>'), 3.92-3.99 (8H, m, 2x O-CH<sub>2</sub>-CH<sub>3</sub>, 2x O-CH<sub>2</sub>-CH<sub>3</sub>'), 4.24-4.68 (2H, m, 2x C5'-CH'), 4.66 (2H, m, 2x C5-CH), 4.78 (1H, s, C2-CH), 4.79 (1H, s, C2''-CH), 4.93 (1H, s, C2'-CH'), 4.93 (1H, s, C2'''-CH'), 5.47-5.50 (2H, m, CH=CH, CH=CH), 5.67-5.69 (2H, m, C'H=CH, CH=C'H);  $\delta_{\text{C}}$  (101 MHz; CDCl<sub>3</sub>) 14.44 (2x O-CH<sub>2</sub>-CH<sub>3</sub>, 2x O-CH<sub>2</sub>-CH<sub>3</sub>'), 39.51 (C4-CH<sub>2</sub>), 39.58 (C4'-CH<sub>2</sub>'), 40.01 (2x C4''-CH<sub>2</sub>'), 53.54 (C5-CH), 53.58 (C5'-CH'), 53.84 (C2''-CH), 53.94 (C2'''-CH'), 61.89

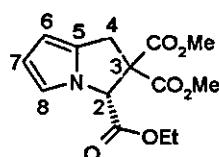
$(\text{O}-\underline{\text{C}}\text{H}_2-\text{CH}_3, \text{O}-\underline{\text{C}}'\text{H}_2-\text{CH}_3)$ , 61.94  $(\text{O}-\underline{\text{C}}''\text{H}_2-\text{CH}_3, \text{O}-\underline{\text{C}}'''\text{H}_2-\text{CH}_3)$ , 64.49  $(\text{C}3'-\underline{\text{C}}')$ ,  
 64.53  $(\text{C}3-\underline{\text{C}})$ , 64.81  $(\text{C}3''-\underline{\text{C}}'')$ , 64.87  $(\text{C}3''-\underline{\text{C}}''')$ , 79.96  $(\text{O}-\underline{\text{C}}\text{H}_3)$ , 80.08  $(\text{O}-\underline{\text{C}}'\text{H}_3)$ ,  
 80.25  $(\text{O}-\underline{\text{C}}\text{H}_3, \text{O}-\underline{\text{C}}'\text{H}_3)$ , 80.36  $(\text{O}-\underline{\text{C}}''\text{H}_3)$ , 81.39  $(\text{O}-\underline{\text{C}}'''\text{H}_3)$ , 81.44  $(\text{O}-\underline{\text{C}}''\text{H}_3)$ , 81.72  
 $(\text{O}-\underline{\text{C}}'''\text{H}_3)$ , 131.96  $(\underline{\text{C}}\text{H}=\text{CH})$ , 132.29  $(\underline{\text{C}}'\text{H}=\text{CH})$ , 133.00  $(\text{CH}=\underline{\text{C}}\text{H})$ , 133.38  
 $(\text{CH}=\underline{\text{C}}'\text{H})$ , 168.14  $(\underline{\text{C}}=\text{O}, \underline{\text{C}}'=\text{O})$ , 168.67  $(\underline{\text{C}}=\text{O}, \underline{\text{C}}'=\text{O})$ , 169.73  $(\underline{\text{C}}''=\text{O})$ , 169.77  
 $(\underline{\text{C}}=\text{O}, \underline{\text{C}}'=\text{O})$ , 169.83  $(\underline{\text{C}}''=\text{O})$ , 170.01  $(\underline{\text{C}}''=\text{O})$ , 170.07  $(\underline{\text{C}}''=\text{O}, \underline{\text{C}}'''\text{O})$ , 170.16  
 $(\underline{\text{C}}'''\text{O})$ ,  $m/z$  (EI) 544 ( $\text{M}^+$ , 6%), 467 (16), 421 (19), 409 (34), 311 (100), 237 (22),  
 214 (20), 179 (14), 141 (16), 113 (19), 59 (18); Accurate mass for  $\text{C}_{24}\text{H}_{32}\text{O}_{14}$  –  
 544.1792, found – 544.1780.

**3-Ethyl-2,2-dimethyl-2,3,5,7a-tetrahydro-1H-pyrrolizine-2,2,3-tricarboxylate (185)**



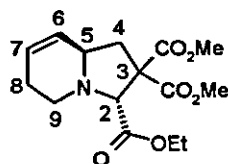
To a solution of de-gassed DCM (100 mL) and *N*-allyl-2-ethyl carbonate-5-vinylpyrrolidine-3,3-dicarboxylic acid dimethyl ester (183) (0.330 g, 1.00 mmol) in a 250 mL round bottomed flask was added the Grubbs first generation catalyst (0.100 g, 0.100 mmol). The solution was stirred positive under nitrogen at RT for 16 hours. After this time the reaction was then filtered through a plug of cotton wool and then concentrated *in vacuo* to afford the crude product as a brown heavy oil. This mixture was then purified using column chromatography (SiO<sub>2</sub>, EtOAc.P.E. 40-60; 1:2, R<sub>f</sub> - 0.30) to afford 3-ethyl-2,2-dimethyl-2,3,5,7a-tetrahydro-1H-pyrrolizine-2,2,3-tricarboxylate (185) (0.170 g, 31%) as a brown oil;  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  2952m (CH str), 2358w, 1737s (C=O), 1434m, 1372w, 1261s, 1203s, 1028m, 948w, 845w, 793w, 709w;  $\delta_{\text{H}}$  (250 MHz; CDCl<sub>3</sub>) 1.15-1.21 (3H, m, O-CH<sub>2</sub>-CH<sub>3</sub>), 2.14 (1H, dd, J=7.2 and 12.4, C4-C(H)H), 2.88 (1H, dd, J=7.6 and 12.8, C4-C(H)H), 3.43 (1H, m, C5-CH), 3.62 (3H, s, O-CH<sub>3</sub>), 3.70 (3H, s, O-CH<sub>3</sub>), 3.91 (1H, m, C7-CH=CH), 4.07-4.18 (3H, m, O-CH<sub>2</sub>-CH<sub>3</sub>, C2-CH), 4.37 (1H, m, C6-CH=CH), 5.65 (2H, s, C8-CH<sub>2</sub>),  $\delta_{\text{C}}$  (101 MHz; CDCl<sub>3</sub>) 14.46 (O-CH<sub>2</sub>-CH<sub>3</sub> ester), 21.46 (C5-CH), 39.38 (C4-CH<sub>2</sub>), 53.46 (C2-CH), 61.49 (C8-CH<sub>2</sub>), 62.62 (O-CH<sub>2</sub> ester), 63.79 (C3-C), 70.61 (O-CH<sub>3</sub>), 74.54 (O-CH<sub>3</sub>), 127.67 (C6-CH=CH), 130.51 (C7-CH<sub>2</sub>=CH), 169.34 (C=O), 170.42 (C=O), 171.29 (C=O);  $m/z$  (EI) 297 (M<sup>+</sup>, 9%), 238 (28), 224 (100), 164 (13), 106 (15), 81 (29), 59 (9); Accurate mass for C<sub>14</sub>H<sub>19</sub>NO<sub>6</sub> - 297.1212, found - 297.1208.

**3-Ethyl-2,2-dimethyl-2,3,5,7a-tetrahydro-1H-pyrrolizine-2,2,3-tricarboxylate (186)**



Prepared following the general RCM procedure for compound (185), 3-ethyl-2,2-dimethyl-2,3,5,7a-tetrahydro-1H-pyrrolizine-2,2,3-tricarboxylate (186) (0.250 g, 86%) was prepared as a brown oil using *N*-allyl-2-ethyl carbonate-5-vinylpyrrolidine-3,3-dicarboxylic acid dimethyl ester (183) (0.330 g, 1.00 mmol),  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  2923m (CH str), 1740s (C=O), 1437m, 1375m, 1272s, 1022m, 967w, 809w;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 1.15-1.21 (3H, m, O-CH<sub>2</sub>-CH<sub>3</sub>), 1.52 (1H, s, C2-CH), 3.38 (2H, m, C4-CH<sub>2</sub>), 3.69 (3H, s, O-CH<sub>3</sub>), 3.70 (3H, s, O-CH<sub>3</sub>), 4.02-4.09 (2H, m, O-CH<sub>2</sub>-CH<sub>3</sub>), 5.23 (1H, s, pyrrole), 6.15 (1H, s, pyrrole), 6.59 (1H, s, pyrrole),  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 14.69 (O-CH<sub>2</sub>-CH<sub>3</sub>), 21.42 (C2-CH), 32.58 (C4-CH<sub>2</sub>), 53.56 (O-CH<sub>3</sub>), 53.79 (C3-C), 54.12 (O-CH<sub>3</sub>), 64.66 (O-CH<sub>2</sub>-CH<sub>3</sub>), 101.14 (Ar-CH), 113.84 (Ar-CH), 114.67 (Ar-CH), 133.50 (Ar-C), 168.42 (C=O), 169.72 (C=O), 171.51 (C=O),  $m/z$  (EI) 295 ( $\text{M}^+$ , 5%), 238 (12), 224 (22), 178 (14), 146 (11), 125 (15), 111 (27), 97 (50), 71 (69), 57 (100), 43 (57); Accurate mass for  $\text{C}_{14}\text{H}_{17}\text{NO}_6$  – 295.1056, found – 295.1049.

## 2-Ethyl-3,3-dimethyl-4,5,6,7,8,9-hexahydroindolizine-2,3,3-tricarboxylate (187)



### Thermal Procedure

Prepared following the general RCM procedure for compound (185), 2-ethyl-3,3-dimethyl-4,5,6,7,8,9-hexahydroindolizine-2,3,3-tricarboxylate (187) (0.270 g, 82%) was prepared as a brown oil using *N*-butene-2-ethyl carbonate-5-vinylpyrrolidine-3,3-dicarboxylic acid dimethyl ester (165) (0.340 g, 1.00 mmol),  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2956w (CH str), 1739s (C=O), 1436m, 1374w, 1269s, 1235s, 1111m, 1068m, 1023m, 971w;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 1.19-1.23 (3H, t,  $J=7.2$ , O-CH<sub>2</sub>-CH<sub>3</sub>), 2.27 (1H, m, C8-CH(H)), 2.53 (1H, m, C8-CH(H)), 2.62 (1H, m, C4-CH(H)), 2.89 (1H, m, C4-CH(H)), 3.67 (3H, s, O-CH<sub>3</sub>), 3.74 (3H, s, O-CH<sub>3</sub>), 4.09-4.14 (3H, m, O-CH<sub>2</sub>-CH<sub>3</sub>), 4.42 (1H, m, C9-CH(H)), 4.81 (1H, m, C9-CH(H)), 4.94 (1H, s, C2-CH), 5.08 (1H, m, C5-CH), 5.63 (C6-CH=CH), 5.84 (C7-CH=CH),  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 14.41 (O-CH<sub>2</sub>-CH<sub>3</sub>), 39.54 (C4-CH<sub>2</sub>), 39.98 (C8-CH<sub>2</sub>), 53.56 (C5-CH), 61.86 (C9-CH<sub>2</sub>), 61.91 (O-CH<sub>2</sub>-CH<sub>3</sub>), 64.83 (C3-C), 80.21 (C2-CH), 81.40 (O-CH<sub>3</sub>), 81.68 (O-CH<sub>3</sub>), 131.92 (C6-CH=CH), 132.95 (C7-CH=CH), 168.62 (C=O), 169.79 (C=O), 170.09 (C=O);  $m/z$  (EI) 311 ( $M^+$ , 11%), 201 (52), 171 (44), 157 (35), 145 (76), 127 (20), 113 (100), 84 (39), 59 (44); Accurate mass for  $\text{C}_{15}\text{H}_{21}\text{NO}_6$  – 311.1368, found – 311.1364.

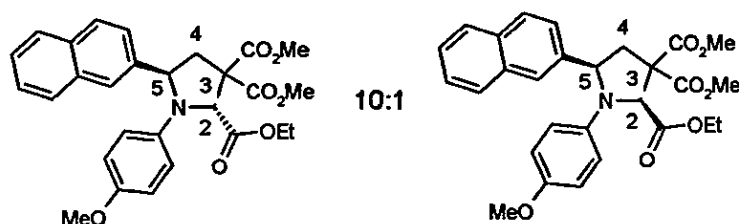
### Microwave Procedure

To a solution of de-gassed DCM (5 mL) and *N*-butene-2-ethyl carbonate-5-vinylpyrrolidine-3,3-dicarboxylic acid dimethyl ester (165) (0.340 g, 1.00 mmol) in a 10 mL tube was added the Grubbs first generation catalyst (0.100 g, 0.100 mmol). The tube was sealed and then placed in the CEM discovery microwave and was then irradiated for 20 minutes at a power setting of 50 watts (250 psi maximum pressure). After this time the reaction was then filtered through a plug of cotton wool and then concentrated *in vacuo* to afford the product. This mixture was then purified using

column chromatography (SiO<sub>2</sub>, EtOAc:P.E. 40-60; 1:4, R<sub>f</sub> - 0.35) to afford the desired bi-cyclic product (187) as a brown oil (0.240 g, 76%); Data as above

**Section 3.09 – Pyrrolidines and tetrahydrofurans derived from aromatic cyclopropanes**

***N*-(4-Methoxy-phenyl)-5-naphthalen-2-yl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (203)**

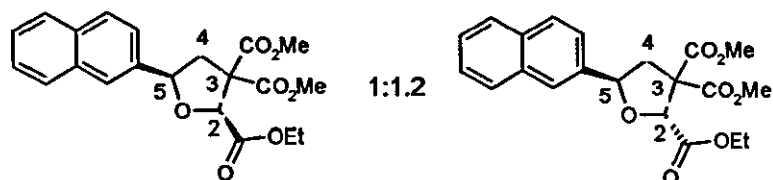


**General Procedure**

*N*-(4-Methoxy-phenyl) ethyl ester imine (0.210 g, 1.00 mmol), zinc bromide (0.460 g 2.00 mmol) and  $\text{Pd}_2(\text{dba})_3$  (0.100 g, 0.100 mmol) were added to a stirred solution of 2-naphthalen-2-yl-cyclopropane-1,1-dicarboxylic acid dimethyl ester (197) (0.280 g, 1.00 mmol) in toluene (10 mL). This mixture was stirred for 14 days at 50 °C, the solvent was evaporated *in vacuo* and the residue partitioned between EtOAc (30 mL) and distilled water (30 mL). The organic layers were separated and washed with aq HCl (1M 2 x 30 mL),  $\text{NaHCO}_3$  (30 mL), and brine solution (2 x 30 mL). The organic layer was dried with  $\text{MgSO}_4$ , filtered and concentrated *in vacuo* to give the crude pyrrolidine product as a brown heavy oil. This was purified using column chromatography ( $\text{SiO}_2$ , EtOAc:P.E. 40-60; 1:4,  $R_f$  - 0.20) to yield the *N*-(4-methoxy-phenyl)-5-naphthalen-2-yl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (203) (0.250 g, 51%) as a yellow oil;  $\nu_{\text{max}}$  (film)/ $\text{cm}^{-1}$  2952w (CH str), 1738s (C=O), 1512s, 1434m, 1245s, 1179m, 1037m, 973w, 859w, 817m, 751w,  $\delta_{\text{H}}$  (250 MHz,  $\text{CDCl}_3$ ) 1.20 (3H, t,  $J=7.5$ , O-CH<sub>2</sub>-CH<sub>3</sub>), 1.34 (3H, t,  $J=7.5$ , O-CH<sub>2</sub>-CH<sub>3</sub>), 2.65 (1H, dd,  $J=1.5$  and 13.1, C4-CH(H)), 2.99 (1H, dd,  $J=4.2$  and 13.1, C4-CH(H)), 3.00 (1H, dd,  $J=4.2$  and 13.1, C4'-CH(H)), 3.33 (3H, s, O-CH<sub>3</sub>), 3.55 (1H, dd,  $J=1.5$  and 13.1, C4'-CH'(H)), 3.62 (3H, s, O-CH<sub>3</sub>), 3.63 (3H, s, O-CH<sub>3</sub>), 3.72 (3H, s, O-CH<sub>3</sub>), 3.73 (3H, s, O-CH<sub>3</sub>), 3.77 (3H, s, O-CH<sub>3</sub>), 4.13-4.18 (2H, m, O-CH<sub>2</sub>-CH<sub>3</sub>), 4.29-4.32 (2H, m, O-CH<sub>2</sub>-CH<sub>3</sub>), 4.80 (1H, m, C5-CH), 5.05 (1H, s, C2-CH), 5.24 (1H, m, C5'-CH'), 5.58 (1H, s, C2'-CH'), 6.52-6.69 (8H, m, 8 x 4-PMB

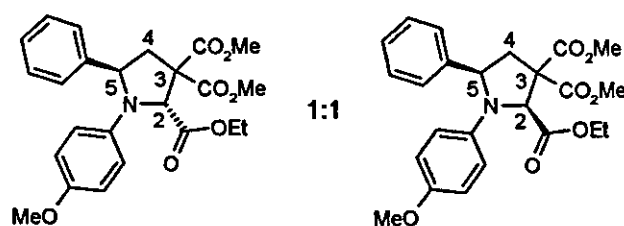
CH and CH'), 7.25-7.88 (14H, m, 14 x naphthyl CH and CH');  $\delta_c$  (101 MHz; CDCl<sub>3</sub>) 14.18 (O-CH<sub>2</sub>-CH<sub>3</sub>), 14.28 (O-CH<sub>2</sub>-CH<sub>3</sub>'), 40.09 (C4-CH<sub>2</sub>), 42.27 (C4'-CH<sub>2</sub>), 53.05 (C2-CH), 53.35 (C2'-CH), 53.64 (C5-CH), 55.55 (C5'-CH), 61.43 (O-CH<sub>2</sub>-CH<sub>3</sub>), 61.66 (O-CH<sub>2</sub>-CH<sub>3</sub>'), 61.74 (O-CH<sub>3</sub>), 62.11 (C3-C), 62.41 (C3'-C'), 63.57 (O-CH<sub>3</sub>'), 67.43 (O-CH<sub>3</sub>), 68.94 (O-CH<sub>3</sub>'), 114.50 (PMB Ar-C'H), 114.56 (PMB Ar-C'H), 114.63 (PMB Ar-CH), 115.47 (PMB Ar-CH), 124.25 (naphthalene Ar-CH), 124.34 (naphthalene Ar-C'H), 124.48 (naphthalene Ar-C'H), 125.09 (naphthalene Ar-CH), 125.65 (naphthalene Ar-C'H), 125.71 (naphthalene Ar-C'H), 126.07 (naphthalene Ar-CH), 126.13 (naphthalene Ar-CH), 127.67 (naphthalene Ar-C'H), 127.77 (naphthalene Ar-C'H), 127.83 (naphthalene Ar-C'H), 127.91 (naphthalene Ar-CH), 128.51 (naphthalene Ar-CH), 128.82 (naphthalene Ar-CH), 132.70 (Ar-C'), 133.44 (Ar-C), 139.38 (Ar-C), 139.91 (Ar-C'), 140.42 (Ar-C'), 152.28 (Ar-C), 152.36 (Ar-C), 168.08 (C'=O), 169.40 (C=O), 169.51 (C'=O), 170.83 (C=O), 170.90 (C'=O), 171.44 (C=O);  $m/z$  (EI) 491 (M<sup>+</sup>, 25%), 418 (100), 359 (7), 326 (9), 253 (6), 165 (19), 155 (12), 134 (13), 77 (6); Accurate mass for - C<sub>28</sub>H<sub>29</sub>NO<sub>7</sub> - 491.1944, found - 491.1941.

**5-Napthalen-2-yl-dihydro-furan-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (204)**



Prepared following the general thermal procedure for compound (203), 5-napthalen-2-yl-dihydro-furan-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (204) (0.210 g, 55%) was prepared as a brown oil using 2-napthalen-2-yl-cyclopropane-1,1-dicarboxylic acid dimethyl ester (197) (0.280 g, 1.00 mmol) and ethyl glyoxalate (0.100 g, 1.00 mmol);  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2953m (CH str), 1750s (C=O), 1456m, 1435m, 1270s, 1233s, 1116m, 1097m, 1067m, 966w, 933w, 859m, 751m,  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 1.20-1.34 (6H, m,  $\text{O}-\text{CH}_2-\text{CH}_3$ ), 2.55 (1H, dd,  $J=7.7$  and 13.2,  $\text{C}_4-\text{CH}(\text{H})$ ), 2.95 (2H, m,  $\text{C}_4'-\text{CH}_2(\text{H})$ ,  $\text{CH}(\text{H}')$ ), 3.32 (1H, dd,  $J=7.7$  and 13.2,  $\text{C}_4-\text{CH}(\text{H})$ ), 3.68 (3H, s,  $\text{O}-\text{CH}_3$ ), 3.71 (3H, s,  $\text{O}-\text{CH}_3$ ), 3.78 (3H, s,  $\text{O}-\text{CH}_3$ ), 3.89 (3H, s,  $\text{O}-\text{CH}_3$ ), 4.22-4.29 (4H, m,  $\text{O}-\text{CH}_2-\text{CH}_3$ ,  $\text{O}-\text{CH}_2-\text{CH}_3$ ), 5.24 (1H, m,  $\text{C}_5'-\text{CH}$ ), 5.29 (1H, s,  $\text{C}_3'-\text{CH}$ ), 5.46 (1H, s,  $\text{C}_3-\text{CH}$ ), 5.65 (1H, s,  $\text{C}_5-\text{CH}$ ), 7.38-7.67 (14H, m, 14 x Ar CH, Ar CH);  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 14.10 ( $\text{O}-\text{CH}_2-\text{CH}_3$ ), 14.12 ( $\text{O}-\text{CH}_2-\text{CH}_3$ ), 41.95 ( $\text{C}_4-\text{CH}_2$ ), 42.35 ( $\text{C}_4'-\text{CH}_2$ ), 53.11 ( $\text{C}_2-\text{CH}$ ), 53.23 ( $\text{C}_2'-\text{CH}$ ), 53.33 ( $\text{C}_5'-\text{CH}$ ), 53.63 ( $\text{C}_5-\text{CH}$ ), 61.56 ( $\text{O}-\text{CH}_2-\text{CH}_3$ ), 61.60 ( $\text{O}-\text{CH}_2-\text{CH}_3$ ), 64.42 ( $\text{C}_3'-\text{CH}$ ), 64.81 ( $\text{C}_3-\text{CH}$ ), 81.31 ( $\text{O}-\text{CH}_3$ ), 81.45 ( $\text{O}-\text{CH}_3$ ), 81.74 ( $\text{O}-\text{CH}_3$ ), 81.89 ( $\text{O}-\text{CH}_3$ ), 123.53 (Ar-CH), 124.20 (Ar-CH), 124.50 (Ar-CH), 125.58 (Ar-CH), 126.01 (Ar-CH), 126.05 (Ar-CH), 126.14 (Ar-CH), 126.24 (Ar-CH), 127.67 (Ar-CH), 127.70 (Ar-CH), 128.01 (Ar-CH), 128.04 (Ar-CH), 128.38 (Ar-CH), 133.02 (Ar-CH), 133.15 (Ar-CH), 133.17 (Ar-CH), 133.28 (Ar-CH), 137.11 (Ar-CH), 138.10 (Ar-CH), 168.03 (C=O), 168.48 (C=O), 169.52 (C=O), 169.70 (C=O), 169.79 (C=O), 169.82 (C=O);  $m/z$  (EI) 386 ( $\text{M}^+$ , 15%), 312 (28), 253 (44), 221 (28), 193 (19), 170 (100), 155 (66), 127 (15); Accurate mass for  $\text{C}_{21}\text{H}_{22}\text{O}_5$  – 386.1365, found – 386.1363.

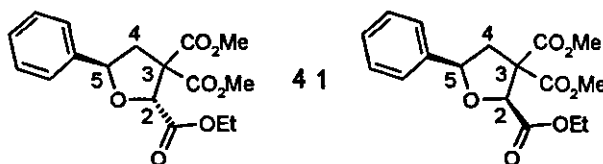
***N*-(4-Methoxy-phenyl)-5-phenyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (205)**



Prepared following the general thermal procedure for compound (203), *N*-(4-methoxy-phenyl)-phenyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (205) (0.190 g, 43%) was prepared as a yellow oil using 2-phenyl-cyclopropane-1,1-dicarboxylic acid dimethyl ester (196) (0.280 g, 1.00 mmol) and *N*-(4-methoxy-phenyl) ethyl ester imine (0.210 g, 1.00 mmol);  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2952m (CH str), 1737s (C=O), 1512s, 1450m, 1353m, 1254s, 1178s, 1029s, 978w, 817m, 761w, 702m;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 1.10 (3H, t,  $J=7.1$ , O-CH<sub>2</sub>-CH<sub>3</sub>), 1.21 (3H, t,  $J=7.1$ , O-CH<sub>2</sub>-CH<sub>3</sub>), 1.87 (1H, dd,  $J=4.1$  and 5.2, C4-CH(H)), 2.36 (1H, dd,  $J=4.1$  and 5.2, C4-CH(H)), 2.54 (1H, dd,  $J=3.6$  and 5.2, C4-CH(H)), 2.63 (1H, dd,  $J=3.6$  and 5.2, C4-CH(H)), 3.36 (3H, s, Ar O-CH<sub>3</sub>), 3.37 (3H, s, Ar O-CH<sub>3</sub>), 3.60 (3H, s, O-CH<sub>3</sub>), 3.67 (3H, s, O-CH<sub>3</sub>), 3.68 (3H, s, O-CH<sub>3</sub>), 3.69 (3H, s, O-CH<sub>3</sub>), 3.72-3.80 (2H, m, O-CH<sub>2</sub>-CH<sub>3</sub>), 3.96-4.00 (2H, m, O-CH<sub>2</sub>-CH<sub>3</sub>), 4.96 (1H, t,  $J=5.4$ , C5-CH), 5.10 (1H, d,  $J=5.4$ , C5-CH), 5.38 (1H, s, C2-CH), 5.42 (1H, s, C2-CH), 6.39 (2H, d,  $J=9.1$ , 2 x Ar-CH), 6.50 (2H, d,  $J=9.1$ , 2 x Ar-CH), 6.62 (2H, d,  $J=9.1$ , 2 x Ar-CH), 6.72 (2H, d,  $J=9.1$ , 2 x Ar-CH), 7.06-7.31 (10H, m, 5 x Ar-CH, 5 x Ar-CH),  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 14.11 (O-CH<sub>2</sub>-CH<sub>3</sub>), 14.17 (O-CH<sub>2</sub>-CH<sub>3</sub>), 42.24 (C4'-CH<sub>2</sub>), 44.13 (C4-CH<sub>2</sub>), 52.84 (C2'-CH), 52.94 (C5'-CH), 53.22 (C2-CH), 53.55 (C5-CH), 61.21 (O-CH<sub>2</sub>-CH<sub>3</sub>), 61.33 (O-CH<sub>2</sub>-CH<sub>3</sub>), 61.60 (C3-C), 62.34 (C3'-C), 63.30 (O-CH<sub>3</sub>), 67.27 (O-CH<sub>3</sub>), 68.80 (O-CH<sub>3</sub>), 114.40 (Ar-CH), 114.51 (Ar-CH), 114.64 (Ar-CH), 115.37 (Ar-CH), 125.79 (Ar-CH), 126.17 (Ar-CH), 126.87 (Ar-CH), 128.45 (Ar-CH), 128.91 (Ar-CH), 128.95 (Ar-CH), 139.30 (Ar-C), 140.70 (Ar-C), 142.18 (Ar-C), 142.77 (Ar-C), 152.20 (Ar-C), 152.28 (Ar-C), 167.97 (C=O), 168.04 (C=O), 169.38 (C=O), 169.61 (C=O), 170.83 (C=O).

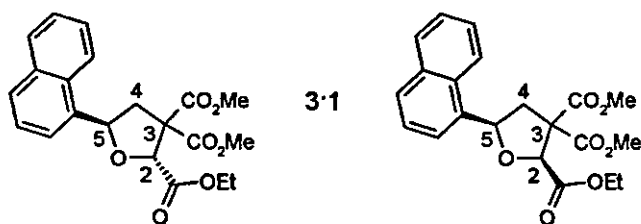
171.37(C=O);  $m/z$  (EI) 441 ( $M^+$ , 20%), 368 (91), 309 (10), 209 (25), 150 (48), 136 (100), 105 (23), 77 (21), 55 (15); Accurate mass for –  $C_{24}H_{27}NO_7$  – 441.1787, found – 441 1780

**5-Phenyl-dihydro-furan-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (206)**



Prepared following the general thermal procedure for compound (203), 5-phenyl-dihydro-furan-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (206) (0.160 g, 48%) was prepared as a brown oil using 2-phenyl-cyclopropane-1,1-dicarboxylic acid dimethyl ester (196) (0.240 g, 1.00 mmol) and ethyl glyoxalate (0.100 g, 1.00 mmol);  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2953m (CH str), 1739s (C=O), 1434s, 1271s, 1235s, 1116s, 1069s, 1026m, 970w, 945w, 863w, 759m, 700s, 668w;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 1.13 (3H, t,  $J=5.4$ , O-CH<sub>2</sub>-CH<sub>3</sub>), 1.22 (3H, t,  $J=5.4$ , O-CH<sub>2</sub>-CH<sub>3</sub>), 2.39 (1H, dd,  $J=7.2$  and 13.1, C4-CH'(H)), 2.71 (1H, dd,  $J=7.2$  and 13.1, C4-CH(H)), 2.83 (1H, dd,  $J=10.4$  and 13.1, C4-CH(H')), 3.16 (1H, dd,  $J=10.4$  and 13.1, C4-CH(H')), 3.62 (3H, s, O-CH<sub>3</sub>), 3.67 (3H, s, O-CH<sub>3</sub>), 3.68 (3H, s, O-CH<sub>3</sub>), 3.79 (3H, s, O-CH<sub>3</sub>), 4.09-4.19 (4H, m, O-CH<sub>2</sub>-CH<sub>3</sub>, O-CH<sub>2</sub>-CH<sub>3</sub>), 4.94 (1H, s, C2-CH), 5.31 (1H, s, C2-CH'), 5.10 (1H, t,  $J=7.4$ , C5-CH), 5.40 (1H, t,  $J=7.4$ , C5-CH'), 7.18-7.27 (10H, m, 5 x Ar CH', 5 x Ar CH);  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 14.05 (O-CH<sub>2</sub>-C'H<sub>3</sub>), 14.09 (O-CH<sub>2</sub>-CH<sub>3</sub>), 41.98 (C4'-C'H<sub>2</sub>), 42.40 (C4'-C'H<sub>2</sub>), 53.07 (C2-CH), 53.19 (C2'-C'H), 53.30 (C5'-C'H), 53.60 (C5-CH), 61.51 (O-C'H<sub>2</sub>-CH<sub>3</sub>), 62.13 (O-CH<sub>2</sub>-CH<sub>3</sub>), 64.38 (C3'-C'), 64.75 (C3-C), 81.18 (O-CH<sub>3</sub>), 81.32 (O-C'H<sub>3</sub>), 81.58 (O-C'H<sub>3</sub>), 81.76 (O-CH<sub>3</sub>), 126.48 (Ar-C'H), 126.72 (Ar-CH), 128.13 (Ar-C'H), 128.38 (Ar-CH), 128.44 (Ar-C'H), 128.83 (Ar-CH), 129.29 (Ar-CH), 139.69 (Ar-C), 140.60 (Ar-C'), 168.02 (C=O), 168.50 (C=O), 169.52 (C'=O), 169.69 (C'=O), 169.78 (C=O), 174.17 (C'=O),  $m/z$  (EI) 336 ( $\text{M}^+$ , 5%), 277 (34), 231 (60), 171 (78), 121 (78), 105 (100), 91 (41), 77 (34), 59 (20); Accurate mass for  $\text{C}_{17}\text{H}_{20}\text{O}_7$  - 336.1209, found - 336.1202

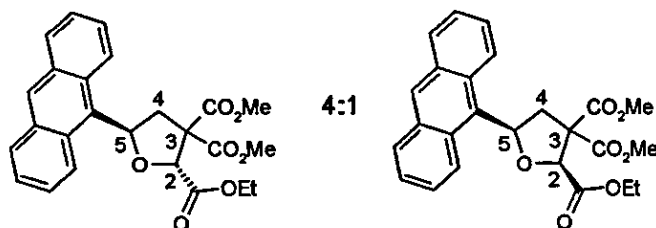
**5-Napthalen-1-yl-dihydro-furan-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (208)**



Prepared following the general thermal procedure for compound (203), 5-napthalen-1-yl-dihydro-furan-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (208) (0.240 g, 62%) was prepared as a brown oil using 2-napthalen-1-yl-cyclopropane-1,1-dicarboxylic acid dimethyl ester (198) (0.280 g, 1.00 mmol) and ethyl glyoxalate (0.100 g, 1.00 mmol);  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2952m (CH str), 1734s (C=O), 1435m, 1264s, 1112m, 1071m, 1022m, 970w, 939w, 802m, 761m;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 1.13 (3H, t,  $J=7.2$ , O-CH<sub>2</sub>-CH<sub>3</sub>), 1.25 (3H, t,  $J=7.2$ , O-CH<sub>2</sub>-CH<sub>3</sub>), 2.45 (1H, dd,  $J=4.2$  and 13.2, C4-CH(H)), 2.64 (1H, dd,  $J=4.2$  and 13.2, C4'-CH(H')), 2.95 (1H, dd,  $J=10.0$  and 13.2, C4'-CH(H')), 3.33 (1H, dd,  $J=10.0$  and 13.2, C4-CH(H)), 3.52 (3H, s, O-CH<sub>3</sub>), 3.54 (3H, s, O-CH<sub>3</sub>), 3.66 (3H, s, O-CH<sub>3</sub>), 3.82 (3H, s, O-CH<sub>3</sub>), 4.02-4.12 (2H, m, O-CH<sub>2</sub>-CH<sub>3</sub>), 4.15-4.21 (2H, m, O-CH<sub>2</sub>-CH<sub>3</sub>), 5.28 (1H, s, C2-CH), 5.47 (1H, s, C2'-CH'), 5.72 (1H, t,  $J=7.0$ , C5-CH), 6.14 (1H, t,  $J=7.0$ , C5'-CH'), 7.04-7.77 (14H, m, 14 x Ar-CH, Ar-CH');  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 14.02 (O-CH<sub>2</sub>-CH<sub>3</sub>), 14.15 (O-CH<sub>2</sub>-CH<sub>3</sub>), 41.23 (C4'-CH<sub>2</sub>), 41.46 (C4'-CH<sub>2</sub>), 53.01 (C2'-CH), 53.25 (C2'-CH), 53.28 (C5'-CH), 53.65 (C5-CH), 61.62 (O-CH<sub>2</sub>-CH<sub>3</sub>), 62.14 (O-CH<sub>2</sub>-CH<sub>3</sub>), 64.31 (C3-CH), 64.52 (C3'-CH), 78.16 (O-CH<sub>3</sub>), 78.60 (O-CH<sub>3</sub>), 81.36 (O-CH<sub>3</sub>), 81.54 (O-CH<sub>3</sub>), 125.37 (Ar-CH), 125.64 (Ar-CH), 126.21 (Ar-CH), 126.24 (Ar-CH), 126.48 (Ar-CH), 126.74 (Ar-CH), 128.44 (Ar-CH), 128.51 (Ar-CH), 128.83 (Ar-CH), 128.90 (Ar-CH), 129.27 (Ar-CH), 129.30 (Ar-CH), 129.49 (Ar-CH), 129.84 (Ar-CH), (Ar-CH), 132.33 (Ar-CH), 133.68 (Ar-CH), 135.43 (Ar-CH), 136.40 (Ar-CH), 136.52 (Ar-CH), 137.00 (Ar-CH), 168.13 (C=O), 168.40 (C=O), 169.44 (C=O), 174.05 (C=O), 174.20 (C=O), 177.00 (C=O);  $m/z$  (EI) 386 ( $\text{M}^+$ , 3%), 312 (5), 234 (50), 195 (50), 165 (25), 155 (15), 121 (100), 93

(41), 84 (30), 77 (27); Accurate mass for  $\text{C}_{21}\text{H}_{22}\text{NO}_7$  – 386.1365, found – 386.1373.

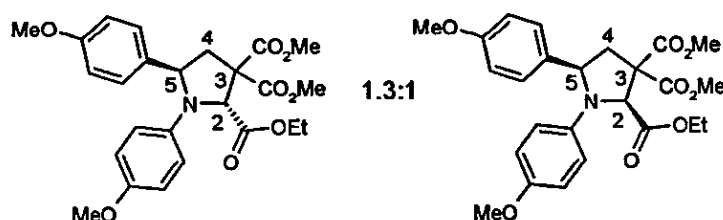
**5-Anthracen-9-yl-dihydro-furan-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (210)**



Prepared following the general thermal procedure for compound (203), 5-anthracen-9-yl-dihydro-furan-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (210) (0.180 g, 42%) was prepared as a brown oil using 2-anthracen-9-yl-cyclopropane-1,1-dicarboxylic acid dimethyl ester (199) (0.330 g, 1.00 mmol) and ethyl glyoxalate (0.100 g, 1.00 mmol);  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2924w (CH str), 1739s (C=O), 1700s, 1444m, 1351m, 1264m, 1218m, 1160m, 1078m, 932w, 760m, 699s;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 1.13 (3H, t,  $J=6.7$ , O-CH<sub>2</sub>-CH<sub>3</sub>), 1.20 (3H, t,  $J=6.7$ , O-CH<sub>2</sub>-CH<sub>3</sub>), 2.27 (1H, dd,  $J=2.6$  and 5.2, C4-CH(H)), 2.64 (1H, dd,  $J=2.6$  and 5.2, C4-CH(H')), 2.99 (1H, dd,  $J=2.7$  and 5.2, C4-CH(H)), 3.05 (1H, dd,  $J=2.7$  and 5.2, C4-CH(H')), 3.50 (3H, s, O-CH<sub>3</sub>), 3.64 (3H, s, O-CH<sub>3</sub>), 3.67 (3H, s, O-CH<sub>3</sub>), 3.73 (3H, s, O-CH<sub>3</sub>), 4.07-4.10 (2H m, O-CH<sub>2</sub>-CH<sub>3</sub>), 4.13-4.19 (2H m, O-CH<sub>2</sub>-CH<sub>3</sub>), 4.55 (1H, s, C5-CH), 4.92 (1H, s, C2-CH), 5.07 (1H, s, C5-CH), 5.21 (1H, s, C2-CH), 7.12-7.46 (18H, m, 9 x Ar CH', 9 x Ar CH);  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 14.10 (O-CH<sub>2</sub>-CH<sub>3</sub>), 14.18 (O-CH<sub>2</sub>-CH<sub>3</sub>), 34.65 (C4-CH<sub>2</sub>), 34.83 (C4'-CH<sub>2</sub>), 51.45 (C2-CH), 52.09 (C2'-CH), 52.48 (C5'-CH), 53.03 (C5-CH), 53.27 (C3'-CH), 53.97 (C3-CH), 61.03 (O-CH<sub>2</sub>-CH<sub>3</sub>), 61.67 (O-CH<sub>2</sub>-CH<sub>3</sub>), 70.42 (O-CH<sub>3</sub>), 70.84 (O-CH<sub>3</sub>), 72.76 (O-CH<sub>3</sub>), 126.96 (Ar-CH), 127.00 (Ar-CH), 127.10 (Ar-CH), 127.87 (Ar-CH), 127.96 (Ar-CH), 128.10 (Ar-CH), 128.45 (Ar-CH), 128.51 (Ar-CH), 128.59 (Ar-CH), 128.74 (Ar-CH), 128.75 (Ar-CH), 128.93 (Ar-CH), 129.01 (Ar-CH), 129.11 (Ar-CH), 129.13 (Ar-CH), 129.24 (Ar-CH), 129.36 (Ar-CH), 129.48 (Ar-CH), 132.32 (Ar-CH), 134.10 (Ar-CH), 135.35 (Ar-CH), 135.71 (Ar-CH), 138.27 (Ar-CH), 138.40 (Ar-CH), 139.95 (Ar-CH), 142.44 (Ar-CH), 169.09 (C=O), 168.09 (C=O), 173.42 (C=O);  $m/z$  (EI) 436 ( $M^+$ , 1%), 325 (11), 234 (100), 205 (43), 191 (82), 178

(98), 121 (56), 91 (79), 77 (38), 57 (35); Accurate mass for  $C_{25}H_{24}O_7$  – 436.1522, found – 436.1531.

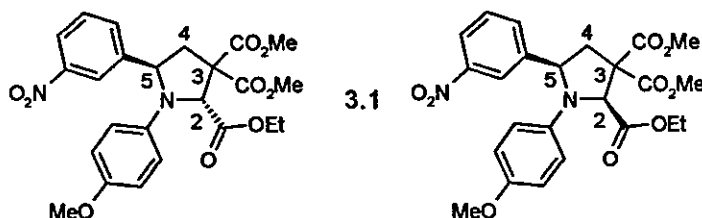
***N*,5-(4-Methoxy-phenyl)-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (211)**



Prepared following the general thermal procedure for compound (203), *N*,5-(4-methoxy-phenyl)-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (211) (0.200 g, 42%) was prepared as a brown oil using 2-(4-methoxy-phenyl)-cyclopropane-1,1-dicarboxylic acid dimethyl ester (201) (0.260 g, 1.00 mmol) and *N*-(4-methoxy-phenyl) ethyl ester imine (0.210 g, 1.00 mmol);  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2952m (CH str), 1737s (C=O), 1610m, 1512s, 1437m, 1246s, 1175m, 1072m, 1033m, 987w, 832m, 817m, 783w;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 1.11 (3H, t,  $J=7.1$ , O-CH<sub>2</sub>-CH<sub>3</sub>), 1.26 (3H, t,  $J=7.1$ , O-CH<sub>2</sub>-CH<sub>3</sub>), 2.33 (1H, dd,  $J=2.5$  and 6.1, C4-CH(H)), 2.50 (1H, dd,  $J=4.7$  and 6.1, C4'-CH(H')), 2.81 (1H, dd,  $J=2.5$  and 6.1, C4'-CH(H)), 3.14 (1H, dd,  $J=4.7$  and 6.1, C4-CH(H)), 3.41 (3H, s, O-CH<sub>3</sub>), 3.41 (3H, s, O-CH<sub>3</sub>), 3.60 (3H, s, O-CH<sub>3</sub>), 3.66 (3H, s, O-CH<sub>3</sub>), 3.67 (3H, s, O-CH<sub>3</sub>), 3.68 (3H, s, O-CH<sub>3</sub>), 3.68 (3H, s, O-CH<sub>3</sub>), 3.69 (3H, s, O-CH<sub>3</sub>), 3.87-4.22 (4H, m, O-CH<sub>2</sub>-CH<sub>3</sub>, O-CH<sub>2</sub>-CH<sub>3</sub>), 4.51 (1H, m, C5-CH), 4.88 (1H, s, C2-CH), 4.95 (1H, m, C5'-CH'), 5.40 (1H, s, C2'-CH'), 6.40 (2H, d,  $J=9.1$ , 2 x Ar-CH), 6.49 (2H, d,  $J=9.1$ , 2 x Ar-CH), 6.62 (2H, d,  $J=9.1$ , 2 x Ar-CH), 6.64 (2H, d,  $J=9.1$ , 2 x Ar-CH), 6.72 (2H, d,  $J=8.7$ , 2 x Ar-CH), 6.77 (2H, d,  $J=8.7$ , 2 x Ar-CH), 6.99 (2H, d,  $J=8.7$ , 2 x Ar-CH), 7.30 (2H, d,  $J=8.7$ , 2 x Ar-CH);  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 14.10 (O-CH<sub>2</sub>-CH<sub>3</sub>), 14.18 (O-CH<sub>2</sub>-CH<sub>3</sub>), 40.32 (C4'-C'H<sub>2</sub>), 42.35 (C4-CH<sub>2</sub>), 52.95 (C2-CH), 53.04 (C2'-C'H), 53.21 (C5'-C'H), 53.52 (C5-CH), 55.19 (O-C'H<sub>3</sub>), 55.27 (O-C'H<sub>3</sub>), 55.53 (O-CH<sub>3</sub>), 55.57 (O-C'H<sub>3</sub>), 61.22 (O-CH<sub>3</sub>), 61.31 (O-CH<sub>2</sub>-CH<sub>3</sub>), 61.58 (C3-C), 61.61 (2H m, O-CH<sub>2</sub>-CH<sub>3</sub>), 62.29 (C3'-C'), 62.73 (O-CH<sub>3</sub>), 67.25 (O-C'H<sub>3</sub>), 68.73 (3H, s, O-CH<sub>3</sub>), 114.15 (Ar-CH), 114.55 (Ar-C'H), 114.96 (Ar-CH), 115.43 (Ar-C'H), 123.68 (Ar-CH), 126.97 (Ar-C'H), 127.18 (Ar-CH), 127.35 (Ar-C'H), 134.14 (Ar-C'), 134.78 (Ar-C), 139.36 (Ar-C'), 140.75 (Ar-C), 152.16 (Ar-

$\underline{\text{C}}'$ ), 152.23 (Ar- $\underline{\text{C}}$ ), 158.43 (Ar- $\underline{\text{C}}'$ ), 158.84 (Ar- $\underline{\text{C}}$ ), 168.03 ( $\underline{\text{C}}'=\text{O}$ ), 168.09 ( $\underline{\text{C}}=\text{O}$ ), 169.51 ( $\underline{\text{C}}'=\text{O}$ ), 169.64 ( $\underline{\text{C}}=\text{O}$ ), 170.84 ( $\underline{\text{C}}'=\text{O}$ ), 171.48 ( $\underline{\text{C}}=\text{O}$ );  $m/z$  (EI) 471 ( $\text{M}^+$ , 27%), 413 (12), 398 (100), 335 (17), 307 (18), 235 (17), 193 (17), 150 (72), 134 (64), 107 (13), 73 (16); Accurate mass for  $\text{C}_{25}\text{H}_{29}\text{NO}_8$  – 471.1843, found – 471.1889

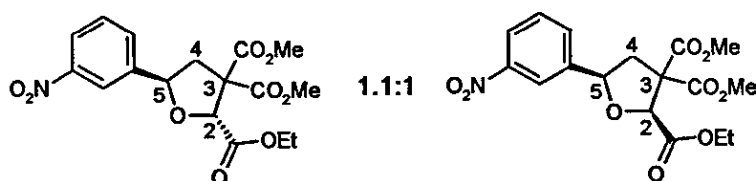
***N*-(4-Methoxy-phenyl)-5-(3-nitro-phenyl)-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (213)**



Prepared following the general thermal procedure for compound (203), *N*-(4-methoxy-phenyl)-5-(3-nitro-phenyl)-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (213) (0.220 g, 45%) was prepared as a brown oil using 2-(3-nitro-phenyl)-cyclopropane-1,1-dicarboxylic acid dimethyl ester (202) (0.280 g, 1.00 mmol) and *N*-(4-methoxy-phenyl) ethyl ester imine (0.210 g, 1.00 mmol),  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2953m (CH str) 1738s (C=O), 1529s, 1435m, 1348s, 1255s, 1179s, 1072m, 1036m, 972w, 911w, 816m, 785m;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 1.12 (3H, t,  $J=7.1$ , O-CH<sub>2</sub>-CH<sub>3</sub>), 1.29 (3H, t,  $J=7.1$ , O-CH<sub>2</sub>-CH<sub>3</sub>), 2.51 (1H, dd,  $J=2.8$  and 7.4, C4'-CH'(H)), 2.80 (1H, dd,  $J=5.5$  and 7.4, C4-CH(H)), 2.91 (1H, dd,  $J=2.8$  and 7.4, C4-CH(H)), 3.43 (1H, dd,  $J=5.5$  and 7.4, C4'-CH(H')), 3.48 (3H, s, O-CH<sub>3</sub>), 3.60 (3H, s, O-CH<sub>3</sub>), 3.67 (3H, s, O-CH<sub>3</sub>), 3.68 (3H, s, O-CH<sub>3</sub>), 3.70 (3H, s, O-CH<sub>3</sub>), 3.75 (3H, s, O-CH<sub>3</sub>), 3.98-4.06 (2H, m, O-CH<sub>2</sub>-CH<sub>3</sub>), 4.20-4.31 (2H, m, O-CH<sub>2</sub>-CH<sub>3</sub>), 4.65 (1H, m, C5-CH), 4.92 (1H, s, C2-CH), 5.07 (1H, m, C5'-CH'), 5.45 (1H, s, C2'-CH'), 6.39 (2H, d,  $J=9.1$ , 2 x Ar-CH'), 6.44 (2H, d,  $J=9.1$ , 2 x Ar-CH), 6.63 (2H, d,  $J=9.1$ , 2 x Ar-CH'), 6.65 (2H, d,  $J=9.1$ , 2 x Ar-CH), 7.19-7.99 (8H, m, 8 x Ar-CH, Ar-CH');  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 14.11 (O-CH<sub>2</sub>-C'H<sub>3</sub>), 14.17 (O-CH<sub>2</sub>-CH<sub>3</sub>), 39.88 (C4'-C'H<sub>2</sub>), 41.94 (C4-CH<sub>2</sub>), 53.18 (C2-CH), 53.37 (C2-C'H), 53.42 (C5'-C'H), 53.75 (C5-CH), 55.49 (O-C'H<sub>3</sub>), 55.54 (O-CH<sub>3</sub>), 61.23 (O-C'H<sub>3</sub>), 61.47 (O-C'H<sub>2</sub>-CH<sub>3</sub>), 61.54 (C3'-C'), 61.01 (O-CH<sub>2</sub>-CH<sub>3</sub>), 62.36 (C3-C), 62.48 (O-CH<sub>3</sub>), 67.47 (O-C'H<sub>3</sub>), 68.88 (O-CH<sub>3</sub>), 114.45 (Ar-C'H), 114.66 (Ar-C'H), 114.71 (Ar-C'H), 115.75 (Ar-C'H), 120.99 (Ar-CH), 121.47 (Ar-C'H), 122.28 (Ar-C'H), 122.64 (Ar-CH), 129.58 (Ar-CH), 129.94 (Ar-CH), 132.20 (Ar-CH), 132.62 (Ar-CH), 138.52 (Ar-C'), 139.83 (Ar-C), 144.79 (Ar-C), 145.52 (Ar-C'), 148.65 (Ar-C'), 148.69 (Ar-C), 152.69 (Ar-C), 152.78 (Ar-C'), 167.63 (C=O), 167.69 (C=O),

169.31 ( $\underline{\text{C}}=\text{O}$ ), 170.43 ( $\underline{\text{C}}=\text{O}$ ), 171.33 ( $\underline{\text{C}}=\text{O}$ );  $m/z$  (EI) 486 ( $\text{M}^+$ , 18%), 413 (100), 383 (8), 354 (10), 255 (5), 150 (5), 134 (10), 84 (22), 59 (6); Accurate mass for  $\text{C}_{24}\text{H}_{26}\text{N}_2\text{O}_9$  – 486 1638, found – 486 1632.

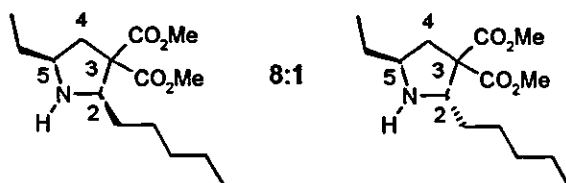
**5-(3-Nitro-phenyl)-dihydro-furan-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (214)**



Prepared following the general thermal procedure for compound (203), 5-(3-Nitro-phenyl)-dihydro-furan-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (214) (0.190 g, 49%) was prepared as a brown oil using 2-(3-nitro-phenyl)-cyclopropane-1,1-dicarboxylic acid dimethyl ester (202) (0.280 g, 1.00 mmol) and ethyl glyoxalate (0.100 g, 1.00 mmol);  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2955m (CH str), 1736s (C=O), 1531s, 1436m, 1349s, 1270s, 1233s, 1067m, 1023m, 961w, 896w, 737m;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 1.22-1.26 (6H, m, O-CH<sub>2</sub>-CH<sub>3</sub>, O-CH<sub>2</sub>-CH<sub>3</sub>), 2.41 (1H, dd,  $J=5.8$  and 13.1, C4-CH(H)), 2.71 (1H, dd,  $J=10.5$  and 13.1, C4'-CH'(H)), 2.92 (1H, dd,  $J=5.8$  and 13.0, C4'-CH'(H)), 3.23 (1H, dd,  $J=10.5$  and 13.0, C4-CH(H)), 3.65 (3H, s, O-CH<sub>3</sub>), 3.66 (3H, s, O-CH<sub>3</sub>), 3.70 (3H, s, O-CH<sub>3</sub>), 3.82 (3H, s, O-CH<sub>3</sub>), 4.14-4.22 (4H, m, O-CH<sub>2</sub>-CH<sub>3</sub>, O-CH<sub>2</sub>-CH<sub>3</sub>), 5.07 (1H, t,  $J=5.8$ , C5'-CH'), 5.16 (1H, s, C2'-CH'), 5.34 (1H, s, C2-CH), 5.51 (1H, t,  $J=5.8$ , C5-CH), 7.19 (1H, s, Ar CH'), 7.49 (2H, q,  $J=7.7$ , 2 x Ar CH'), 7.80 (1H, d,  $J=7.6$ , Ar CH'), 7.82 (1H, d,  $J=7.6$ , Ar CH), 8.10 (2H, q,  $J=7.7$ , 2 x Ar CH), 8.30 (1H, s, Ar CH),  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 14.05 (O-CH<sub>2</sub>-C'H<sub>3</sub>), 14.10 (O-CH<sub>2</sub>-CH<sub>3</sub>), 41.65 (C4'-C'H<sub>2</sub>), 42.02 (C4-CH<sub>2</sub>), 53.31 (C2'-C'H), 53.40 (C2-CH), 53.67 (C5-CH), 53.82 (C5'-C'H), 61.77 (O-CH<sub>2</sub>-CH<sub>3</sub>), 61.90 (O-C'H<sub>2</sub>-CH<sub>3</sub>), 64.16 (C3-C), 64.76 (C3'-C'), 80.12 (O-CH<sub>3</sub>), 80.45 (O-C'H<sub>3</sub>), 81.27 (O-C'H<sub>3</sub>), 81.84 (O-CH<sub>3</sub>), 120.63 (Ar-C'H), 121.49 (Ar-C'H), 122.84 (Ar-C'H), 123.06 (Ar-C'H), 128.82 (Ar-CH), 129.53 (Ar-CH), 131.77 (Ar-CH), 132.52 (Ar-CH), 137.06 (Ar-C'), 142.35 (Ar-C), 143.10 (Ar-C'), 148.31 (Ar-C), 167.50 (C=O), 168.09 (C=O), 169.22 (C'=O), 169.26 (C=O), 169.48 (C'=O), 169.68 (C'=O);  $m/z$  (EI) 381 ( $M^+$ , 1%), 322 (58), 276 (68), 248 (100), 201 (9), 195 (59), 150 (46), 115 (67), 59 (73). Accurate mass for  $\text{C}_{17}\text{H}_{19}\text{NO}_9$  - 381.1060, found - 381.1066.

**Section 3.10 – Pyrrolidines Formed as an Intermediate on Route to Natural Products**

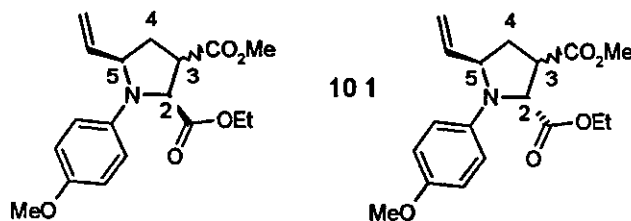
**2-Ethyl-2-pentyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (230)**



To a solution of *N*-benzyl-2-pentyl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (**109**) (0.370 g, 1.00 mmol) in methanol (60 mL) in a 100 mL flask equipped with a three necked adaptor and a magnetic stirrer bar. This was then flushed five times with hydrogen, was added the palladium on activated carbon 10 mol% (0.100 g, 1.00 mmol). The flask was flushed five more times using hydrogen via a balloon. The reaction was allowed to stir overnight under positive pressure of hydrogen with stirring to remove benzyl group and vinyl bonds. The product was filtered through a plug of cotton wool and evaporated *in vacuo* to afford 2-ethyl-5-pentyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (**230**) (0.260 g, 97%);  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2954s (CH str), 1734s (C=O), 1436m, 1269m, 1211m, 1095w, 1051w, 963w;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 0.77-0.84 (6H m,  $\text{CH}_3$ ), 0.88-0.94 (6H m,  $\text{CH}_3$ ), 1.13-1.24 (16H, m, 4 x  $\text{CH}_2$ , 4 x  $\text{CH}_2$ ), 1.41 (1H, m, br, N-H), 1.60-1.75 (4H, m,  $\text{CH}_2$ ,  $\text{CH}_2$ ), 1.91 (1H, dd,  $J=9.3$  and  $14.2$ , C4'-CH(H)), 2.35 (1H, dd,  $J=8.3$  and  $14.1$ , C4-CH(H)), 2.45 (1H, dd,  $J=9.3$  and  $14.2$ , C4-CH(H)), 2.71 (1H, dd,  $J=8.3$  and  $14.1$ , C4'-CH(H)), 3.31 (1H, m, br, N-H), 3.68 (1H, m, C2'-CH), 3.71 (3H, s, O-CH<sub>3</sub>), 3.72 (3H, s, O-CH<sub>3</sub>), 3.75 (3H, s, O-CH<sub>3</sub>), 3.76 (3H, s, O-CH<sub>3</sub>), 3.81 (1H, m, C2'-CH), 3.91 (1H, m, C5-CH), 4.06 (1H, m, C5'-N-CH);  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 10.74 ( $\text{CH}_3$ ), 11.09 ( $\text{C}'\text{H}_3$ ), 13.93 ( $\text{CH}_3$ ), 14.07 ( $\text{C}'\text{H}_3$ ), 22.26 ( $\text{C}'\text{H}_2$ ), 22.34 ( $\text{C}'\text{H}_2$ ), 25.86 ( $\text{CH}_2$ ), 26.17 ( $\text{CH}_2$ ), 26.65 ( $\text{C}'\text{H}_2$ ), 26.85 ( $\text{C}'\text{H}_2$ ), 29.33 ( $\text{CH}_2$ ), 29.63 ( $\text{C}'\text{H}_2$ ), 31.19 ( $\text{CH}_2$ ), 31.48 ( $\text{CH}_2$ ), 38.42 (C4-CH<sub>2</sub>), 38.98 (C4'-CH<sub>2</sub>), 53.13 (C5-CH), 53.17 (C5'-CH), 53.22 (C2'-CH), 53.27 (C2-CH), 54.47 (C3'-CH), 54.70 (C3-CH), 59.87 (O-CH<sub>3</sub>), 62.09 (O-CH<sub>3</sub>), 63.06 (O-CH<sub>3</sub>), 64.43 (O-CH<sub>3</sub>), 168.76 ( $\text{C}=\text{O}$ ), 169.24 ( $\text{C}=\text{O}$ ), 169.89 ( $\text{C}=\text{O}$ ), 170.26 ( $\text{C}=\text{O}$ ),  $m/z$  (EI) 285

( $M^+$ , 7%), 256 (50), 224 (20), 214 (100), 192 (13), 142 (15), 112 (37), 84 (17), 55 (12), Accurate mass for  $C_{15}H_{27}NO_4$  – 285.1940, found – 285.1936.

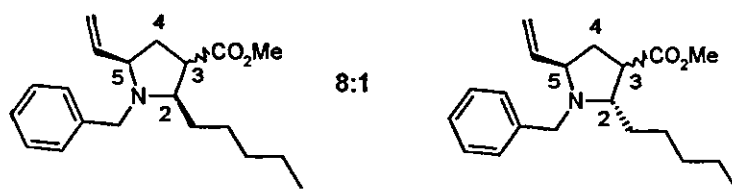
***N*-(4-Methoxy-phenyl)-5-vinyl-pyrrolidine-2,3-dicarboxylic acid 2-ethyl ester 3-methyl ester (231)**



To a solution of the *N*-(4-methoxy-phenyl)-5-vinyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (122) (0.390 g, 1.00 mmol) and THF (2 mL) in a 30 mL pressure tube equipped with a magnetic stirrer bar was added dimethyl carbonate (0.010 g, 0.100 mmol), triethyl amine (0.010 g, 0.100 mmol) and ethylene glycol (0.060 g, 1.00 mmol). The tube was sealed and heated to 170 °C with stirring at for 6 hours at the end of this time the heat was removed and the reaction mixture was allowed to cool to RT. The mixture was purified using column chromatography (SiO<sub>2</sub>, EtOAc:P.E. 40-60; 1:4, R<sub>f</sub> - 0.40) to yield the *N*-(4-methoxy-phenyl)-5-vinyl-pyrrolidine-2,3-dicarboxylic acid 2-ethyl ester 3-methyl ester (231) (0.240 g, 73%) as a brown oil;  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2951m (CH str), 1736s (C=O), 1512s, 1437m, 1355m, 1242s, 1179s, 1039s, 925w, 814m, 783w,  $\delta_{\text{H}}$  (250 MHz; CDCl<sub>3</sub>) 1.01-1.11 (3H m, O-CH<sub>2</sub>-CH<sub>3</sub>), 1.17-1.22 (3H m, O-CH<sub>2</sub>-CH<sub>3</sub>), 1.75-1.79 (1H, m, C4-CH(H)), 2.19-2.26 (1H, m, C4-CH(H')), 2.36-2.44 (1H, m, C4-CH(H)), 2.52-2.60 (1H, m, C4-CH(H')), 3.06 (1H, m, C3'-CH'), 3.22 (1H, m, C3-CH), 3.64 (3H, s, O-CH<sub>3</sub>), 3.65 (3H, s, O-CH<sub>3</sub>), 3.66 (3H, s, O-CH<sub>3</sub>), 3.67 (3H, s, O-CH<sub>3</sub>), 4.00-4.06 (2H, m, O-CH<sub>2</sub>-CH<sub>3</sub>), 4.07-4.09 (2H, m, O-CH<sub>2</sub>-CH<sub>3</sub>), 4.10 (1H, m, C5'-CH'), 4.32 (1H, m, C5-CH), 4.90 (1H, d, J=2.2, C2-CH), 4.92 (1H, d, J=2.2, C2'-CH), 4.98-5.04 (2H, m, CH=CH<sub>2</sub>), 5.14-5.22 (2H, m, CH=CH<sub>2</sub>), 5.63 (1H, m, CH'=CH<sub>2</sub>), 5.79 (1H, m, CH=CH<sub>2</sub>), 6.67-6.34 (4H, m, Ar-CH, Ar-CH'), 6.67-6.74 (4H, m, 2 x Ar-CH, 2 x Ar-CH');  $\delta_{\text{C}}$  (101 MHz; CDCl<sub>3</sub>) 14.09 (O-CH<sub>2</sub>-CH<sub>3</sub>), 14.18 (O-CH<sub>2</sub>-CH<sub>3</sub>), 34.17 (C4'-CH<sub>2</sub>), 35.31 (C4-CH<sub>2</sub>), 40.45 (C5'-CH), 46.45 (C5-CH), 52.44 (C2-CH), 53.23 (C2'-CH), 55.63 (C3'-CH), 55.76 (C3-CH), 61.18 (O-CH<sub>2</sub>-CH<sub>3</sub>), 61.29 (O-CH<sub>3</sub>), 61.37 (O-CH<sub>3</sub>), 61.43 (O-CH<sub>2</sub>-CH<sub>3</sub>), 63.97 (O-CH<sub>3</sub>), 64.25 (O-CH<sub>3</sub>), 113.93 (Ar-CH), 114.52 (Ar-CH), 114.64 (Ar-CH), 114.68 (Ar-CH),

115.58 ( $\underline{\text{C}}'\text{H}_2=\text{CH}$ ), 116.29 ( $\underline{\text{C}}\text{H}_2=\text{CH}$ ), 139.31 ( $\text{CH}_2=\underline{\text{C}}\text{H}$ ), 139.56 ( $\text{CH}_2=\underline{\text{C}}'\text{H}$ ), 151.87 ( $\text{Ar}-\underline{\text{C}}$ ), 151.91 ( $\text{Ar}-\underline{\text{C}}'$ ), 151.97 ( $\text{Ar}-\underline{\text{C}}'$ ), 152.11 ( $\text{Ar}-\underline{\text{C}}$ ), 172.60 ( $\underline{\text{C}}=\text{O}$ ), 172.64 ( $\underline{\text{C}}=\text{O}$ ), 172.67 ( $\underline{\text{C}}'=\text{O}$ ), 173.12 ( $\underline{\text{C}}'=\text{O}$ );  $m/z$  (EI) 333 ( $\text{M}^+$ , 15%), 318 (10), 274 (26), 260 (100), 200 (14), 174 (6), 134 (13), 108 (6), 77 (7), Accurate mass for  $\text{C}_{18}\text{H}_{23}\text{NO}_4$  – 333.1576, found – 333.1571.

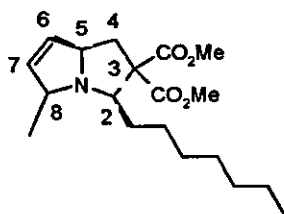
***N*-Benzyl-2-pentyl-5-vinyl-pyrrolidine-3-carboxylic acid methyl ester (232)**



To a solution of the *N*-benzyl-2-pentyl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (**109**) (0.370 g, 1.00 mmol) and THF (2 mL) in a 30 mL pressure tube equipped with a magnetic stirrer bar was added dimethyl carbonate (0.010 g, 0.100 mmol), triethyl amine (0.010 g, 0.100 mmol) and ethylene glycol (0.060 g, 1.00 mmol). The tube was sealed and heated to 170 °C with stirring at for 6 hours at the end of this time the heat was removed and the reaction mixture was allowed to cool to RT. The mixture was purified using column chromatography (SiO<sub>2</sub>, EtOAc.P.E. 40-60; 1:4, *R<sub>f</sub>* - 0.40) to yield the *N*-benzyl-2-pentyl-5-vinyl-pyrrolidine-3-carboxylic acid methyl ester (**232**) (0.240 g, 76%) as a brown oil;  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  2927s, 2857s (CH str), 1731s (C=O), 1455m, 1377m, 1266m, 1167m, 1073w, 916w, 728w, 699w,  $\delta_{\text{H}}$  (250 MHz; CDCl<sub>3</sub>) 0.78-0.88 (6H, m, aliphatic CH<sub>3</sub>, CH<sub>3</sub>), 1.18-1.23 (16H, m, aliphatic CH<sub>2</sub>, CH<sub>2</sub>), 1.60 (2H, s, benzyl CH<sub>2</sub>), 2.02 (2H, s, benzyl CH<sub>2</sub>), 2.17 (1H, m, C4-CH(H)), 2.31 (1H, s, C3-CH), 2.46 (1H, s, C3'-CH), 2.48 (1H, m, C4'-CH(H)), 2.65 (1H, m, C4'-CH(H)), 2.99 (1H, m, C4-CH(H)), 3.41 (1H, m, C2-CH), 3.61 (3H, s, O-CH<sub>3</sub>), 3.63 (3H, s, O-CH<sub>3</sub>), 3.71-3.91 (2H, m, C5'-CH, C5-CH), 4.14 (1H, m, C2'-CH), 4.97-5.00 (4H, m, CH=CH<sub>2</sub>, CH=C-H<sub>2</sub>), 5.53-5.81 (2H, m, CH=CH<sub>2</sub>, CH=CH<sub>2</sub>), 7.15-7.25 (10H, m, 5 x Ar-CH, 5 x Ar-CH);  $\delta_{\text{C}}$  (101 MHz; CDCl<sub>3</sub>) 13.92 (CH<sub>3</sub>), 14.08 (C-H<sub>3</sub>), 22.69 (C'H<sub>2</sub>), 23.00 (C'H<sub>2</sub>), 29.63 (CH<sub>2</sub>), 29.71 (C'H<sub>2</sub>), 31.88 (CH<sub>2</sub>), 31.91 (CH<sub>2</sub>), 32.09 (C'H<sub>2</sub>), 32.28 (CH<sub>2</sub>), 32.99 (C4-CH<sub>2</sub>), 33.38 (C4'-C'H<sub>2</sub>), 37.63 (C5'-C'H), 48.42 (C5-CH), 48.48 (C2'-C'H), 48.81 (C3'-C'H), 52.00 (C3-CH), 62.44 (benzyl C'H<sub>2</sub>), 62.05 (benzyl CH<sub>2</sub>), 66.40 (O-CH<sub>3</sub>), 68.15 (O-C'H<sub>3</sub>), 114.54 (CH<sub>2</sub>=CH), 116.85 (C'H<sub>2</sub>=CH), 128.48 (Ar-C'H), 128.80 (Ar-C'H), 130.90 (Ar-C'H), 136.23 (CH<sub>2</sub>=C'H), 137.00 (CH<sub>2</sub>=CH), 146.23 (Ar-C'), 167.79 (C=O); *m/z* (EI) 314 (M<sup>+</sup> -H, 10%), 300 (15),

260 (13), 232 (32), 218 (30), 205 (23), 190 (37), 163 (100), 149 (32), 91 (69), 73 (69), 55 (50); Accurate mass for  $C_{20}H_{29}NO_2$  – 314.21200, found – 314.21123

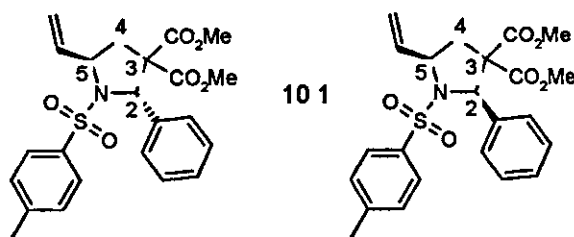
**2-Pentane-3,3-dimethyl-8-methyl-4,6,7-trihydro-1H-pyrrolizine-3,3-tricarboxylate (237)**



Prepared following the general RCM procedure for compound (165), 2-pentane-3,3-dimethyl-8-methyl-4,6,7-trihydro-1H-pyrrolizine-3,3-tricarboxylate (237) (0.080 g, 24%) was prepared as a brown oil using To a solution of de-gassed DCM (100 mL), *N*-(1-methyl-allyl)-2-heptyl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (236) (0.370 g, 1.00 mmol) and Grubbs second generation catalyst (0.010 g, 0.100 mmol),  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2924s (CH str), 1753s (C=O), 1598w, 1434m, 1386m, 1263s, 1177m, 1073m, 969m;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 0.80 (3H, t,  $J=6.9$ , N-CH-CH<sub>3</sub>), 1.18-1.28 (15H, m, 6 x CH<sub>2</sub> and CH<sub>3</sub>), 2.38 (1H, m, C4-CH(H)), 2.79 (1H, m, C4-CH(H)), 3.66 (3H, s, O-CH<sub>3</sub>), 3.67 (3H, s, O-CH<sub>3</sub>), 4.20 (1H, m, C8-CH), 4.36 (1H, m, C5-CH), 4.65 (1H, m, C2-CH), 5.67 (1H, m, CH=CH), 5.77 (1H, m, CH=CH),  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 14.05 (CH<sub>3</sub>), 14.07 (N-CH-CH<sub>3</sub>), 21.61 (CH<sub>2</sub>), 26.77 (CH<sub>2</sub>), 29.16 (CH<sub>2</sub>), 29.25 (CH<sub>2</sub>), 29.31 (CH<sub>2</sub>), 29.48 (CH<sub>2</sub>), 31.55 (C3-C), 40.29 (C4-CH<sub>2</sub>), 52.28 (C5-N-CH), 52.67 (C2-N-CH), 53.15 (C8-N-CH), 82.85 (O-CH<sub>3</sub>), 82.96 (O-CH<sub>3</sub>), 132.80 (CH=CH), 133.87 (CH=CH), 169.95 (C=O), 170.35 (C=O),  $m/z$  (EI) 337 ( $\text{M}^+$ , 25%), 311 (49), 285 (58), 239 (60), 201 (51), 145 (55), 113 (56), 91 (100), 69 (58), 57 (83); Accurate mass for  $\text{C}_{19}\text{H}_{31}\text{NO}_4$  – 337.2253, found – 337.2248.

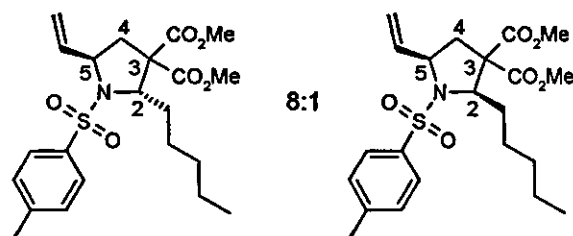
### Section 3.11 – Other Pyrrolidine Products

#### *N*-(Toluene-4-sulfonyl)-2-phenyl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (113)



Prepared following the general thermal procedure for compound (81), *N*-(Toluene-4-sulfonyl)-2-phenyl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (113) (0.280 g, 64%) was prepared as a yellow oil using *N*-(toluene-4-sulfonyl)-phenyl imine (0.260 g, 1.00 mmol) for 96 hours;  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  3356m, 3259m (CH str), 1735m (C=O), 1434w, 1304s, 1160s, 1095m, 1018w, 997w, 903w, 817m, 694;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 2.27 (3H, s, Ar-CH<sub>3</sub>), 2.38 (1H, dd,  $J=6.0$  and  $13.7$ , C4-CH(H)), 2.66 (1H, dd,  $J=11.7$  and  $13.7$ , C4-CH(H)), 3.15 (3H, s, O-CH<sub>3</sub>), 3.56 (3H, s, O-CH<sub>3</sub>), 3.90 (1H, m, C5-CH), 5.10-5.25 (2H, m, CH=CH<sub>2</sub>), 5.71 (1H, s, C2-CH), 5.84 (1H, m, CH=CH<sub>2</sub>), 4.91 (1H, s, C2-CH), 5.35 (2H, m, CH=CH<sub>2</sub>), 5.74 (1H, m, CH=CH<sub>2</sub>), 5.82 (1H, m, CH=CH<sub>2</sub>), 7.03-7.67 (18H, m, 9 x Ar-CH);  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 14.91 (Ar-CH<sub>3</sub>), 21.56 (Ar-C'H<sub>3</sub>), 37.42 (C4-CH<sub>2</sub>), 37.80 (C4-C'H<sub>2</sub>), 52.70 (C2-C'H), 52.82 (C2-CH), 53.61 (C5-CH), 53.85 (C5-C'H), 61.53 (C3-C'), 62.05 (C3-C), 63.80 (O-CH<sub>3</sub>), 64.38 (O-C'H<sub>3</sub>), 67.61 (O-CH<sub>3</sub>), 67.78 (O-C'H<sub>3</sub>), 117.55 (CH<sub>2</sub>=CH), 118.49 (C'H<sub>2</sub>=CH), 126.45 (Ar-C'H), 127.44 (Ar-CH), 127.66 (Ar-C'H), 127.98 (Ar-CH), 128.19 (Ar-C'H), 128.23 (Ar-CH), 128.35 (Ar-C'H), 129.09 (Ar-CH), 129.24 (Ar-C'H), 129.75 (Ar-CH), 135.46 (Ar-C'), 136.70 (CH<sub>2</sub>=C'H), 137.41 (CH<sub>2</sub>=CH), 137.47 (Ar-C), 138.25 (Ar-C'), 138.40 (Ar-C), 143.35 (Ar-C), 143.73 (Ar-C'), 166.79 (C'=O), 166.85 (C=O), 170.02 (C'=O), 170.56 (C=O);  $m/z$  (EI) 443 ( $\text{M}^+$ , 0.5%), 288 (92), 228 (9), 185 (50), 171 (26), 153 (33), 121 (14), 91 (100), 65 (26), Accurate mass for  $\text{C}_{23}\text{H}_{25}\text{NO}_6\text{S}$  – 443.1402, found – 443.1411.

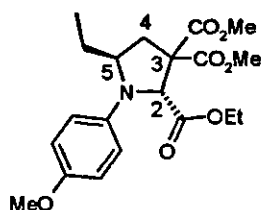
***N*-(Toluene-4-sulfonyl)-2-pentyl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (115)**



Prepared following the general thermal procedure for compound (81), *N*-(toluene-4-sulfonyl)-2-pentyl-5-vinyl pyrrolidine-3,3-dicarboxylic acid dimethyl ester (115) (0.330 g, 75%) was prepared as a yellow oil using *N*-(toluene-4-sulfonyl)-pentyl imine (0.250 g, 1.00 mmol) for 96 hours;  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2933s (CH str), 1737s (C=O), 1597w, 1434s, 1341s, 1264s, 1163s, 1091m, 924w, 815m, 666m;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 0.76-1.49 (22H m, 11 x alkane  $\text{CH}'$ , 11 x alkane  $\text{CH}$ ), 2.24 (1H, dd,  $J=4.8$  and 13.6, C4- $\text{CH}(\text{H})$ ), 2.30 (3H, s, Ar- $\text{CH}_3$ ), 2.33 (3H, s, Ar- $\text{CH}_3$ ), 2.40 (1H, dd,  $J=4.8$  and 13.6, C4- $\text{CH}'(\text{H})$ ), 2.58 (1H, dd,  $J=7.1$  and 13.6, C4- $\text{CH}(\text{H})$ ), 3.00 (1H, dd,  $J=7.1$  and 13.6, C4- $\text{CH}'(\text{H})$ ), 3.61 (3H, s, O- $\text{CH}_3$ ), 3.65 (3H, s, O- $\text{CH}_3$ ), 3.67 (3H, s, O- $\text{CH}_3$ ), 3.68 (3H, s, O- $\text{CH}_3$ ), 3.81 (1H, m, C2- $\text{CH}'$ ), 4.81 (1H, m, C2- $\text{CH}$ ), 4.90 (1H, m, C5- $\text{CH}$ ), 4.97 (1H, m, C5- $\text{CH}'$ ), 5.04-5.07 (2H, m,  $\text{CH}=\text{CH}_2$ ), 5.21-5.24 (2H, m,  $\text{CH}=\text{CH}_2$ ), 5.67 (1H, m,  $\text{CH}'=\text{CH}_2$ ), 5.88 (1H, m,  $\text{CH}=\text{CH}_2$ ), 7.21 (2H, d,  $J=5.8$ , 2 x Ar- $\text{CH}'$ ), 7.46 (2H, d,  $J=5.8$ , 2 x Ar- $\text{CH}$ ), 7.62 (2H, d,  $J=5.8$ , 2 x Ar- $\text{CH}'$ ), 7.74 (2H, d,  $J=5.8$ , 2 x Ar- $\text{CH}$ );  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 13.79 (alkane  $\text{CH}_3$ ), 13.98 ( $\text{C}'\text{H}_3$ ), 21.63 (Ar- $\text{C}'\text{H}_3$ ), 21.76 (Ar- $\text{CH}_3$ ), 22.25 ( $\text{C}'\text{H}_2$ ), 22.43 ( $\text{CH}_2$ ), 25.12 ( $\text{C}'\text{H}_2$ ), 25.63 ( $\text{CH}_2$ ), 29.25 ( $\text{C}'\text{H}_2$ ), 31.13 ( $\text{CH}_2$ ), 31.73 ( $\text{C}'\text{H}_2$ ), 32.83 ( $\text{CH}_2$ ), 38.37 (C4- $\text{CH}_2$ ), 39.36 (C4'- $\text{C}'\text{H}_2$ ), 52.57 (C2- $\text{CH}$ ), 52.78 (C5- $\text{CH}$ ), 52.93 (C2'- $\text{C}'\text{H}$ ), 53.21 (C5'- $\text{C}'\text{H}$ ), 60.41 (O- $\text{CH}_3$ ), 60.49 (O- $\text{C}'\text{H}_3$ ), 62.34 (C3- $\text{C}$ ), 62.71 (C3'- $\text{C}'$ ), 64.67 (O- $\text{C}'\text{H}_3$ ), 64.85 (O- $\text{CH}_3$ ), 115.69 ( $\text{CH}_2=\text{CH}$ ), 116.32 ( $\text{C}'\text{H}_2=\text{CH}$ ), 127.05 (Ar- $\text{C}'\text{H}$ ), 127.16 (Ar- $\text{C}'\text{H}$ ), 127.49 (Ar- $\text{C}'\text{H}$ ), 127.57 (Ar- $\text{CH}$ ), 127.85 (Ar- $\text{C}'\text{H}$ ), 128.29 (Ar- $\text{CH}$ ), 128.95 (Ar- $\text{CH}$ ), 129.15 (Ar- $\text{CH}$ ), (Ar- $\text{C}'\text{H}$ ), 135.84 (Ar- $\text{C}$ ), 135.89 (Ar- $\text{C}'$ ), 138.92 ( $\text{CH}_2=\text{C}'\text{H}$ ), 139.81 ( $\text{CH}_2=\text{CH}$ ), 141.92 (Ar- $\text{C}$ ), 142.31 (Ar- $\text{C}'$ ), 169.40 ( $\text{C}'=\text{O}$ ), 169.58 ( $\text{C}=\text{O}$ ), 170.07 ( $\text{C}=\text{O}$ ), 171.55 ( $\text{C}'=\text{O}$ );  $m/z$  (EI) 438

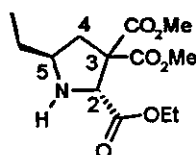
(M<sup>+</sup>, 11%), 366 (13), 254 (57), 185 (20), 155 (55), 121 (19), 91 (100), 69 (51), 55 (77), Accurate mass for – C<sub>22</sub>H<sub>31</sub>NO<sub>6</sub>S – 438.2150, found – 438.2147.

***N*-(4-Methoxy-phenyl)-5-ethyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (133)**<sup>88</sup>



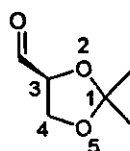
To a solution of the *N*-(4-Methoxy-phenyl)-5-vinyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (**122**) (0.390 g, 1.00 mmol) in methanol (60 mL) in a 100 mL flask equipped with a three necked adaptor and equipped with a magnetic stirrer bar. This was flushed five times with hydrogen, was added the Pd/C (10 mol%) (0.100 g, 0.100 mmol). The flask was flushed five more times using hydrogen via a balloon. The reaction was allowed to stir overnight under positive pressure of hydrogen with stirring to remove benzyl group and vinyl bonds. The product was filtered through a plug of cotton wool and the filtrate evaporated *in vacuo* to afford the *N*-(4-Methoxy-phenyl)-5-ethyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (**133**) as a colourless oil (0.390 g, 98%);  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  2957s, 2836m (CH str), 1735s (C=O), 1513s, 1436s, 1247s, 1126s, 1074s, 1036s, 972m, 915m, 819s, 784m, 733m;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 0.84 (2H, t,  $J=7.2$ , alkane  $\text{CH}_2\text{-CH}_3$ ), 1.00 (3H, t,  $J=7.2$ , O- $\text{CH}_2\text{-CH}_3$ ), 1.10 (3H, t,  $J=7.2$ , alkane  $\text{CH}_2\text{-CH}_3$ ), 2.47 (1H, dd,  $J=1.6$  and 15.2, C4- $\text{CH}(\text{H})$ ), 2.95 (1H, dd,  $J=7.5$  and 15.2, C4- $\text{CH}(\text{H})$ ), 3.40 (1H, t,  $J=7.2$ , C5- $\text{CH}$ ), 3.64 (3H, s, O- $\text{CH}_3$ ), 3.65 (3H, s, O- $\text{CH}_3$ ), 3.72 (3H, s, O- $\text{CH}_3$ ), 3.84-3.93 (2H, m, O- $\text{CH}_2\text{-CH}_3$ ), 5.17 (1H, s, C2- $\text{CH}$ ), 6.56 (2H, d,  $J=6.8$ , 2 x Ar  $\text{CH}$ ), 6.72 (2H, d,  $J=6.8$ , 2 x Ar  $\text{CH}$ );  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 10.88 ( $\text{CH}_2\text{-CH}_3$ ), 14.55 (O- $\text{CH}_2\text{-CH}_3$ ), 26.34 ( $\text{CH}_2\text{-CH}_3$ ), 35.42 (C4- $\text{CH}_2$ ), 52.97 (C2- $\text{CH}$ ), 53.74 (C5- $\text{CH}$ ), 55.96 (O- $\text{CH}_3$ ), 59.70 (O- $\text{CH}_2\text{-CH}_3$ ), 61.35 (C3- $\text{C}$ ), 68.25 (O- $\text{CH}_3$ ), 115.01 (Ar- $\text{CH}$ ), 116.76 (Ar- $\text{CH}$ ), 139.65 (Ar- $\text{CH}$ ), 152.91 (Ar- $\text{CH}$ ), 168.82 (C=O), 170.56 (C=O), 170.96 (C=O);  $m/z$  (EI) 393 ( $\text{M}^+$ , 13%), 364 (12), 320 (100), 232 (11), 200 (7), 134 (10), 113 (2), 77 (3), 59 (3); Accurate mass for  $\text{C}_{20}\text{H}_{27}\text{NO}_7$  – 393.1787, found – 393.1787.

**5-Ethyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (134)<sup>88</sup>**



To a solution of the *N*-(4-Methoxy-phenyl)-5-ethyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (133) (0.390 g, 1.00 mmol) in acetonitrile (15 mL) at 0 °C, in a 50 mL round bottomed flask equipped with a magnetic stirrer bar, was added a solution of cerium ammonium nitrate (1.100 g, 2.00 mmol) in water (3 mL) drop-wise over 5 minutes. This solution was allowed to stir for 20 minutes after which time the mixture was allowed to rise to RT before being extracted with ethyl acetate (20 mL) and washed with saturated sodium hydrogen carbonate solution (2 x 20 mL) and saturated brine solution (2 x 20 mL). The organic layer was dried using magnesium sulphate and the product purified by column chromatography (SiO<sub>2</sub>, EtOAc:P.E. 40-60; 1:2), to afford the 5-Ethyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (134) as a colourless oil (0.120 g, 42%);  $\nu_{\text{max}}(\text{film})/\text{cm}^{-1}$  2957m, 2880w (CH str), 1744s (C=O), 1434s, 1278s, 1239s, 1214s, 1133m, 1023m, 969w;  $\delta_{\text{H}}$  (250 MHz; CDCl<sub>3</sub>) 0.99-1.03 (3H, m, CH-CH<sub>2</sub>-CH<sub>3</sub>), 1.20 (3H, t, J=7.1, O-CH<sub>2</sub>-CH<sub>3</sub>), 1.26 (1H, m, C4-CH(H)), 1.64 (1H, m, CH-CH(H)-CH<sub>3</sub>), 2.20 (1H, m, C4-CH(H)), 3.03 (1H, m, CH-CH(H)-CH<sub>3</sub>), 3.65 (3H, s, O-CH<sub>3</sub>), 3.75 (3H, s, O-CH<sub>3</sub>), 4.03-4.14 (2H, m, O-CH<sub>2</sub>-CH<sub>3</sub>), 4.64 (1H, m, C5-CH), 5.36 (1H, s, C2-CH);  $\delta_{\text{C}}$  (101 MHz; CDCl<sub>3</sub>) 11.17 (CH-CH<sub>2</sub>-CH<sub>3</sub>), 14.56 (O-CH<sub>2</sub>-CH<sub>3</sub>), 27.71 (CH-CH<sub>2</sub>-CH<sub>3</sub>), 36.95 (C4-CH<sub>2</sub>), 53.85 (C5-CH), 54.12 (C2-CH), 59.28 (C3-C), 62.50 (O-CH<sub>2</sub>-CH<sub>3</sub>), 62.85 (O-CH<sub>3</sub>), 64.67 (O-CH<sub>3</sub>), 165.97 (C=O), 165.76 (C=O), 169.33 (C=O);  $m/z$  (EI) 286 (M<sup>+</sup> -H, 60%), 243 (47), 212 (55), 180 (25), 155 (44), 145 (39), 123 (31), 113 (100), 94 (18), 59 (41); Accurate mass for C<sub>13</sub>H<sub>21</sub>NO<sub>6</sub> – 286.1290, found – 286.1286

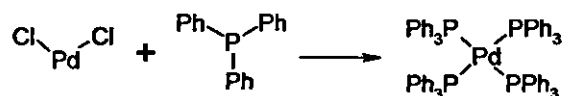
***D*-Glyceraldehyde acetonide (249)<sup>88</sup>**



To a vigorously stirred suspension of chromatographic grade silica gel (10.00 g) in DCM (80 mL) in a 150 mL conical flask was added a 0.650 M aq solution of sodium periodate (10 mL) drop-wise with stirring, forming a flaky suspension. 1,2:5,6-*Di*-*O*-isopropylidene-*D*-mannitol (1.310 g, 5.00 mmol) in DCM (10 mL) was added, and the reaction monitored by TLC until disappearance of the *D*-mannitol (usually less than 15 min). The mixture was filtered and the silica gel thoroughly washed with DCM (2 x 50 mL). Evaporation of the solvent *in vacuo* affords the *D*-glyceraldehyde acetonide as a colourless oil (1.260 g, 97%),  $\nu_{\max}(\text{film})/\text{cm}^{-1}$  2987s, 2895m (CH str), 1735m (C=O), 1257s, 1213s, 1153s, 1072s, 920w, 848s, 794w;  $\delta_{\text{H}}$  (250 MHz;  $\text{CDCl}_3$ ) 1.38 (3H, s,  $\text{CH}_3$ ), 1.44 (3H, s,  $\text{CH}_3$ ), 4.07-4.13 (2H, m, C4- $\text{CH}_2$ ), 4.35 (1H, m, C3- $\text{CH}$ ), 9.67 (1H, s,  $\text{CHO}$ );  $\delta_{\text{C}}$  (101 MHz;  $\text{CDCl}_3$ ) 25.43 ( $\text{CH}_3$ ), 26.54 ( $\text{CH}_3$ ), 53.78 (C1-C), 65.84 (C4- $\text{CH}_2$ ), 80.15 (C3- $\text{CH}$ ), 202.09 ( $\text{HC=O}$ );  $m/z$  (EI) 131 ( $\text{M}^+ + \text{H}$ , 24%), 115 (13), 101 (53), 89 (10), 59, (42) 43 (100), Accurate mass for  $\text{C}_6\text{H}_{10}\text{O}_3$  – 131.0710, found – 131.0710;  $[\alpha]_{\text{D}}^{20} = +65.12^\circ$  lit =  $+64.90^\circ$

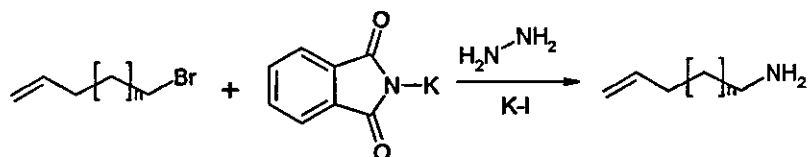
### Section 3.12 – Other Reactions Performed

#### Palladium Tetrakis(triphenylphosphine) (250)<sup>89</sup>



A mixture of palladium chloride (1.770 g), triphenyl phosphine (13 100 g) and dimethyl sulfoxide (120 mL), was placed in a 3 neck round bottomed flask equipped with a magnetic stirrer bar. Nitrogen was passed through it to purge the flask of oxygen. The yellow mixture was heated by means of an oil bath until complete solution occurred (~ 140 °C). The oil bath was taken away and the solution was rapidly stirred for 15 minutes, hydrazine hydrate (2 mL) was rapidly added over 1 minute. A vigorous reaction took place with the evolution of nitrogen. The dark solution was immediately cooled in a water bath until crystallization occurred (at ~125 °C), at this point ice bath was removed and the mixture was allowed to cool with out external cooling. After the mixture reached RT it was filtered under a stream of nitrogen, and the solid washed with ethanol (2 x 50 mL) and ether (2 x 50 mL). To yield the Pd(PPh<sub>3</sub>)<sub>4</sub> (250) (10 420 g, 97% yield) as a bright yellow crystalline material.

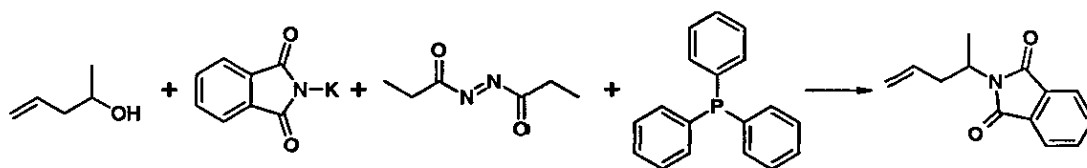
#### Gabriel Synthesis (251 and 252)<sup>84</sup>



To potassium phthalimide (5 650 g, 35.00 mmol) and 4-bromobut-1-ene (3 780 g, 35.000 mmol) or 5-bromopent-1-ene (5.210 g, 35 00 mmol) in dimethyl formamide (20 mL) in a stirred 100 mL round bottomed flask with nitrogen gas inlet, potassium iodine (0.400 g) was added. The mixture was heated to 120 °C with stirring for 30 minutes and at 160 °C for a further 30 minutes. The hot suspension was poured onto ice (22 g) to form a creamy white solid and extracted with chloroform (4 x 10 mL). The combined extracts were shaken successively with 1 mol dm<sup>-3</sup> potassium

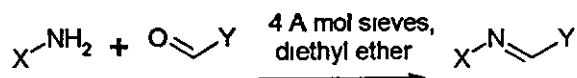
hydroxide, water and hydrochloric acid ( $0.500 \text{ mol dm}^{-3}$ ) and dried over magnesium sulphate. Removal of chloroform by rotary evaporation gave a yellow oily liquid that solidified upon standing. The solid was refluxed with hydrazine hydrate (2.00 g) in ethanol (30 mL) for 1 hour and after cooling in an ice bath, treated slowly with  $10 \text{ mol dm}^{-3}$  hydrochloric acid (3.7 mL). The white solid formed was removed by filtration and the filtrate concentrated to yield a syrup that solidified upon standing at RT. This was treated with a cold solution of potassium hydroxide (2.600 g) in water (5 mL). The precipitated potassium chloride was filtered off and the remaining aqueous solution extracted with ether (4 x 5 mL). The combined ether extracts were dried over potassium hydroxide and concentrated in vacuo to give the 1-aminopropane (**251**) as light yellow oil (1.660 g, 67%), or the 1-aminopentane (**252**) (1.250 g, 42%) as a light yellow oil. Crude NMR showed the desired products before they were used to prepare the imines.

#### Mitsunobu coupling (**253**)<sup>90</sup>



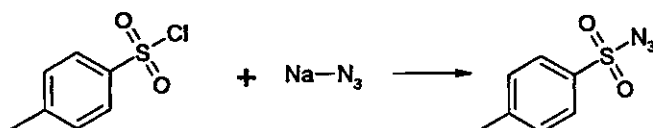
To a solution of pent-4-en-2-ol (0.850 g, 10.00 mmol), triphenyl phosphine (2.650 g, 10.100 mmol), and phthalimide (1.870 g, 10.100 mmol) in dry THF (100 mL) at 0 °C under nitrogen was added DEAD (1.420 g, 10.00 mmol) drop-wise over 20 min. After stirring for 24 hours saturated sodium chloride solution was added (50 mL) and the mixture was washed with ether (3 x 50 mL). The combined ether extracts were dried over  $\text{MgSO}_4$  and the solvent removed in vacuo. The resulting solid was purified by column chromatography ( $\text{SiO}_2$ , ether:PE, 40-60, 1:6) and concentrated to give the *N*-(pent-4-ene)-phthalimide (**253**) (1.440 g, 67%) as a yellow amorphous solid. Crude NMR showed the desired product before it was converted to the amine through addition of anhydrous  $\text{HCl}$ .<sup>90</sup>

## Imines<sup>86</sup>



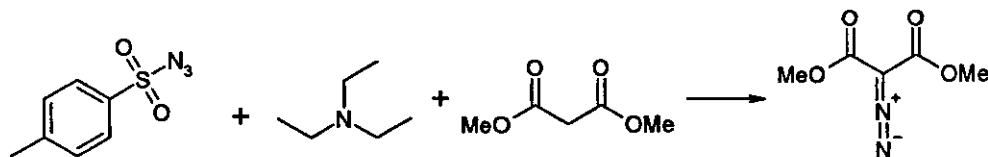
To a solution of the aldehyde (20.00 mmol) and ether (30 mL) in a 100 mL round-bottomed flask equipped with a magnetic stirrer bar was slowly added the amine (20.00 mmol) over a period of 1 minute. To this reaction mixture was added dry molecular sieves (5.00 g), the reaction vessel was flushed with nitrogen and reacted under positive pressure of nitrogen with stirring for 24 hours. At the end of this time the molecular sieves were filtered off and the excess solvent evaporated in vacuo to afford the desired imine.

## Tosyl Azide (254)<sup>86</sup>



To a solution of tosyl chloride (7.00 g, 36.700 mmol) in 60 mL of acetone and distilled water (40 mL) in a 250 mL round bottom flask was added sodium azide (5.00 g, 98.00 mmol) the resulting mixture was refluxed for 3 hours. After the reaction was completed 40 mL of distilled water was added to the mixture, the tosyl azide was extracted using DCM (2 x 100 mL). Magnesium sulphate was used to dry the organic layer which was filtered and the filtrate concentrate in vacuo to afford the tosyl azide (254) (5.200 g, 77%) as an amorphous white solid. Crude NMR showed the desired product before it was used to prepare the diazomalonate.

## Diazomalonate (255)<sup>74</sup>



To a solution of dimethyl malonate (7.200 g, 45.00 mmol) and triethylamine (4.650 g, 46.00 mmol) in benzene (75 mL) is added tosyl azide (9.00 g, 45.00 mmol), and the reaction was allowed to stand at RT for 24 h. Readily volatile components are removed in vacuo. The residue was triturated with benzene (100 mL). The resultant solution is washed with a solution of potassium hydroxide (5.400 g) in water (200 mL), the aqueous phase was saturated with sodium sulphate, and extracted with ether (100 mL). Acidification of the combined ethereal extracts with 6M hydrochloric acid, the ether extracts are dried with sodium sulphate. Removal of solvent in vacuo afforded the diazomalonate (255) (8.110 g, 95%). Crude NMR showed the desired product before it was used to prepare the aromatic cyclopropanes.

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## Chapter 5 – Appendices

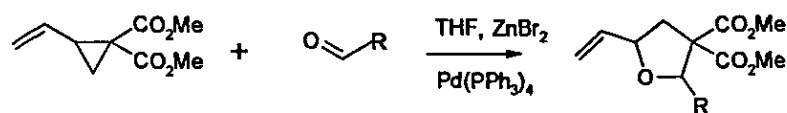
### Appendices 1 – Reactions with Aldehydes

It was observed on several occasions that there was hydrolysis of the imines used in our [2+3]-cycloaddition reactions to give the amine and the aldehyde. This meant the aldehyde reacting with the vinyl cyclopropane to generate the tetrahydrofuran product (Scheme 94). It was therefore necessary when this occurred to synthesise the cyclic product, again using the corresponding aldehyde to determine if it was the hydrolysis product being formed or a secondary reaction (Table 62).

Over the course of the project several tetrahydrofurans were synthesized and all of these have confirmed the presence of the hydrolysis product in the reaction mixture. The hydrolysis product seen in the reaction mixture was thought to be caused by imines breaking down in the presence of small quantities of water to the reaction mixture. This caused the hydrolysis of the imine to the amine and aldehyde. The aldehyde then reacted with the vinyl cyclopropane to form the THF product.

Overall the tetrahydrofuran products have been prepared in good yield and in fast reaction times. All the tetrahydrofurans were synthesized in yields which were comparable to the corresponding benzyl imines. The results shown that the simple phenyl and alkane chains react the best.

The only substrate which had different reaction conditions was ethyl glyoxalate (entry 3, Table 62) this had proven to be a highly reactive substrate and TLC of the reaction mixture showed that it had reached completion after only 16 hours, and required no Lewis acid.



**Scheme 94 – Tetrahydrofuran formation**

	<i>R</i>	<i>Solvent</i>	<i>Temp (°C)</i>	<i>Time (h)</i>	<i>Yield (%)</i>	<i>Cis:Trans</i>
1		THF	35	48	72 (239)	3:1
2		THF	35	48	0 (240)	-
3		THF	35	48	96 (241)	1:1
4		THF	35	48	0 (242)	-
5		THF	35	48	72 (243)	3:1
6		THF	35	48	0 (244)	-
7		THF	35	48	54 (245)	1:1
8		THF	35	48	30 (246)	1:1
9		THF	35	48	49 (247)	4:1

1 mmol scale and had 2 eq of ZnBr<sub>2</sub> and 10 mol% Pd(PPh<sub>3</sub>)<sub>4</sub>

**Table 62 – Aldehyde cyclisation**

**Appendices 2 –**

**X-ray Crystal Data for N-(4-methoxy-phenyl)-5-vinyl-pyrrolidine-  
2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester**

F. Hoffmann-La Roche AG

Crystal data and structure refinement for x1269,  
Probe: MDT.20, Dr.A.Thomas

Author	André Alker Pharma Research Basel 65/310 Phone: 80935 Email: andre_m.alker@roche.com
Data deposition	Roche intranet structure No. 1269
WWW address	<a href="http://xbaw01.bas.roche.com:8080/apps/sxray/sxray.html">http://xbaw01.bas.roche.com:8080/apps/sxray/sxray.html</a>
Date of data deposition	20.10.2003
Empirical formula	C20 H25 N O7
Formula weight	391.41
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, Pna2(1)
Unit cell dimensions	a = 40.279(8) Å    alpha = 90 deg. b = 8.0051(16) Å    beta = 90 deg. c = 6.2460(12) Å    gamma = 90 deg.
Volume	2014.0(7) Å <sup>3</sup>
Z, Calculated density	4, 1.291 Mg/m <sup>3</sup>
Absorption coefficient	0.098 mm <sup>-1</sup>
F(000)	832
Crystal size	0.3 x 0.1 x 0.03 mm
Theta range for data collection	2.59 to 24.02 deg.
Limiting indices	-46<=h<=46, -9<=k<=9, -6<=l<=6
Reflections collected / unique	16200 / 3023 [R(int) = 0.0866]
Completeness to theta = 24.02	95.9 %
Refinement method	Full-matrix least-squares on F <sup>2</sup>
Data / restraints / parameters	3023 / 1 / 257
Goodness-of-fit on F <sup>2</sup>	0.856
Final R indices [I>2sigma(I)]	R1 = 0.0396, wR2 = 0.0746
R indices (all data)	R1 = 0.0702, wR2 = 0.0811
Absolute structure parameter	-1.2(14)
Largest diff. peak and hole	0.153 and -0.137 e.Å <sup>-3</sup>

Table 2. Atomic coordinates ( $\times 10^4$ ) and equivalent isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ) for x1269.  $U(\text{eq})$  is defined as one third of the trace of the orthogonalized  $U_{ij}$  tensor.

	x	y	z	$U(\text{eq})$
O(1)	9377(1)	5610(3)	5034(4)	67(1)
O(2)	9683(1)	4923(3)	7857(4)	67(1)
O(3)	9525(1)	745(3)	7895(4)	79(1)
O(4)	9428(1)	1525(3)	4554(4)	61(1)
O(5)	8559(1)	1152(3)	7601(5)	92(1)
O(6)	8670(1)	1102(3)	4146(5)	83(1)
O(7)	7454(1)	7150(3)	5557(5)	83(1)
N(8)	8705(1)	4615(3)	7451(5)	47(1)
C(9)	8837(1)	4624(4)	9659(5)	50(1)
C(10)	9116(1)	3323(4)	9606(6)	51(1)
C(11)	9213(1)	3248(4)	7237(5)	42(1)
C(12)	8872(1)	3399(4)	6120(5)	41(1)
C(13)	8962(1)	6290(5)	10323(6)	65(1)
C(14)	8985(1)	7621(5)	9203(7)	74(1)
C(15)	8386(1)	5173(4)	6971(5)	45(1)
C(16)	8204(1)	6127(4)	8413(6)	55(1)
C(17)	7896(1)	6749(4)	7878(6)	62(1)
C(18)	7755(1)	6442(4)	5904(7)	59(1)
C(19)	7929(1)	5467(4)	4475(6)	57(1)
C(20)	8240(1)	4843(4)	5014(5)	50(1)
C(21)	7309(1)	6950(6)	3516(7)	90(1)
C(22)	8689(1)	1755(4)	6064(6)	50(1)
C(23)	8475(1)	-411(5)	3853(8)	102(2)
C(24)	8170(1)	-42(6)	2842(11)	137(2)
C(25)	9404(1)	1698(4)	6652(6)	46(1)
C(26)	9588(1)	45(4)	3744(7)	76(1)
C(27)	9424(1)	4734(4)	6558(5)	48(1)
C(28)	9892(1)	6371(4)	7506(8)	85(1)

Table 3. Bond lengths [Å] and angles [deg] for x1269.

O(1)-C(27)	1.197 (3)
O(2)-C(27)	1.328 (4)
O(2)-C(28)	1.450 (4)
O(3)-C(25)	1.193 (4)
O(4)-C(25)	1.321 (4)
O(4)-C(26)	1.440 (4)
O(5)-C(22)	1.195 (4)
O(6)-C(22)	1.309 (4)
O(6)-C(23)	1.455 (4)
O(7)-C(18)	1.353 (4)
O(7)-C(21)	1.413 (5)
N(8)-C(15)	1.393 (3)
N(8)-C(12)	1.446 (4)
N(8)-C(9)	1.477 (4)
C(9)-C(13)	1.485 (5)
C(9)-C(10)	1.532 (4)
C(10)-C(11)	1.531 (4)
C(11)-C(25)	1.507 (4)
C(11)-C(27)	1.524 (4)
C(11)-C(12)	1.543 (4)
C(12)-C(22)	1.510 (4)
C(13)-C(14)	1.278 (5)
C(15)-C(20)	1.384 (4)
C(15)-C(16)	1.391 (4)
C(16)-C(17)	1.378 (4)
C(17)-C(18)	1.380 (5)
C(18)-C(19)	1.378 (5)
C(19)-C(20)	1.389 (4)
C(23)-C(24)	1.414 (5)
C(27)-O(2)-C(28)	117.0 (3)
C(25)-O(4)-C(26)	117.8 (3)
C(22)-O(6)-C(23)	118.5 (3)
C(18)-O(7)-C(21)	117.9 (3)
C(15)-N(8)-C(12)	121.4 (2)
C(15)-N(8)-C(9)	122.0 (2)
C(12)-N(8)-C(9)	111.9 (2)
N(8)-C(9)-C(13)	112.8 (3)
N(8)-C(9)-C(10)	103.9 (2)
C(13)-C(9)-C(10)	111.5 (2)
C(11)-C(10)-C(9)	103.5 (3)
C(25)-C(11)-C(27)	106.8 (2)
C(25)-C(11)-C(10)	113.4 (3)
C(27)-C(11)-C(10)	112.4 (3)
C(25)-C(11)-C(12)	114.2 (3)
C(27)-C(11)-C(12)	108.1 (2)
C(10)-C(11)-C(12)	102.0 (2)
N(8)-C(12)-C(22)	111.8 (2)
N(8)-C(12)-C(11)	101.9 (2)
C(22)-C(12)-C(11)	112.2 (2)
C(14)-C(13)-C(9)	128.3 (4)
C(20)-C(15)-C(16)	116.8 (3)
C(20)-C(15)-N(8)	121.5 (3)
C(16)-C(15)-N(8)	121.6 (3)
C(17)-C(16)-C(15)	121.1 (3)
C(16)-C(17)-C(18)	121.6 (3)
O(7)-C(18)-C(19)	126.1 (4)
O(7)-C(18)-C(17)	115.9 (3)
C(19)-C(18)-C(17)	118.0 (3)
C(18)-C(19)-C(20)	120.4 (3)

C(15)-C(20)-C(19)	122.0(3)
O(5)-C(22)-O(6)	123.3(3)
O(5)-C(22)-C(12)	123.3(3)
O(6)-C(22)-C(12)	113.4(3)
C(24)-C(23)-O(6)	110.6(4)
O(3)-C(25)-O(4)	123.3(3)
O(3)-C(25)-C(11)	125.3(3)
O(4)-C(25)-C(11)	111.4(3)
O(1)-C(27)-O(2)	122.8(3)
O(1)-C(27)-C(11)	126.2(3)
O(2)-C(27)-C(11)	110.9(3)

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Symmetry transformations used to generate equivalent atoms:

*Appendices 3 –*

*X-ray Crystal Data for N-(toluene-4-sulfonyl)-5-vinyl-pyrrolidine-  
2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester*

Table 1. Crystal data and structure refinement for gp3.

Identification code	gp3	
Chemical formula	$C_{20}H_{25}NO_8S$	
Formula weight	439.47	
Temperature	120(2) K	
Radiation, wavelength	MoK $\alpha$ , 0.71073 Å	
Crystal system, space group	monoclinic, Pn	
Unit cell parameters	a = 8.9899(9) Å	$\alpha = 90^\circ$
	b = 8.4230(9) Å	$\beta = 96.354(5)^\circ$
	c = 28.777(3) Å	$\gamma = 90^\circ$
Cell volume	2165.7(4) Å <sup>3</sup>	
Z	4	
Calculated density	1.348 g/cm <sup>3</sup>	
Absorption coefficient $\mu$	0.195 mm <sup>-1</sup>	
F(000)	928	
Crystal colour and size	colourless, 0.36 × 0.20 × 0.04 mm <sup>3</sup>	
Reflections for cell refinement	45811 ( $\theta$ range 2.91 to 27.48°)	
Data collection method	Bruker-Nonius KappaCCD	
	$\varphi$ & $\omega$ scans	
$\theta$ range for data collection	3.23 to 25.00°	
Index ranges	h -10 to 10, k -9 to 9, l -34 to 34	
Completeness to $\theta = 25.00^\circ$	91.4 %	
Intensity decay	0%	
Reflections collected	11465	
Independent reflections	5810 ( $R_{int} = 0.1586$ )	
Reflections with $F^2 > 2\sigma$	4747	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.933 and 0.992	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on $F^2$	
Weighting parameters a, b	0.1499, 3.3182	
Data / restraints / parameters	5810 / 2 / 549	
Final R indices [ $F^2 > 2\sigma$ ]	$R1 = 0.0885$ , $wR2 = 0.2365$	
R indices (all data)	$R1 = 0.1063$ , $wR2 = 0.2545$	
Goodness-of-fit on $F^2$	1.045	
Absolute structure parameter	-0.17(16)	
Largest and mean shift/su	0.001 and 0.000	
Largest diff. peak and hole	0.661 and -0.598 e Å <sup>-3</sup>	

Table 2. Atomic coordinates and equivalent isotropic displacement parameters ( $\text{\AA}^2$ ) for gp3.  $U_{eq}$  is defined as one third of the trace of the orthogonalized  $U^{\dagger}$  tensor.

	x	y	z	$U_{eq}$
N(1)	0.8705(8)	0.5093(8)	0.2353(2)	0.0310(16)
C(2)	0.8301(9)	0.4256(10)	0.1918(3)	0.0278(18)
C(3)	0.7025(10)	0.3153(9)	0.2043(3)	0.0290(18)
C(4)	0.6277(10)	0.4152(10)	0.2383(3)	0.0327(19)
C(5)	0.7568(9)	0.4972(9)	0.2689(3)	0.0266(17)
S(1)	1.0460(2)	0.5513(2)	0.25067(7)	0.0292(5)
O(1)	1.0490(7)	0.6515(7)	0.2908(2)	0.0368(14)
O(2)	1.1037(7)	0.6060(7)	0.2090(2)	0.0381(14)
C(6)	1.1393(9)	0.3718(10)	0.2676(3)	0.0298(18)
C(7)	1.1234(11)	0.3069(11)	0.3112(3)	0.038(2)
C(8)	1.1961(10)	0.1705(10)	0.3234(3)	0.038(2)
C(9)	1.2875(11)	0.0918(11)	0.2946(3)	0.040(2)
C(10)	1.3008(11)	0.1601(11)	0.2511(3)	0.040(2)
C(11)	1.2278(10)	0.3019(10)	0.2378(3)	0.036(2)
C(12)	1.3631(12)	-0.0610(12)	0.3079(4)	0.054(3)
C(13)	0.7812(9)	0.5430(10)	0.1521(3)	0.0284(18)
O(3)	0.7285(9)	0.6707(8)	0.1580(2)	0.0501(18)
O(4)	0.8084(8)	0.4806(7)	0.11171(19)	0.0426(16)
C(14)	0.7663(12)	0.5787(12)	0.0699(3)	0.044(2)
C(15)	0.8177(12)	0.4909(13)	0.0304(3)	0.049(3)
C(16)	0.7590(10)	0.1581(10)	0.2265(3)	0.0312(19)
O(5)	0.6846(8)	0.0837(8)	0.2507(3)	0.0538(18)
O(6)	0.8898(7)	0.1120(7)	0.2147(2)	0.0373(14)
C(17)	0.9403(12)	-0.0424(10)	0.2298(4)	0.047(3)
C(18)	0.5923(11)	0.2738(10)	0.1595(3)	0.036(2)
O(7)	0.4776(9)	0.3394(9)	0.1491(2)	0.060(2)
O(8)	0.6516(8)	0.1588(8)	0.1358(2)	0.0492(17)
C(19)	0.5621(14)	0.1141(14)	0.0927(3)	0.058(3)
C(20)	0.7113(9)	0.6502(10)	0.2880(3)	0.0324(19)
C(21)	0.7071(11)	0.6770(11)	0.3330(3)	0.043(2)
N(1')	0.7644(8)	0.2277(8)	0.4634(2)	0.0314(16)
C(2')	0.7661(10)	0.1447(10)	0.5076(3)	0.0309(19)
C(3')	0.6293(9)	0.0301(10)	0.4990(3)	0.0290(18)
C(4')	0.5225(10)	0.1207(11)	0.4642(3)	0.035(2)
C(5')	0.6232(10)	0.1992(11)	0.4306(3)	0.035(2)
S(1')	0.9235(2)	0.2662(2)	0.44463(7)	0.0295(5)
O(1')	1.0153(7)	0.3389(7)	0.4830(2)	0.0386(15)
O(2')	0.8901(7)	0.3490(7)	0.40104(18)	0.0326(14)
C(6')	1.0047(9)	0.0852(10)	0.4336(3)	0.0315(19)
C(7')	1.1253(9)	0.0268(9)	0.4647(3)	0.0285(18)
C(8')	1.1903(11)	-0.1150(11)	0.4559(3)	0.042(2)
C(9')	1.1430(10)	-0.2046(9)	0.4157(3)	0.0306(19)
C(10')	1.0240(10)	-0.1427(10)	0.3853(3)	0.0329(19)
C(11')	0.9575(10)	-0.0027(9)	0.3940(3)	0.0292(18)
C(12')	1.2185(12)	-0.3566(11)	0.4051(3)	0.042(2)
C(13')	0.7447(10)	0.2619(11)	0.5472(2)	0.0276(18)
O(3')	0.6893(8)	0.3855(8)	0.5436(2)	0.0433(16)
O(4')	0.8109(7)	0.1976(7)	0.58784(19)	0.0361(14)
C(14')	0.7991(14)	0.2914(12)	0.6297(3)	0.051(3)

C(15')	0.8746(12)	0.1937(13)	0.6692(3)	0.048(3)
C(16')	0.6702(11)	-0.1303(10)	0.4784(3)	0.035(2)
O(5')	0.5786(8)	-0.2082(8)	0.4541(3)	0.0536(19)
O(6')	0.8099(7)	-0.1738(7)	0.4911(2)	0.0353(14)
C(17')	0.8474(12)	-0.3337(10)	0.4781(3)	0.042(2)
C(18')	0.5559(12)	-0.0044(11)	0.5434(4)	0.041(2)
O(7')	0.4518(10)	0.0602(10)	0.5546(3)	0.068(2)
O(8')	0.6265(8)	-0.1240(8)	0.5673(2)	0.0496(17)
C(19')	0.5697(15)	-0.1664(16)	0.6111(4)	0.068(4)
C(20')	0.5580(11)	0.3424(11)	0.4085(4)	0.043(2)
C(21')	0.5154(12)	0.3504(15)	0.3634(4)	0.057(3)

Table 3. Bond lengths [Å] and angles [°] for gp3.

N(1)-C(2)	1.450(10)	N(1)-C(5)	1.485(10)
N(1)-S(1)	1.630(8)	C(2)-C(13)	1.537(10)
C(2)-C(3)	1.549(12)	C(3)-C(4)	1.504(12)
C(3)-C(16)	1.533(11)	C(3)-C(18)	1.576(11)
C(4)-C(5)	1.541(11)	C(5)-C(20)	1.476(12)
S(1)-O(1)	1.429(6)	S(1)-O(2)	1.434(6)
S(1)-C(6)	1.771(9)	C(6)-C(11)	1.367(12)
C(6)-C(7)	1.390(12)	C(7)-C(8)	1.349(13)
C(8)-C(9)	1.398(14)	C(9)-C(10)	1.394(14)
C(9)-C(12)	1.486(14)	C(10)-C(11)	1.395(13)
C(13)-O(3)	1.195(10)	C(13)-O(4)	1.324(10)
O(4)-C(14)	1.474(10)	C(14)-C(15)	1.472(13)
C(16)-O(5)	1.194(10)	C(16)-O(6)	1.319(11)
O(6)-C(17)	1.429(11)	C(18)-O(7)	1.179(11)
C(18)-O(8)	1.330(11)	O(8)-C(19)	1.450(11)
C(20)-C(21)	1.318(13)	N(1')-C(2')	1.451(10)
N(1')-C(5')	1.514(10)	N(1')-S(1')	1.616(7)
C(2')-C(13')	1.536(11)	C(2')-C(3')	1.561(12)
C(3')-C(4')	1.514(11)	C(3')-C(18')	1.529(13)
C(3')-C(16')	1.535(12)	C(4')-C(5')	1.545(12)
C(5')-C(20')	1.456(13)	S(1')-O(2')	1.437(6)
S(1')-O(1')	1.439(6)	S(1')-C(6')	1.735(9)
C(6')-C(11')	1.385(11)	C(6')-C(7')	1.414(12)
C(7')-C(8')	1.365(13)	C(8')-C(9')	1.408(12)
C(9')-C(10')	1.405(12)	C(9')-C(12')	1.497(13)
C(10')-C(11')	1.358(12)	C(13')-O(3')	1.154(10)
C(13')-O(4')	1.364(10)	O(4')-C(14')	1.455(10)
C(14')-C(15')	1.502(14)	C(16')-O(5')	1.212(11)
C(16')-O(6')	1.320(11)	O(6')-C(17')	1.448(11)
C(18')-O(7')	1.160(11)	C(18')-O(8')	1.340(12)
O(8')-C(19')	1.457(12)	C(20')-C(21')	1.314(15)
C(2)-N(1)-C(5)	113.9(7)	C(2)-N(1)-S(1)	118.8(6)
C(5)-N(1)-S(1)	123.6(5)	N(1)-C(2)-C(13)	110.6(7)
N(1)-C(2)-C(3)	102.2(6)	C(13)-C(2)-C(3)	113.6(7)
C(4)-C(3)-C(16)	111.3(7)	C(4)-C(3)-C(2)	102.3(6)

C(16)-C(3)-C(2)  
 C(16)-C(3)-C(18)  
 C(3)-C(4)-C(5)  
 C(20)-C(5)-C(4)  
 O(1)-S(1)-O(2)  
 O(2)-S(1)-N(1)  
 O(2)-S(1)-C(6)  
 C(11)-C(6)-C(7)  
 C(7)-C(6)-S(1)  
 C(7)-C(8)-C(9)  
 C(10)-C(9)-C(12)  
 C(9)-C(10)-C(11)  
 O(3)-C(13)-O(4)  
 O(4)-C(13)-C(2)  
 C(15)-C(14)-O(4)  
 O(5)-C(16)-C(3)  
 C(16)-O(6)-C(17)  
 O(7)-C(18)-C(3)  
 C(18)-O(8)-C(19)  
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 O(4)-C(14)-C(15)  
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 O(7)-C(18)-C(3)  
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 N(1)-C(5)-C(4)  
 O(1)-S(1)-N(1)  
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 N(1)-S(1)-C(6)  
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 O(3)-C(13)-C(2)  
 C(13)-O(4)-C(14)  
 O(5)-C(16)-O(6)  
 O(6)-C(16)-C(3)  
 O(7)-C(18)-O(8)  
 O(8)-C(18)-C(3)  
 C(21)-C(20)-C(5)  
 C(2)-N(1)-S(1)  
 N(1)-C(2)-C(13)  
 C(13)-C(2)-C(3)  
 C(4)-C(3)-C(16)  
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 C(16)-C(3)-C(2)  
 C(20)-C(5)-N(1)  
 N(1)-C(5)-C(4)  
 O(2)-S(1)-N(1)  
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 N(1)-S(1)-C(6)  
 C(11)-C(6)-S(1)  
 C(8)-C(7)-C(6)  
 C(10)-C(9)-C(8)  
 C(8)-C(9)-C(12)  
 C(10)-C(11)-C(6)  
 O(3)-C(13)-C(2)  
 C(13)-O(4)-C(14)  
 O(5)-C(16)-O(6)  
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 O(7)-C(18)-O(8)  
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Table 4. Anisotropic displacement parameters ( $\text{\AA}^2$ ) for gp3. The anisotropic displacement factor exponent takes the form:  $-2\pi^2[h^2a^{*2}U^{11} + \dots + 2hka^*b^*U^{12}]$

	$U^{11}$	$U^{22}$	$U^{33}$	$U^{23}$	$U^{13}$	$U^{12}$
N(1)	0.037(4)	0.037(4)	0.017(3)	-0.004(3)	-0.003(3)	0.010(3)
C(2)	0.031(5)	0.032(4)	0.019(4)	-0.001(3)	-0.003(3)	0.007(4)
C(3)	0.035(5)	0.030(4)	0.022(4)	0.003(3)	-0.001(3)	-0.001(4)
C(4)	0.033(5)	0.030(5)	0.034(4)	-0.004(3)	0.000(4)	0.004(4)
C(5)	0.025(4)	0.029(4)	0.027(4)	-0.001(3)	0.005(3)	-0.001(3)
S(1)	0.0311(11)	0.0303(11)	0.0264(9)	0.0004(8)	0.0035(8)	-0.0020(9)
O(1)	0.046(4)	0.037(4)	0.027(3)	-0.008(2)	0.001(3)	-0.001(3)
O(2)	0.039(4)	0.044(4)	0.034(3)	0.003(3)	0.011(3)	0.001(3)
C(6)	0.017(4)	0.037(5)	0.036(4)	-0.003(3)	0.002(3)	-0.007(4)
C(7)	0.041(6)	0.037(5)	0.036(5)	-0.005(4)	0.001(4)	0.004(4)
C(8)	0.033(5)	0.036(5)	0.043(5)	0.006(4)	-0.005(4)	-0.005(4)
C(9)	0.033(5)	0.037(5)	0.049(6)	0.004(4)	0.001(4)	-0.003(4)
C(10)	0.035(5)	0.043(5)	0.041(5)	-0.019(4)	0.005(4)	0.003(4)
C(11)	0.034(5)	0.040(5)	0.033(5)	-0.010(4)	-0.001(4)	0.001(4)
C(12)	0.038(6)	0.043(6)	0.081(8)	0.005(5)	0.008(5)	0.000(5)
C(13)	0.032(5)	0.035(5)	0.019(4)	0.005(3)	0.004(3)	0.004(4)
O(3)	0.073(5)	0.037(4)	0.039(4)	0.005(3)	-0.002(3)	0.016(4)
O(4)	0.064(4)	0.042(4)	0.021(3)	0.004(2)	0.000(3)	0.002(3)
C(14)	0.062(7)	0.053(6)	0.018(4)	0.011(4)	0.007(4)	0.000(5)
C(15)	0.057(7)	0.062(6)	0.026(4)	-0.001(4)	0.002(4)	0.009(5)
C(16)	0.035(5)	0.030(5)	0.028(4)	0.004(3)	0.000(4)	-0.004(4)
O(5)	0.054(5)	0.046(4)	0.061(5)	0.017(3)	0.004(4)	-0.002(4)
O(6)	0.036(4)	0.027(3)	0.048(4)	0.007(3)	0.002(3)	0.000(3)
C(17)	0.046(6)	0.017(5)	0.075(7)	0.004(4)	-0.001(5)	0.000(4)
C(18)	0.047(6)	0.035(5)	0.026(4)	-0.007(3)	0.005(4)	-0.003(4)
O(7)	0.056(5)	0.073(5)	0.046(4)	-0.013(3)	-0.021(4)	0.017(4)
O(8)	0.055(4)	0.051(4)	0.038(4)	-0.014(3)	-0.009(3)	0.000(3)
C(19)	0.078(8)	0.068(7)	0.026(5)	-0.014(5)	-0.002(5)	-0.008(6)
C(20)	0.028(5)	0.034(5)	0.035(5)	0.005(3)	0.001(4)	0.004(4)
C(21)	0.044(6)	0.042(5)	0.041(5)	-0.009(4)	0.001(4)	0.009(4)
N(1')	0.040(4)	0.044(4)	0.010(3)	-0.004(3)	0.005(3)	0.008(3)
C(2')	0.036(5)	0.031(5)	0.027(4)	-0.002(3)	0.007(4)	0.005(4)
C(3')	0.023(4)	0.033(5)	0.030(4)	0.000(3)	0.000(3)	-0.002(4)
C(4')	0.035(5)	0.045(5)	0.026(4)	-0.001(3)	0.003(4)	0.006(4)
C(5')	0.030(5)	0.046(5)	0.027(4)	-0.002(4)	-0.002(4)	-0.008(4)
S(1')	0.0322(11)	0.0330(11)	0.0237(9)	-0.0020(8)	0.0048(8)	-0.0021(9)
O(1')	0.046(4)	0.031(3)	0.037(3)	-0.010(2)	-0.008(3)	-0.008(3)
O(2')	0.039(4)	0.039(3)	0.020(3)	0.005(2)	0.007(2)	-0.003(3)
C(6')	0.029(5)	0.042(5)	0.024(4)	0.000(3)	0.001(3)	-0.006(4)
C(7')	0.035(5)	0.031(5)	0.020(4)	0.001(3)	0.004(3)	-0.002(4)
C(8')	0.043(6)	0.040(5)	0.039(5)	-0.004(4)	-0.009(4)	0.002(5)
C(9')	0.035(5)	0.027(4)	0.030(4)	0.002(3)	0.002(4)	-0.003(4)
C(10')	0.028(4)	0.043(5)	0.027(4)	-0.001(3)	0.003(3)	0.000(4)
C(11')	0.034(5)	0.026(4)	0.027(4)	-0.004(3)	-0.001(3)	-0.003(4)
C(12')	0.046(6)	0.036(5)	0.043(5)	-0.004(4)	-0.001(4)	0.007(4)
C(13')	0.031(4)	0.039(5)	0.014(4)	0.003(3)	0.010(3)	-0.004(4)
O(3')	0.067(5)	0.035(4)	0.029(3)	0.000(3)	0.009(3)	0.010(3)

O(4')	0.054(4)	0.035(3)	0.020(3)	-0.002(2)	0.008(3)	0.007(3)
C(14')	0.078(8)	0.045(6)	0.028(5)	-0.003(4)	0.003(5)	0.005(5)
C(15')	0.060(7)	0.071(7)	0.016(4)	-0.001(4)	0.016(4)	-0.011(6)
C(16')	0.041(6)	0.033(5)	0.031(4)	0.002(3)	0.005(4)	-0.014(4)
O(5')	0.052(4)	0.040(4)	0.065(5)	-0.015(3)	-0.011(4)	-0.005(3)
O(6')	0.043(4)	0.028(3)	0.034(3)	0.000(2)	0.002(3)	0.006(3)
C(17')	0.053(6)	0.039(5)	0.035(5)	0.003(4)	0.007(4)	0.009(5)
C(18')	0.037(6)	0.038(5)	0.048(6)	-0.007(4)	0.013(5)	-0.003(5)
O(7')	0.074(6)	0.078(6)	0.058(5)	0.015(4)	0.031(4)	0.030(5)
O(8')	0.055(4)	0.055(4)	0.041(4)	0.015(3)	0.014(3)	0.003(3)
C(19')	0.079(9)	0.088(9)	0.039(6)	0.030(6)	0.011(6)	-0.016(7)
C(20')	0.032(5)	0.039(5)	0.059(6)	0.008(4)	0.009(4)	-0.005(4)
C(21')	0.040(6)	0.073(8)	0.055(6)	0.033(5)	-0.010(5)	-0.022(5)

Table 5. Hydrogen coordinates and isotropic displacement parameters ( $\text{\AA}^2$ ) for gp3.

	x	y	z	U
H(2)	0.9167	0.3607	0.1836	0.033
H(4A)	0.5682	0.3482	0.2576	0.039
H(4B)	0.5607	0.4949	0.2215	0.039
H(5)	0.7947	0.4252	0.2952	0.032
H(7)	1.0630	0.3574	0.3319	0.046
H(8)	1.1845	0.1255	0.3531	0.046
H(10)	1.3605	0.1095	0.2302	0.048
H(11)	1.2394	0.3491	0.2085	0.043
H(12A)	1.4497	-0.0744	0.2904	0.081
H(12B)	1.2928	-0.1488	0.3007	0.081
H(12C)	1.3966	-0.0604	0.3415	0.081
H(14A)	0.6566	0.5942	0.0650	0.053
H(14B)	0.8153	0.6839	0.0733	0.053
H(15A)	0.7698	0.3863	0.0280	0.073
H(15B)	0.9266	0.4778	0.0356	0.073
H(15C)	0.7910	0.5503	0.0014	0.073
H(17A)	0.8712	-0.1227	0.2152	0.070
H(17B)	0.9436	-0.0496	0.2639	0.070
H(17C)	1.0406	-0.0609	0.2206	0.070
H(19A)	0.5531	0.2049	0.0713	0.087
H(19B)	0.4623	0.0814	0.0997	0.087
H(19C)	0.6104	0.0256	0.0781	0.087
H(20)	0.6834	0.7339	0.2667	0.039
H(21A)	0.7344	0.5955	0.3551	0.051
H(21B)	0.6768	0.7780	0.3433	0.051
H(2')	0.8612	0.0834	0.5147	0.037
H(4'1)	0.4673	0.2021	0.4803	0.043
H(4'2)	0.4494	0.0479	0.4471	0.043
H(5')	0.6444	0.1212	0.4060	0.042
H(7')	1.1610	0.0863	0.4917	0.034
H(8')	1.2694	-0.1541	0.4775	0.050
H(10')	0.9891	-0.2003	0.3578	0.039

H(11')	0.8773	0.0355	0.3727	0.035
H(12D)	1.1683	-0.4457	0.4187	0.063
H(12E)	1.3236	-0.3531	0.4184	0.063
H(12F)	1.2130	-0.3707	0.3711	0.063
H(14C)	0.6930	0.3106	0.6341	0.061
H(14D)	0.8501	0.3950	0.6277	0.061
H(15D)	0.9785	0.1733	0.6637	0.072
H(15E)	0.8216	0.0925	0.6709	0.072
H(15F)	0.8728	0.2514	0.6987	0.072
H(17D)	0.8292	-0.3453	0.4440	0.063
H(17E)	0.7852	-0.4096	0.4930	0.063
H(17F)	0.9532	-0.3543	0.4884	0.063
H(19D)	0.4661	-0.2036	0.6048	0.103
H(19E)	0.5729	-0.0731	0.6316	0.103
H(19F)	0.6317	-0.2509	0.6266	0.103
H(20')	0.5459	0.4331	0.4273	0.051
H(21C)	0.5268	0.2608	0.3440	0.069
H(21D)	0.4733	0.4458	0.3501	0.069

Table 6. Torsion angles [°] for gp3.

C(5)-N(1)-C(2)-C(13)	105.1(8)	S(1)-N(1)-C(2)-C(13)	-95.6(7)
C(5)-N(1)-C(2)-C(3)	-16.1(8)	S(1)-N(1)-C(2)-C(3)	143.1(6)
N(1)-C(2)-C(3)-C(4)	34.0(7)	C(13)-C(2)-C(3)-C(4)	-85.2(8)
N(1)-C(2)-C(3)-C(16)	-85.9(8)	C(13)-C(2)-C(3)-C(16)	154.9(7)
N(1)-C(2)-C(3)-C(18)	153.2(7)	C(13)-C(2)-C(3)-C(18)	34.0(9)
C(16)-C(3)-C(4)-C(5)	81.1(8)	C(2)-C(3)-C(4)-C(5)	-40.2(8)
C(18)-C(3)-C(4)-C(5)	-158.9(7)	C(2)-N(1)-C(5)-C(20)	-129.1(7)
S(1)-N(1)-C(5)-C(20)	72.8(8)	C(2)-N(1)-C(5)-C(4)	-8.0(8)
S(1)-N(1)-C(5)-C(4)	-166.1(6)	C(3)-C(4)-C(5)-C(20)	152.8(7)
C(3)-C(4)-C(5)-N(1)	29.9(8)	C(2)-N(1)-S(1)-O(1)	172.1(6)
C(5)-N(1)-S(1)-O(1)	-30.8(7)	C(2)-N(1)-S(1)-O(2)	42.7(7)
C(5)-N(1)-S(1)-O(2)	-160.2(6)	C(2)-N(1)-S(1)-C(6)	-72.0(7)
C(5)-N(1)-S(1)-C(6)	85.1(7)	O(1)-S(1)-C(6)-C(11)	-141.5(7)
O(2)-S(1)-C(6)-C(11)	-9.5(8)	N(1)-S(1)-C(6)-C(11)	104.1(7)
O(1)-S(1)-C(6)-C(7)	37.2(8)	O(2)-S(1)-C(6)-C(7)	169.2(7)
N(1)-S(1)-C(6)-C(7)	-77.2(7)	C(11)-C(6)-C(7)-C(8)	-1.1(13)
S(1)-C(6)-C(7)-C(8)	-179.7(7)	C(6)-C(7)-C(8)-C(9)	0.6(14)
C(7)-C(8)-C(9)-C(10)	-0.6(13)	C(7)-C(8)-C(9)-C(12)	-178.1(9)
C(8)-C(9)-C(10)-C(11)	1.1(13)	C(12)-C(9)-C(10)-C(11)	178.7(9)
C(7)-C(6)-C(11)-C(10)	1.5(12)	S(1)-C(6)-C(11)-C(10)	-179.8(6)
C(9)-C(10)-C(11)-C(6)	-1.6(13)	N(1)-C(2)-C(13)-O(3)	-26.8(12)
C(3)-C(2)-C(13)-O(3)	87.5(10)	N(1)-C(2)-C(13)-O(4)	152.6(7)
C(3)-C(2)-C(13)-O(4)	-93.2(8)	O(3)-C(13)-O(4)-C(14)	-1.2(13)
C(2)-C(13)-O(4)-C(14)	179.5(7)	C(13)-O(4)-C(14)-C(15)	175.6(8)
C(4)-C(3)-C(16)-O(5)	42.1(11)	C(2)-C(3)-C(16)-O(5)	156.7(8)
C(18)-C(3)-C(16)-O(5)	-80.5(10)	C(4)-C(3)-C(16)-O(6)	-140.9(7)
C(2)-C(3)-C(16)-O(6)	-26.3(10)	C(18)-C(3)-C(16)-O(6)	96.5(9)
O(5)-C(16)-O(6)-C(17)	4.1(13)	C(3)-C(16)-O(6)-C(17)	-172.8(7)

C(4)-C(3)-C(18)-O(7)	15.1(13)	C(16)-C(3)-C(18)-O(7)	137.4(10)
C(2)-C(3)-C(18)-O(7)	-98.3(11)	C(4)-C(3)-C(18)-O(8)	-166.4(7)
C(16)-C(3)-C(18)-O(8)	-44.1(9)	C(2)-C(3)-C(18)-O(8)	80.2(9)
O(7)-C(18)-O(8)-C(19)	0.4(14)	C(3)-C(18)-O(8)-C(19)	-178.0(8)
N(1)-C(5)-C(20)-C(21)	-130.4(9)	C(4)-C(5)-C(20)-C(21)	115.0(10)
C(5)-N(1)-C(2)-C(13)	-107.6(8)	S(1)-N(1)-C(2)-C(13)	99.9(7)
C(5)-N(1)-C(2)-C(3)	10.8(9)	S(1)-N(1)-C(2)-C(3)	-141.6(6)
N(1)-C(2)-C(3)-C(4)	-30.5(8)	C(13)-C(2)-C(3)-C(4)	87.8(8)
N(1)-C(2)-C(3)-C(18)	-149.4(7)	C(13)-C(2)-C(3)-C(18)	-31.1(10)
N(1)-C(2)-C(3)-C(16)	88.6(8)	C(13)-C(2)-C(3)-C(16)	-153.1(7)
C(18)-C(3)-C(4)-C(5)	160.1(7)	C(16)-C(3)-C(4)-C(5)	-81.3(8)
C(2)-C(3)-C(4)-C(5)	39.4(8)	C(2)-N(1)-C(5)-C(20)	134.3(8)
S(1)-N(1)-C(5)-C(20)	-74.7(9)	C(2)-N(1)-C(5)-C(4)	12.7(9)
S(1)-N(1)-C(5)-C(4)	163.7(6)	C(3)-C(4)-C(5)-C(20)	-154.3(8)
C(3)-C(4)-C(5)-N(1)	-31.9(8)	C(2)-N(1)-S(1)-O(2)	-179.5(6)
C(5)-N(1)-S(1)-O(2)	30.7(7)	C(2)-N(1)-S(1)-O(1)	-49.8(7)
C(5)-N(1)-S(1)-O(1)	160.5(6)	C(2)-N(1)-S(1)-C(6)	64.7(6)
C(5)-N(1)-S(1)-C(6)	-85.1(7)	O(2)-S(1)-C(6)-C(11)	-37.6(8)
O(1)-S(1)-C(6)-C(11)	-169.4(7)	N(1)-S(1)-C(6)-C(11)	76.7(8)
O(2)-S(1)-C(6)-C(7)	140.4(7)	O(1)-S(1)-C(6)-C(7)	8.5(8)
N(1)-S(1)-C(6)-C(7)	-105.3(7)	C(11)-C(6)-C(7)-C(8)	-1.4(12)
S(1)-C(6)-C(7)-C(8)	-179.5(7)	C(6)-C(7)-C(8)-C(9)	1.6(13)
C(7)-C(8)-C(9)-C(10)	-1.0(14)	C(7)-C(8)-C(9)-C(12)	177.4(9)
C(8)-C(9)-C(10)-C(11)	0.1(13)	C(12)-C(9)-C(10)-C(11)	-178.2(8)
C(9)-C(10)-C(11)-C(6)	0.0(13)	C(7)-C(6)-C(11)-C(10)	0.6(12)
S(1)-C(6)-C(11)-C(10)	178.6(6)	N(1)-C(2)-C(13)-O(3)	23.2(13)
C(3)-C(2)-C(13)-O(3)	-90.5(10)	N(1)-C(2)-C(13)-O(4)	-153.5(7)
C(3)-C(2)-C(13)-O(4)	92.9(8)	O(3)-C(13)-O(4)-C(14)	4.5(13)
C(2)-C(13)-O(4)-C(14)	-178.8(8)	C(13)-O(4)-C(14)-C(15)	178.0(8)
C(4)-C(3)-C(16)-O(5)	-37.7(11)	C(18)-C(3)-C(16)-O(5)	82.6(10)
C(2)-C(3)-C(16)-O(5)	-152.3(8)	C(4)-C(3)-C(16)-O(6)	144.2(7)
C(18)-C(3)-C(16)-O(6)	-95.5(8)	C(2)-C(3)-C(16)-O(6)	29.6(9)
O(5)-C(16)-O(6)-C(17)	-6.4(13)	C(3)-C(16)-O(6)-C(17)	171.6(7)
C(4)-C(3)-C(18)-O(7)	-18.1(13)	C(16)-C(3)-C(18)-O(7)	-138.5(10)
C(2)-C(3)-C(18)-O(7)	96.5(12)	C(4)-C(3)-C(18)-O(8)	160.3(8)
C(16)-C(3)-C(18)-O(8)	39.8(10)	C(2)-C(3)-C(18)-O(8)	-85.1(9)
O(7)-C(18)-O(8)-C(19)	-3.1(15)	C(3)-C(18)-O(8)-C(19)	178.6(8)
N(1)-C(5)-C(20)-C(21)	132.4(9)	C(4)-C(5)-C(20)-C(21)	-113.0(10)

