Palladium-catalysed routes to the tricyclic core of the Stemona alkaloids

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Palladium Catalysed Routes to the Tricyclic Core of the *Stemona* Alkaloids

By Danial Leybourne

A Doctoral Thesis

Submitted in partial fulfilment of the requirements for the award of PhD at Loughborough University

Department of Chemistry
Loughborough University
Loughborough
Leicestershire
LE11 3NW
# Contents

<table>
<thead>
<tr>
<th>Page Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>i</td>
</tr>
<tr>
<td>ii</td>
</tr>
<tr>
<td>iii</td>
</tr>
<tr>
<td>vi</td>
</tr>
</tbody>
</table>

## Chapter 1  New routes to heterocyclic families

### Introduction

1.1.i. Routes to the tricyclic core of the stenine group of *Stemona* Alkaloids 1
1.1.ii. Transition metal assisted [3+2]-cycloadditions 26
1.1.iii. Palladium catalysed [3+2]-cycloadditions using methylene cyclopropanes derivatives 26
1.1.iv. Nucleophilic addition to cyclopropanes 29
1.1.v. Palladium catalysed [3+2]-cycloadditions with vinylcyclopropanes 32
1.1.vi. Previous work 35

## Chapter 2  Synthesis of bicyclic cyclopropanes

2.1.i. Reterosynthesis of 5-membered heterocycles 45
2.1.ii. Preparation of activated vinylcyclopropanes 47
2.1.iii. Proposed construction of activated bicyclic cyclopropanes 49
2.2. Preparation of dimethyl bicyclo[4.1.0]hept-2-ene-7,7-dicarboxylate 53
2.3. Preparation of dimethyl bicyclo[3.1.0]hept-2-ene-7,7-dicarboxylate 65
2.4. Preparation of bicyclo[5.1.0]oct-2-ene-8,8-dicarboxylic acid dimethyl ester 68
Chapter 3  Reactions of [4.1.0]-activated cyclopropanes

3.1.i  Synthesis of heterocycles using palladium(0) catalysis 74
3.1.ii. Proposed route to the heterocyclic compounds 75
3.2.  Palladium(0) mediated cycloadditions of the dimethyl bicyclo[4.1.0]hex-2-ene-7,7-dicarboxylate with a range of aldehydes 78
3.3.  Palladium(0) mediated cycloadditions of the dimethyl bicyclo[4.1.0]hex-2-ene-7,7-dicarboxylate with a selection of activated ketones 85
3.4.  Palladium(0) mediated cycloadditions of dimethyl bicyclo[4.1.0]hex-2-ene-7,7-dicarboxylate with a selection of imines 89
3.5.  Palladium(0) mediated cycloadditions of bicyclo[4.1.0]hex-2-ene-7-carboxylic acid ethyl ester 98
3.6.  Palladium(0) mediated cycloadditions of dimethyl bicyclo[5.1.0]hex-2-ene-7,7-dicarboxylate and dimethyl bicyclo[6.1.0]hex-2-ene-7,7-dicarboxylate 99
3.7.  Proposed mechanism of bicyclic tetrahydrofuran ring formation 100
3.8.  Conclusion 101
### Chapter 4  Reactions of [3.1.0]-activated cyclopanes

<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1.i.</td>
<td>Synthesis of heterocycles using palladium(0) catalysis</td>
<td>103</td>
</tr>
<tr>
<td>4.1.ii.</td>
<td>Proposed route to the heterocyclic compounds</td>
<td>104</td>
</tr>
<tr>
<td>4.2.</td>
<td>Palladium(0) mediated cycloadditions of the dimethyl bicyclo[3.1.0]hex-2-ene-7,7-dicarboxylate with a selection of aldehydes</td>
<td>105</td>
</tr>
<tr>
<td>4.3.</td>
<td>Palladium(0) mediated cycloadditions of the dimethyl bicyclo[3.1.0]hex-2-ene-7,7-dicarboxylate with a selection of activated ketones</td>
<td>113</td>
</tr>
<tr>
<td>4.4.</td>
<td>Palladium(0) mediated cycloadditions of dimethyl bicyclo[3.1.0]hex-2-ene-7,7-dicarboxylate with a selection of imines</td>
<td>116</td>
</tr>
<tr>
<td>4.5.</td>
<td>Palladium(0) mediated cycloadditions of bicyclo[3.1.0]hex-2-ene-7-carboxylic acid ethyl ester</td>
<td>126</td>
</tr>
<tr>
<td>4.6.</td>
<td>Proposed mechanism of bicyclic tetrahydrofuran ring formation</td>
<td>127</td>
</tr>
<tr>
<td>4.7.</td>
<td>Conclusion</td>
<td>130</td>
</tr>
</tbody>
</table>

### Chapter 5  Heck mediated coupling

<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.1.i.</td>
<td>The Heck reaction</td>
<td>132</td>
</tr>
<tr>
<td>5.1.ii.</td>
<td>Synthesis of vinylcyclopropane</td>
<td>133</td>
</tr>
<tr>
<td>5.1.iii.</td>
<td>Proposed route to bicyclic pyrrolidines and tetrahydrofurans using an intramolecular Heck cyclisation</td>
<td>133</td>
</tr>
<tr>
<td>5.2.</td>
<td>Palladium(0) mediated cycloadditions of vinylcyclopropane with phenyl isocyanate</td>
<td>135</td>
</tr>
<tr>
<td>5.3.</td>
<td>Palladium(0) mediated cycloadditions of vinylcyclopropane with a range of 2-bromo substituted aldehydes</td>
<td>136</td>
</tr>
<tr>
<td>5.4.</td>
<td>Palladium(0) mediated cycloadditions of vinylcyclopropane with a range of 2-bromobenzyl substituted imines</td>
<td>143</td>
</tr>
<tr>
<td>5.5.</td>
<td>Intramolecular Heck cyclisations with tetrahydrofurans</td>
<td>149</td>
</tr>
<tr>
<td>5.6.</td>
<td>Intramolecular Heck cyclisations with pyrrolidines</td>
<td>151</td>
</tr>
</tbody>
</table>
Chapter 6 Experimental

General information

6.1.i. Solvents and Reagents
6.1.ii. Chromatographic Procedures
6.1.iii. FT-IR
6.1.iv. $^1$H NMR
6.1.v. $^{13}$C NMR
6.1.vi. Mass Spectra
6.1.vii. Other Data

6.2. Experimental procedures for Chapter 2
6.3. Experimental procedures for Chapter 3
6.4. Experimental procedures for Chapter 4
6.5. Experimental procedures for Chapter 5

Chapter 7 References

7.1. References
Palladium Catalysed Routes to the Tricyclic Core of the *Stemona* Alkaloids

Heterocyclic product families include a wide and diverse range of natural and synthetic molecules, which exhibit a variety of biological activities. In particular this study will focus on the construction of the *Stemona* alkaloids, isolated from the roots and rhizomes of the *Stemonaceae* plant family. They possess the structurally novel and unique azepinoindole skeleton "B,C,D ring system."

Studies towards the development of a novel methodology has been achieved. During our investigation we have developed a palladium(O) catalysed [3+2]-cycloaddition strategy towards the rapid synthesis of heterocyclic skeletons, assembling polycyclic pyrrolidines and furan heterocycles from fused doubly activated vinylcyclopropanes.

We have briefly investigated our palladium(O) catalysed [3+2]-cycloaddition methodology towards doubly activated vinylcyclopropanes, preparing a selection of tetrahydrofuran and pyrrolidine precursors which underwent a Heck mediated cyclisation. As well as further developing this methodology towards a tandem cycloaddition/Heck one pot strategy. We hoped this initial ground work could be applied towards the construction of the tricyclic core of *Stemona* alkaloids.
Acknowledgements

Without the hard work and help of so many this would not have been possible. Firstly, I must thank my supervisor Dr Gareth Pritchard. His immense patience and unwavering support has been inspirational. Without his enthusiasm and guidance none of this would have been possible. I would like to take this opportunity to wish him continued success for the future.

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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
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<tr>
<td>Aloc</td>
<td>allyloxy carbonyl</td>
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<td>Ar</td>
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<td>9-borabicyclo[3.3.1]nonyl</td>
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<td>camphorsulfonic acid</td>
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<td>dibenzylideneacetone</td>
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<td>distortionless enhancement by polarisation transfer</td>
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<td>DIBAL</td>
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<td>N,N-dimethylformaldehyde</td>
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<td>electron withdrawing group</td>
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<td>FAB</td>
<td>fast atom bombardment</td>
</tr>
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<td>h</td>
<td>hour</td>
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<td>Abbreviation</td>
<td>Definition</td>
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<td>------------------------------------------------</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoramide</td>
</tr>
<tr>
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<td>hertz</td>
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<tr>
<td>IR</td>
<td>infra-red</td>
</tr>
<tr>
<td>L</td>
<td>ligand</td>
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<td>J</td>
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<tr>
<td>KHMDS</td>
<td>potassium hexamethyldisilazide</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropyl amide</td>
</tr>
<tr>
<td>LHMDS</td>
<td>lithium hexamethyldisilazide</td>
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<td>m-CPBA</td>
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<td>min.</td>
<td>minutes</td>
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<tr>
<td>mp</td>
<td>melting point</td>
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<tr>
<td>MPM</td>
<td>para-methoxybenzene</td>
</tr>
<tr>
<td>Ms</td>
<td>mesyl, MeSO₂</td>
</tr>
<tr>
<td>m/z</td>
<td>mass to charge ratio</td>
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<tr>
<td>nOe</td>
<td>nuclear Overhauser effect</td>
</tr>
<tr>
<td>o</td>
<td>ortho</td>
</tr>
<tr>
<td>p</td>
<td>para</td>
</tr>
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<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>PMB</td>
<td>para-methoxybenzene</td>
</tr>
<tr>
<td>PPTS</td>
<td>pyridinium p-toluenesulfonate</td>
</tr>
<tr>
<td>q</td>
<td>quartet</td>
</tr>
<tr>
<td>Red-Al</td>
<td>Sodium bis(2-methoxyethoxy)aluminium hydride</td>
</tr>
<tr>
<td>RT</td>
<td>room temperature</td>
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<td>s</td>
<td>singlet</td>
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<td>S₂N₂</td>
<td>bimolecular nucleophilic substitution</td>
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<tr>
<td>str.</td>
<td>stretch</td>
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<tr>
<td>t</td>
<td>triplet</td>
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<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TBAI</td>
<td>tetrabutylammonium iodide</td>
</tr>
<tr>
<td>TBDPS</td>
<td>tert-butylidiphenylsilyl</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------------------</td>
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<tr>
<td>TBSOTf</td>
<td>tetrabutylsilyl triflate</td>
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<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
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<td>TIBSOTf</td>
<td>triisobutylsilyl triflate</td>
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<tr>
<td>Tol</td>
<td>toluene</td>
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<tr>
<td>Ts</td>
<td><em>para</em>-toluenesulfonyl</td>
</tr>
</tbody>
</table>
Compound numbering

Vinylcyclopropanes

Tetrahydrofurans/pyrrolidines

Bicyclic vinylcyclopropanes

Fused bicyclic heterocycles

Fused tricyclic heterocycles

NMR assignment:

Where mixtures of diastereoisomers are formed, C' will be used to denote a carbon atom corresponding to the cis isomer. Trans isomer carbons will be presented as C.
Chapter 1 - New routes to heterocyclic families

Introduction

1.1.1. Routes to the tricyclic core of the stenine group of Stemona alkaloids

The Stemona alkaloids are a structurally interesting class of alkaloids isolated from the roots and rhizomes of the Stemonacae plant family. Physiologically active Stemonacous plants possess the structurally novel and unique azepinoindole skeleton (B,C,D-ring system) (Figure 1). Stemonacea represents a rather isolated family within the monocohyedons consisting of 3 genera Stemona, Croomia and Stichoneuron. Approximately 50 structurally novel polycyclic metabolites have been isolated to date.

Figure 1: Azepinoindole B,C,D skeleton.

Stemona is the largest genus with about 25 species occurring as subshrubs or twinning herbs, mostly perennial tuberous roots. Many species prefer a seasonal climate and occur in dry vegetation. Even though the genus Stemona has long been recognised for its broad range of bioactivities, phytochemical investigations have only been restricted to a few species. Further progress was restricted by using plant material which often was not properly identified. This was caused by popular use of the tuberous fleshy roots of different species purchased on the markets under the same vernacular name. Chinese and Japanese folk medicine has recorded extensive use of these extracts in herbal teas of Stemonacae as remedies for a range of respiratory diseases, such as bronchitis, pertussis and tuberculosis, and as anthelmintics. In addition this class of compounds also show extraordinary insecticidal activity. Dried plant materials are utilised as powerful insecticidal materials for the treatment of livestock throughout East Asia.
The alkaloids of this family, having relatively complex polycyclic structures have been classified into six groups according to their structural features. Five of these groups containing the pyrorole[1,2-α]azepine nucleus which characterises the Stemona alkaloids receive the name of the simplest member; stenine (I), stemoamide (II), tuberostemospironine (III), stemonamine (IV) and parvistemoline (V), while the sixth group comprises eight alkaloids (e.g. stemofoline VI) some of them lacking the mentioned nucleus (Figure 2).4

![Figure 2: Stemona alkaloids containing the pyrrolo[1,2-α] azepine core.](image)

The stenine group is a sub-class of the common Stemona alkaloids (compounds 1, 2 and 3, Figure 3), named after the parent compound stenine which possesses the structurally novel azepinoindole skeleton “B,C,D-ring system” (Compounds 4, 5 and 6, Figure 3). The polycyclic cores of these natural products which possess diverse physiological properties as well as structural complexity pose challenging synthetic problems. This has culminated in an impressive series of strategies that showcase novel synthetic methodology, with respect to developing new ring forming reactions,
in the quest to construct the 1-azabicyclo-[5.3.0]-decane as an integral part of the molecular architecture. The facile stereochemical formation of this moiety is a strategic issue (Figure 3).

![Figure 3: Representatives of the Stemona alkaloids.](image)

To date there is no general, facile route to these compounds though a number of long, demanding total syntheses to stenine and related compounds do exist. We intend to address this issue in constructing a facile, novel and efficient route to this motif.

Since the first complete structural elucidation of a Stemona alkaloid in 1967, there has been limited progress towards their preparation until the total synthesis of (+)-cromine in 1989 by Williams. He has since worked extensively in this area including the total synthesis of (-)-stemospironine and (-)-stemonine, which is described below.

The first total synthesis of (-)-stemonine was reported by Williams in 2003, nearly 75 years after its initial discovery. He applied a convergent strategy assembling a fully functionalised acyclic carbon chain as a preface to sequential, late stage ring closure in a total synthesis of 23 steps (Scheme 1).
Scheme 1: Functionalised acyclic carbon chain precursor for the synthesis of stemonine.  

Cyclisation of the acyclic carbon chain (14) to the perhydroazepine (15) proceeded via the Staudinger reaction of aldehydic azide (14), which generated a 7-membered imine by an intramolecular aza-Wittig process. Immediate reductive quench with NaBH₄ gave the desired amine (15). Stereocontrolled formation of the C,D-ring scaffold resulted as a consequence of an iodine-induced cyclisation in a single step (18) (Scheme 2).
Recent years have seen the evolution of several distinguished total syntheses of other members within this family. Each characterised by the presence of the distinctive 1-azabicyclo[5.3.0]-decane as an fundamental component of the molecular design.

Hart’s elegant synthesis of stenine$^9$ utilises an intramolecular Diels-Alder strategy to build the B-ring. Then D,A,C-rings were constructed in sequence. Treatment of (E)-3,5-hexadienol (19) with methyl furmaroyl chloride (20) gave the desired cycloaddition substrate which underwent a Lewis acid promoted cycloaddition to afford the desired trans cycloadduct (21). Introduction of the lone nitrogen of stenine (4) was accomplished using an aminimidine variant of the Curtius re-arrangement. Treatment of (21) with hydrazine in deoxygenated methanol, followed by exhaustive

Scheme 2: Cyclisation of the acyclic carbon chain to synthesise (-)-stemonine.$^8$
methylation followed by acylation served as the handle to insert the nitrogen into the B,C scaffold (22). Thermolysis of the intermediate isocyanate and subsequent addition of methanol afforded the carbamate. Hydroboration, oxidation and mesylation set the scaffold to afford the desired cyclisation to construct the B,C-hydroindole framework (23). Installation of the allylic alcohol proceeded using a halolactonization-dehydrogenation sequence. Dehydrohalogenation followed by reduction of the lactone (24) and protection of the primary alcohol afforded the desired Clasien re-arrangement which furnished the desired amide (25) after treatment with the appropriate amide acetal. Electrophile initiated cyclisation afforded the iodolactone which was accompanied by the loss of the TBS-group. The desired functionality was inserted using a Keck allylation displacing the iodine at this position (27). Finally, alkylation was achieved through the enolate of the A-ring. The construction of the azepine to complete the stenine scaffold was achieved after deprotection of the carbamate and subsequent conversion of the side arm through oxidation, Wittig olefination and conjugate reduction (27). The synthesis was completed in a straight forward manner. Johnson-Lemieux oxidation furnished the aldehyde, which was converted to the thio-ketal. Treatment with Lawesson's reagent gave the thiolactam (29) and simultaneous reduction of the thio-ketal and thiolactam afforded racemic stenine (4) (Scheme 3).
Scheme 3: Hart's elegant synthesis of stenine.9
Wipf has developed a general synthetic strategy for the construction of the B,C-ring structure of the *Stemona* alkaloid based on the oxidation of tyrosine and applied it towards the total synthesis of tuberostemonine, the major structural isomer isolated from *Stemonaceae*. The hydro-indolenone ring was constructed by the oxidation of Aloe-tyramine (30) with iodobenzene diacetate to afford dienone (31) followed by an intramolecular Michael cyclisation of the dienone (31) to afford the B,D bicyclic ring structure (32). Under careful conditions the lithium dienolate of the bicyclic core (32) was allylated exclusively on the less hindered $\beta$-face to give a single isomer (33). Luche reduction of the enone (33) afforded the desired allylic alcohol (34). Protection of the hydroxyl group (35) and deprotection of the silyl ether (36) allowed palladium(0) catalysed hydrostannolytic cleavage of the allyloxy carbonyl moiety (37). The side chain olefin was selectively hydrogenated in the presence of the endocyclic double bond (38) which allowed a Mitsunobu cyclisation of the resulting amino alcohol after deprotection of the benzyl ether (39) to afford the tricyclic core (40) (Scheme 4).
Scheme 4: Wipf's synthetic strategy for the construction for the tricyclic core of tuberostemonine. An alternative intramolecular Diels-Alder/Beckmann rearrangement strategy to stenine has been proposed by Jung. They also report a novel construction of the B,C,D-tricyclic ring skeleton of stenine based on a Beckmann rearrangement of an oxime (48). A Stille coupling of vinyl iodide and vinylstannane facilitated the desired alcohol (41) which was converted into the desired ester (42). Subsequent reaction with dimethyl lithiomethylphosphonate followed by a Horner-Emmons coupling of the
resultant ketophosphonate and appropriate aldehyde synthesised the desired tri-enone (45). The precursor ketone to oxime was envisioned to be obtained through a Diels-Alder reaction of the tri-enone which underwent a Beckmann rearrangement to form the B,D-ring skeleton (49). The final 5-membered C-ring was constructed in two steps (50) (Scheme 5).

Scheme 5: Jung's intramolecular Diels-Alder/Beckmann rearrangement strategy to stenine.11
The asymmetric synthesis of stenine has been accomplished by Morimoto.\textsuperscript{12} It features an intramolecular diastereoselective Diels-Alder reaction of the (E,E,E)-triene (53) prepared in a convergent fashion from three readily available compounds. Efficient construction of the tricyclic A,B,C-ring system is achieved through a modified Curtius rearrangement of the bicyclic ketone (55). Iodolactonisation (57) and radical alkylation (58) were incorporated into the synthesis to ensure the desired functionality was obtained before finally assembling the 7-membered D-ring through an intramolecular alkylation ensured the successful synthesis of the target compound (Scheme 6).
Scheme 6: Morimoto’s asymmetric synthesis of (-)-stenine.¹²
Padwa has utilised an intramolecular [4+2]-cycloaddition of a 2-methylthio-5-amido furan to create the azepinoindole skeleton in stenine which contains no less than six contiguous stereocentres. They incorporated the azepine ring early into the synthetic sequence as a template to set the required stereochemistry. The caprolactam (60) was reacted with bis-(methylsulfanylacetaldehyde) followed by quenching with acetic anhydride to give amide (61). Acylation afforded the imide (62). Methyl sulfonylation of one of the methylthio groups of (62) with dimethyl(methylthio)sulfonium (DMTSF) induced thionium-promoted cyclisation. The resulting dihydrofuran readily lost acetate to furnish the desired furan (63). Rapid re-arrangement at room temperature of (63) afforded the azepinoindole (64). Removal of the thiomethyl group was achieved by treating (64) with Raney Ni and reduction under Luche conditions afforded the alcohol (65). Controlled hydrogenation of the enamidene bond affording the syn-anti stereochemical relationship at the incipient ring fusion sites was achieved with a Crabtree catalyst directed hydrogenation using [Ir(cod)pyr(PCy3)]PF6/CH2Cl2. Conversion of the alcohol to the corresponding mesylate followed by treatment with base provided (66) which underwent the desired iodolactonisation after hydrolysis of the methylester (67). Final conversion to stenine was accomplished in a similar manner to Hart/Wipf, utilising a Keck alkylation with allylic tributyl-stannane and a Johnson-Lemieux oxidation to afford the desired aldehyde. Conversion of the amide to the thioamide using Lawesson's reagent. Desulfurisation with Raney-Nickel and methylation of the lactone enolate with methyl iodide afforded racemic stenine (4) (Scheme 7).
Scheme 7: Padwa’s synthetic strategy for the construction of stenine.  

Construction of the hydroindolone building block directed towards azepinoindole framework within the context of stenine and neotuberostenionine as target alkaloids has also been undertaken by Rigby. They have utilised previous work undertaken within their group to construct the hydroindolone building block by means of a [4+1]-
cycloaddition between an appropriate vinyl isocyanate (68) and alkyl isocyanate (69) as a nucleophilic 1,1-dipole equivalent.\textsuperscript{16} N-Alkylation of the resultant enamide (70) with 1,4-diiodobutane afforded the precursor for a 7-endo-trig radical cyclisation or a metalloenamine based cycloheptannulation to assemble the azepine ring moiety (71). Heating in the presence of EtMgBr afforded the desired tricyclic enamide (72). Hydrolysis of the enamide (72) followed by treatment with \textit{m}-CPBA afforded the desired product (74) (Scheme 8).

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\includegraphics[scale=0.5]{reaction_diagram}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 8:} Rigby’s synthetic strategy for the construction of the azepinoindole alkaloid framework.\textsuperscript{15}

Another method which has initially been studied for the synthesis of manzamine-A (a novel alkaloid) by Leonard has also been proposed as a potential route to explore the \textit{Stemona} alkaloids.\textsuperscript{17} It involves the simple preparation of sulfolene (77). The sulfolene ring is a masked diene which can be incorporated into intramolecular Diels-Alder precursor (76), which releases SO\textsubscript{2} and cyclises upon heating to form (75) (Scheme 9).
Scheme 9: Reterosynthesis for the construction of the B,C,D-tricyclic core by Leonard.\textsuperscript{17}

In his synthesis of (±)-stemoamide (1),\textsuperscript{18} Jacobi envisaged using a butenolide derivative as the key intermediate to establish the desired trans relative stereochemistry (Figure 4).

They identified oxazole (84) as a logical precursor to the butenolide derivative (78) which could be prepared using oxazole Diels-Alder chemistry.\textsuperscript{19} Offering the potential of forming the entire stemoamide skeleton in a single step. Initial condensation of acid chloride (79) and methyl alaninate (80) followed by cyclo-dehydration furnished the desired methoxyoxazole (82). N-Alkylation of succinamide with (82) afforded the oxazole imide (83). The selective reduction of (83) with NaBH\textsubscript{4} followed by treatment with MeOH/H\textsuperscript{+} gave the required methoxylactam (84). Finally, Lewis acid catalysed condensation afforded the desired oxazole precursor (85). Refluxing (85) in diethylbenzene afforded (78). Although (86) was the major product it suffered rapid hydrolysis to (78). A stereoselective cis reduction of (78) was achieved with a nickel-boride catalyst affording (±)-stemoamide (1) (Scheme 10).
Another total synthesis of stemoamide has been accomplished by Mori. At the heart of their methodology lies a ruthenium-catalysed enyne metathesis developed by Grubbs. The starting enyne was prepared from the alkylation of the amide (87), deprotection of the alcohol (88). Subsequent oxidation, followed by addition of CBr₄ and PPh₃ in a one pot reaction afforded the dibromoalkene which upon treatment with base and the desired acid chloride afforded enyne (89). The desired ruthenium catalysed enyne metathesis proceeded smoothly to afford the desired 5,7-fused compound (90). Reduction with NaBH₄ afforded (91), and the final ring was achieved through the bromolactonisation to afford (92/93). Compound (92) was easily converted into (93) by treatment with base. Treatment of the enone (93) with NaBH₄, in the presence of NiCl₂.H₂O in MeOH gave (-)-stemoamide. They have shown how
intramolecular enyne metathesis is an attractive tool for the formation of the *Stemona* alkaloids (Scheme 11).

![Scheme 11: Mori synthesis of (-)-stemoamide.](image)

A carbohydrate synthesis of stemoamide based on D-glucose has been reported by Gurjar. They began their synthesis from the starting material (95) derived from D-glucose. This underwent a Swern oxidation affording an unstable aldehyde which was immediately treated with allyl bromide (96) under Barbier reaction conditions (activated zinc in THF-saturated NH₄Cl solution at 0°C). Hydroboration-oxidation followed by a protection-deprotection sequence furnished the mesylate and treatment with NaN₃ afforded the azido alcohol. Swern oxidation and treatment of the resulting
aldehyde with NaClO₂ gave the azido acid and was isolated after esterification as the methyl ester (97). Hydrogenation of (97) took place with concomitant cyclisation affording the pyrrolodinone derivative (98). Installation of the 7-membered azepine ring was achieved through Grubbs’ ring closing metathesis. N-alkylation proceeded in a biphasic system of 50% KOH-benzene with tetra-n-butyl ammonium iodide and formation of the 5,6-ene derivative (99) involved the selective deprotection of the acetonide moiety, dimesylation of the resultant diol and elimination with NaI. The azepine ring was accomplished using Grubbs’ ring closing metathesis (100).²¹ Hydrogenation of the double bond, treatment with MeOH and Amberlyst-15 afforded the β-isomer (101). Removal of the hydroxy substituent using thiocarbonyl diimidazole and in situ addition of n-BuSn₃H, AIBN (cat.) afforded (102). Finally the γ-lactone was installed using Grieco’s procedure (103).²³ Methylation of (103) completed the total synthesis of stemoamide (1) (Scheme 12).
Scheme 12: Gurjar's synthesis of stemoamide.\textsuperscript{22}

Work synthesising the spirocyclic stemonamide nucleus has been undertaken by Kende, as well as the total synthesis of isostamofoline.\textsuperscript{24} A 15 step total synthesis of stemonamide (104) and isostemonamide (105) has been reported. Isolated by Xu\textsuperscript{4} in 1994 from the roots of \textit{Stemona Japonica}, it contains the characteristic tetracyclic core with two contiguous spirocyclic centres differing in relative stereochemistry at...
the quaternary centres. The heteroatoms are of an *anti* disposition in stemonamide (104) but *syn* in isostemonamide (105) (Figure 5).

![Stemonamide and isostemonamide](image)

**Figure 5:** Stemonamide and isostemonamide.

They envisaged the use of acyliminium chemistry to form the 9aC quaternary centre, followed by aldol spirocyclisation to obtain the 12C quaternary centre. The remaining carbon framework was installed by conjugate Grignard addition to a tricyclic enone intermediate. Synthesis of the tricyclic enone intermediate began with Grignard addition to succinimide (106). The resulting hemiaminal was protected as the methoxy derivative (107), which upon hydrogenolytic debenzylation afforded the spiro compound (109). Addition of (108) to the *N*-acyliminium ion generated from (109) generated the first quaternary centre. A 1:2 mixture of diastereomeric alcohols (110) were produced. Swern oxidation afforded aldehydes which were cyclised directly with DBU to afford the tricyclic aldol products and converted by Swern oxidation to a 1:1 mixture of tricyclic ketones (111) and (112). The ketones were readily separated by column chromatography. The desired enones were synthesised by treatment with *tert*-butyldimethylsilyl enol ethers with Pd(OAc)$_2$, to produce enone (113) and (114) setting the platform for the parallel synthesis of both stemonamide and isostemonamide (Scheme 13).
Scheme 13: Synthesis of the tricyclic enone intermediate for the construction of stemonamide and isostemonamide.\textsuperscript{24}

The total synthesis of stemonamide was achieved by conjugate addition of the Grignard reagent to (113) in the presence of CuBr-Me\textsubscript{2}S, which occurred predominantly \textit{anti} to the C-N bond (115). A Mannich reaction installed the \(\alpha\)-methyl group as well as unsaturation by deprotonation with KH and treatment with dimethylmethyleneammonium trifluoroacetate (116). Removal of the PMB group allowed the unprotected lactam to undergo RhCl\textsubscript{3}-mediated isomerisation to afford the desired enone (118). Azepine ring closure was achieved by nucleophilic displacement of the mesylate with NaI to afford racemic stemonamide (104) (Scheme 14).
Scheme 14: Synthesis of stemonamide from the appropriate tricyclic enone intermediate.²⁴

Similarly, the synthesis of isostemonamide followed a parallel strategy. Conjugate addition of the Grignard reagent to (114) in the presence of CuBr-Me₂S afforded (118) and (119). The TMS enol ether (118) was converted to (120) by direct treatment with the Mannich reagent at RT where as the ketone (119) underwent an identical Mannich reaction as previously outlined in the formation of (116). Isomerisation of the exocyclic double bond and azepine ring closure followed an identical pathway as described for the synthesis of stemonamide (Scheme 15).
Scheme 15: Synthesis of isostemonamide from the desired tricyclic enone intermediate.\textsuperscript{24}

A short efficient route to (+)-croomeine has been developed by Martin.\textsuperscript{25} They have employed a vinylogous Mannich addition of (124) to a chiral N-acyliminium ion to connect the A and C-rings with the appropriate stereochemistry (126). Hydrogenation of (126) set the desired stereochemistry for the methyl substituent. Ring B was put in place by an intramolecular nitrogen alkylation. The thermally unstable acid chloride from intermediate (128) gave rise to the corresponding iminium ion which was trapped with 2-triisopropylsilyloxy-3-methylfuran affording the second vinylogous Mannich reaction (129). Finally, selective hydrogenation afforded (+)-croomeine (3) in 9 steps (Scheme 16).
Scheme 16: Synthesis of (+)-croomine by Martin.\textsuperscript{25}

A strategy to access the tricyclic core of the \textit{Stemona} alkaloid family has also been proposed by Heathcock.\textsuperscript{26} The approach was to control the stereochemistry of the groups on the core 5,7-ring system (130) by a [3,3]-sigmatropic rearrangement of acyliminium ion (131) followed by selective reduction (132). However, brief exploration of the possibilities of carrying out the foregoing process with more elaborate allyl groups to facilitate the construction of the crucial butyrolactone ring proved unsuccessful and further work was abandoned (Scheme 17).
Scheme 17: A novel strategy to construct the *Stemona* alkaloid core proposed by Heathcock.  

1.1.ii. Transition metal assisted [3+2]-cycloadditions

A [3+2]-cycloaddition reaction generates two chemical bonds during a ring forming step, usually in respect to forming five membered heterocycles and to a lesser extent cyclopentenes. Cycloadditions can be promoted by an array of external factors including; light, heat, Lewis acids, high pressure or sonication. The presence of polarised functional groups are frequently encouraged to facilitate this transformation. However, the development of transition metal catalysts has facilitated the versatility, selectivity and reactivity of such cycloaddition reactions through complexation of the metal to the olefin. This strategy has enabled the rapid synthesis of highly functionalised cyclic scaffolds with inherent biological interest. Transition metals have become increasingly common, as an effective template in combining these types of reacting species. An overview of transition metal catalysed heterocyclic synthesis has recently been reported by Nakamura and Yamamoto.  

1.1.iii. Palladium catalysed [3+2]-cycloadditions using methylene cyclopropanes derivatives

Cyclopropane (133) and its derivatives are capable of ring-opening reactions under the influence of many different reacting species, including electrophilic, nucleophilic, and radical reagents, as well as external physical forces such as heat or light. Unlike other straight chain hydrocarbons, the C—C single bond of the cyclopropane
resembles that of a C=C double bond. The cyclic arrangement of a propane chain inherently results in significant angular (Bayer) strain, where the bond angles must deviate to 60° from the ideal 109.5° for sp^3-hybridised systems. Additional torsional (Pitzer) strain is observed, as the coplanar nature of the carbon atoms requires the C—H bonds to be eclipsed. It is the strained nature of the 3C unit and the subsequent relief of this strain during ring opening, which provides the crucial thermodynamic driving force for the reaction.\(^{28}\)

An example of how these useful intermediates have been used for complex molecule synthesis can be seen through palladium catalysed [3+2]-cycloadditions of methylene cyclopropanes and its derivatives. The exocyclic double bond enforces additional strain on the three membered ring by increasing the 1C bond angle and therefore lengthening the 2C-3C bond (134) (Figure 6).\(^{28}\)

![Figure 6: Cyclopropane and methylene cyclopropane derivatives.\(^{28}\)](image)

Methylene cyclopropanes participate in reactions which are characteristic of olefins e.g. electrophilic additions, radical additions, addition to carbenes and nitrenes, various thermally activated cycloadditions or in the presence of strong electron withdrawing groups. However, they are also recognised as versatile building blocks in [3+2]-cycloaddition reactions catalysed by transition metals such as Ni(0) and Pd(0) under mild conditions.\(^{29}\)

Initial studies which were extensively studied within this field were carried out by independently by Binger and Noyori.\(^{29,30}\) A mechanism can be shown for the two reaction pathways in which the metal-catalysed cycloaddition can proceed to afford regioisomeric products (Scheme 18).
Scheme 18: Mechanism of the possible two metal-catalysed cycloaddition reaction pathways.

The transition metal can oxidatively insert into the distal bond (2C-3C, 136a). Subsequent carbometallation onto the double bond and reductive elimination afford cyclopentane (137a) inserting a two carbon unit in the distal position to the double bond. Alternatively the proximal bond cleavage between (1C-3C, 136b) leads to isomeric metallacyclobutane (137b) although the two carbon unit is introduced in the proximal position to the exocyclic double bond. Both regio-isomeric cyclopentenes (137a and 137b) can be isolated in the presence of Ni(0) whereas only type (137a) can be isolated when the reaction is catalysed by Pd(0).[^30]

The regio-chemical outcome of the reactions are highly dependant on the nature of the metal and its associated ligands.[^31] The ability to control both the regio and stereochemical outcome suggests this might provide a powerful cycloaddition process for natural product synthesis.

Recently, Yamamoto[^32] has explored ring opening of the proximal bond employing an intermolecular [3+2]-palladium catalysed cycloaddition strategy. This has led to the formation of novel methylenetetrahydrofuran and methylenepyrrolidine skeletons from a range of alkylidenecyclopropanes with aldehydes and N-tosyl imines (Scheme 19).
Scheme 19: General depiction for the formation of novel methylenetetrahydrofuran and methyleneipyrrolidine skeletons.\textsuperscript{32}

1.1.iv. Nucleophilic addition to cyclopropanes

In direct analogy with reactions of olefins, cyclopropanes are susceptible to addition reactions. The major difference is the presence of an extra carbon, the "synthetic wedge", which improves the number of rearrangement pathways compared to those available to alkenes. Disconnections of similarly functionalised alkenes and cyclopropanes via donor and acceptor interactions, lead to a resonance form in the case of the alkene, and a new compound being formed in the cyclopropane case (Figure 7).\textsuperscript{28}

Bone and Perkin discovered that cleavage of the cyclopropane bond was only possibly in the presence of an electron-withdrawing group on the ring.\textsuperscript{33} Subsequent work by Best found activated cyclopropane (142) undergoes 1,5 ring opening with diethyl
malonate (141) to form tetraester (143), with subsequent intramolecular cyclisation to form the cyclopentanone (144) (Scheme 20).\textsuperscript{34}

\textbf{Scheme 20: Activated cyclopropane intramolecular cyclisation.}\textsuperscript{34}

Geminally placed activating groups observed in many nucleophilic openings of this type, help doubly stabilise the anion formed upon ring opening. However, vigorous reaction conditions are still required to facilitate ring opening with nucleophiles (Nu) such as amines,\textsuperscript{35} mercaptans,\textsuperscript{36} malonate ion,\textsuperscript{33} enamines,\textsuperscript{37} and cuprates,\textsuperscript{38} exposing difficulties in cleaving the strained 2C-3C cyclopropane bond (Scheme 21).

\textbf{Scheme 21: Nucleophilic openings of the 2C-3C cyclopropane bond.}\textsuperscript{33,34-38}

Linstead applied analogous methodology to vinylcyclopropanes and reported both 1,5 and 1,7 modes of ring opening.\textsuperscript{39} He reported cyclopentanone (144) as the major product when reacting with diethyl malonate, with trace amounts of the 1,7-ring opened alkene (147) (Scheme 22).
The chemical properties of cyclopropanes drastically change upon the incorporation of a neighbouring \( \pi \)-system. The extension of conjugation seen in vinylcyclopropanes has been harnessed by Burgess, who reported mild, selective ring opening reaction using catalytic amounts of a palladium(0).\(^{40}\) The ratio of mono- and bis-alkylated products depends not only on the concentration of starting materials, but also the nature of the electron-withdrawing-groups (EWG) present on the vinylcyclopropane and the nucleophile. It was established that the stabilising effect of the EWG on the cyclopropane must be greater or comparable to that of the EWG on the nucleophile to facilitate ring opening of the cyclopropane (Table 1).

Scheme 22: 1,5 and 1,7 modes of ring opening vinylcyclopropane.\(^{39}\)
Table 1: Nucleophile facilitated ring opening of the cyclopropanes.\(^{40}\)

<table>
<thead>
<tr>
<th>EWG</th>
<th>EWG'</th>
<th>Ratio 148:149</th>
<th>Time/h</th>
<th>Yields/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeCO</td>
<td>CO₂Me</td>
<td>1:1</td>
<td>8</td>
<td>30</td>
</tr>
<tr>
<td>MeCO</td>
<td>CO₂Me</td>
<td>2:1</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>MeCO</td>
<td>CO₂Me</td>
<td>1:3</td>
<td>8</td>
<td>58</td>
</tr>
<tr>
<td>SO₂Ph</td>
<td>CO₂Me</td>
<td>1:1</td>
<td>5</td>
<td>94</td>
</tr>
<tr>
<td>SO₂Ph</td>
<td>CO₂Me</td>
<td>2:1</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>SO₂Ph</td>
<td>CO₂Me</td>
<td>1:3</td>
<td>5</td>
<td>98</td>
</tr>
<tr>
<td>CO₂Me</td>
<td>SO₂Ph</td>
<td>1:3</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td>CO₂Me</td>
<td>CO₂Et</td>
<td>1:1</td>
<td>2</td>
<td>23</td>
</tr>
<tr>
<td>CO₂Me</td>
<td>CO₂Et</td>
<td>1:3</td>
<td>8</td>
<td>26</td>
</tr>
</tbody>
</table>

**Early work within this area centred upon palladium catalysed [3+2]-cycloadditions by Morizawa in the early eighties.**\(^{41}\) They reported that doubly activated cyclopropanes can undergo formal retro-aldol rearrangement to 1,3-zwitterionic intermediates which in essence can be considered 1,3-dipole equivalents. Initial work within this area allows a significant insight into how this type of chemistry can be developed and applied towards the construction of the tricyclic core of the *Stemona* alkaloids.

They reported doubly activated vinylcyclopropanes (152) could rearrange under palladium-catalysed conditions affording cyclopentenes (Scheme 23).
Morizawa proposed that a zwitterionic π-pentadienylpalladium intermediate (153) was generated by the oxidative addition of the Pd(0) species to the dienic group. This cleaved the cyclopropane bond with the anion moiety stabilised by the two electron withdrawing substituents. He proposed that this intermediate collapsed to form the cyclopentane derivative (154).

Advancements within this area have been reported by Tsuji. He has reported the synthesis of 5-membered carbocycles (157) by using similar palladium catalysed [3+2]-cycloadditions between doubly activated cyclopropanes (155) and electron deficient olefins (95) (Scheme 24).

Tsuji also believed that the palladium species oxidatively added into the vinyl substituent, ring opening the cyclopropane to form a π-allyl palladium complex (156).
He describes this synthon as a 1,3 dipolar equivalent, as an inter-molecular trap with the desired electron-deficient olefin (95) to form the corresponding 5-membered rings (157). This observation led to the investigation of a variety of electron deficient olefins to explore the versatility of this type of reaction. Their work led them to assemble a variety of γ-lactams (160) from a variety of activated vinylcyclopropanes (155) and aryl isocyanates (158) using analogous palladium catalysed cycloaddition conditions (Scheme 25).

![Scheme 25: Synthesis of a 5-membered heterocycle.](image)

This work provided an elegant insight into the capacity of this type of reaction. It was also a novel route into the formation of 5-membered heterocycles and a potential platform to delve into a variety of structurally interesting and biologically important heterocycles. There were a few drawbacks within this route. Primarily, the use of hexamethylphosphoramide (HMPA) a highly toxic solvent, which if at all possible would be advantageous to avoid. The second is the use of two equivalents of the isocyanate. It was envisaged that these problems could be overcome by modifying the reaction conditions. The powerful concept behind this methodology provides an exciting pathway to a variety of functionalised heterocycles, by utilising alternative electrophiles and a variety of solvents it was thought that the hurdles could be overcome.
More recently Pohlhaus and Johnson reported the synthesis of 2,5-disubstituted tetrahydrofurans (163) from donor acceptor cyclopropanes (161) and benzaldehyde (162) in the presence of a catalytic amount of Sn(OTf)$_2$ (Scheme 26).

\[
\begin{align*}
(161) & \quad + \quad (162) \\
& \quad \xrightarrow{\text{Sn(OTf)$_2$ (5 mol%), } \text{CH$_2$Cl$_2$, RT, 2.5h, (100%)}} \quad (163)
\end{align*}
\]

**Scheme 26: Synthesis of 5-membered heterocycles.**

They reported a range of substituted cyclopropanes (161) these included phenyl, 2-furyl and 4-nitrobenzaldehyde which successfully cyclised with benzaldehyde, albeit requiring 3 equivalents, in excellent yields (89-100%). Although the reaction favoured the cis isomer, a range of diastereomeric ratios were observed. Reaction durations were reported to take between 2.5-6h at room temperature. They postulated that the Lewis acid chelated to the electron withdrawing groups to facilitate the ring opening of the cyclopropane (Figure 8).

**Figure 8: Probable chelating zwitterionic transition state.**

These relatively mild conditions provide enormous scope for this type of reaction giving a valuable insight into how changing the reaction parameters can utilise the full power of this type of methodology.

**1.1 vi. Previous work**

At Oxford University, under the supervision of Dr G. J. Pritchard and Prof. Sir J. Baldwin, L. Tang$^{45}$ researched possible variations of Tsuji's conditions in an attempt
to harness the true potential of this methodology. His worked centred on using the versatile doubly activated vinylcyclopropane building block to develop palladium(0) catalysed [3+2]-cycloadditions.

Tang reported a variety of novel palladium catalysed [3+2]-cycloadditions using the versatile doubly activated vinylcyclopropane. A variety of trapping agents were explored affording a selection of tetrahydrofurans and pyrrolidines when reacted in conjunction with their respective aldehydes and imines. The respective tetrahydrofurans and pyrrolidines appeared as a pair of diastereoisomers which were assumed to occur in part due to the formation of the zwitterionic species during oxidative addition of the palladium within the reaction sequence. Careful optimisation led to excellent yields under mild reaction conditions (Scheme 27).

\[
\text{R} = \text{Me or Et} \quad \text{R} = \text{Me or Et}
\]

Scheme 27: Synthesis of 5-membered heterocycles.\(^{45}\)

After careful scrutiny Tang concluded that the inclusion of a Lewis acid resulted in a marked increase in yield. He was able to suggest parameters which in general would furnish the desired heterocycle in the majority of cases. These optimum conditions included a stoichiometric amount of the vinylcyclopropane and electrophile, 10 mol\% Pd(PPh\(_3\))\(_4\), two equivalents of ZnBr\(_2\) in THF at room temperature. Through these results and previous studies, it is possible to propose a tentative reaction mechanism
that takes into the account the affects of the palladium(0) catalyst, Lewis acid, solvent and temperature. As the reaction only requires a catalytic (10 mol%) amount of palladium(0) reagent the implication is a catalytic cycle is set up regenerating the palladium(0) species during the [3+2]-stepwise cycloaddition, which results in the formation of the 5-membered heterocyclic product. An oxidative addition of the palladium(0) catalyst to the vinylcyclopropane generates a zwitterion that subsequently undergoes nucleophilic attack on the electrophilic substrate affording a second transient zwitterion. The resultant alkoxy/amide moiety subsequently displaces the palladium reagent from the π-allyl site with concomitant reductive elimination of the transition metal catalyst to give the required heterocycle (Scheme 28).

Scheme 28: General palladium catalysed cyclisation with vinylcyclopropane.⁴⁵

He detailed a range of functional groups which tolerated these conditions and utilised this methodology to provide a range of precursors which could potentially be used to construct a multitude of biologically interesting compounds. Tang took significant steps to realising the potential of this methodology to set the foundation to construct highly functionalised 5-membered heterocycles under relatively mild conditions. Mild
conditions, high yields, with a host of electrophiles showed the importance and the enormous potential of this type of reaction.

Work within the group has explored this methodology as a versatile building block within organic synthesis expanding on the variety of aldehydes and imines to construct various tetrahydrofurans and pyrrolidines. Like other chemists we strive to obtain the shortest and most efficient route to our destination. The first example our group worked towards showing the application of our methodology, provided a pathway towards the synthesis of monocerin (164). It has been identified to exhibit antifungal, insecticidal and phytotoxic activities. The core chemistry constructs the tetrahydrofuran ring (168) via the palladium catalysed [3+2]-cycloaddition strategy between the substituted vinylcyclopropane (169) and the appropriate brominated aldehyde (170). This retrosynthesis involves construction of a lactone ring via palladium catalysed lactonisation with insertion of CO gas incorporating the alcohol of the reduced carbonyl of (166) (Scheme 29).
A second illustration of a natural product pursued within our group includes the potential natural product monmorine I (172). It shows the significance of this methodology in setting up the pyrrolidine heterocycle from the vinylcyclopropane and appropriate functionalised imine in one step, providing the scaffold for the natural product (176) before employing Grubbs ring closing metathesis to set the final 6-membered ring (175) (Scheme 30).
Chapter 1

Scheme 30: Retrosynthesis of target biological compound.\textsuperscript{48}

We intend to employ an adaptation of this facile palladium catalysed [3+2]-methodology in the construction of the tricyclic core of the \textit{Stemona} alkaloids.

1.1.vi. Proposed route to the tricyclic core of the \textit{Stemona} alkaloids

In this investigation we intend to develop a novel synthetic method for the construction of the tricyclic core of the \textit{Stemona} alkaloids using the facile palladium catalyzed route. The pyrrolidine ring present in all the \textit{Stemona} alkaloids will be constructed using our palladium catalysed [3+2]-cycloaddition chemistry. Work within our group over the past year or so has used this strategy in an attempt to ascertain the \textit{Stemona} scaffold. A variety of approaches are currently in progress.

One current area of concentration within the group is in the development of a method for the synthesis of ring-fused derivatives such as pyrrolizidines, indolizidines, and azepines. The stereochemical outcome of the reaction maybe affected by the size of the cyclic imine ring, making it possible to control two stereogenic centres in one step. The presence of such saturated heterocyclic rings in not just the \textit{Stemona} alkaloids but a large range of biologically important compounds make it a particular focal point within our group (Scheme 31).\textsuperscript{49}
More specifically, when cyclic 7-membered imines (180) are used, our proposed palladium catalysed [3+2]-cycloaddition methodology will be able to access compounds of type (181), which contains the 1-azabicyclo[5.3.0]decane system present in the Stemona alkaloids. The incorporation of functionality on the cyclic imine substrate at 3C would create a foundation for the inclusion of the cyclohexane ring later in the process, revealing a potentially powerful route towards the azepinoindole core of the stenine group of alkaloids (Scheme 32).

Scheme 32: Route towards the azepinoindole core of the stenine group of alkaloids.49

A second related route to the azepinoindole core currently being developed within the group, involves the palladium [3+2]-cycloaddition of an allyl-substituted vinylcyclopropane (183) to form the corresponding pyrrolidine (182), which can undergo a suitable succession of carbo palladation reactions to generate the azepine ring and cyclohexane ring (Scheme 33).50
Scheme 33: Retrosynthesis of a proposed route to the azepinoindole core.\textsuperscript{50}

The initial approach we took towards ascertaining the tricyclic core of the \textit{Stemona} alkaloids follows a similar design. We believed that it would be possible to employ our facile palladium catalysed [3+2]-cycloaddition towards a range of bicyclic cyclopropanes. It was envisaged that this general methodology would allow rapid assembly of the highly functionalised hydroindole building block as well as access to bicyclic tetrahydrofuran and pyrrolidine scaffolds which could possibly be used for a variety of biologically active compounds. The proposed route consists of a palladium(0) catalysed [3+2]-cycloaddition of a suitable imine trapping reagent and \textit{N}-alkylation to form an appropriate tether capable of an intramolecular Heck cyclisation (185). However, an appropriate imine containing the desired tether would allow us to achieve an analogous result (Scheme 34).
Scheme 34: Proposed synthesis towards tricyclic core of the Stemona alkaloids.

Further developing this methodology could allow potential access to a range of bicyclic tetrahydrofurans and pyrrolidines. The strategy would employ bicyclic vinylcyclopropanes of varying ring sizes, increasing the scope of this methodology to include a variety of hetero-bicycles of variable ring size and functionality (Scheme 35).

Scheme 35: Retrosynthesis for hetero-bicycles of variable ring size

We intend to work towards exploring our methodology in the formation of the elusive tricyclic core of the Stemona alkaloids. It is hoped we can access a range of bicyclic cyclopropanes from where we can explore the scope and versatility of palladium [3+2]-catalysed cycloaddition forming a range of tetrahydrofuran and pyrrolidine scaffolds. Finally, we intend to develop a route to access the hydroindole core of the
Stemona alkaloids and form the apezine 7-membered ring through a palladium catalysed Heck reaction. It is hoped that this investigation would provide a facile, practical and efficient route towards these objectives potentially accessing the tricyclic core of the Stemona alkaloids (Scheme 36).

We wished to achieve two main objectives. The first was to form a highly functionalised bicyclic scaffold from a [3+2]-palladium(O) catalysed cycloaddition with a suitable trapping agent and a bicyclic cyclopropane. The second was to explore the viability of a Heck cyclisation establishing a route to form a ring from the tether on the nitrogen to the vinyl substituent. Work towards these objectives are reported herein.
Chapter 2- Synthesis of bicyclic cyclopropanes

2.1.i. Retrosynthesis of 5-membered heterocycles

We wished to design a novel method that would allow us access to a range of bicyclic vinylcyclopropanes activated with electron withdrawing groups (EWG). It was believed we would be able to utilise these precursors to form the corresponding bicyclic heterocycles through a palladium(0) catalysed [3+2]-cycloaddition reaction. Previous work within the group has shown that doubly activated vinylcyclopropanes can undergo palladium(0) catalysed [3+2]-cycloadditions with a variety of trapping agents (Scheme 37).\[45,47,48\]

\[
\begin{align*}
&\text{1,3-dipole} + \text{1,3-dipolarphile} \\
&\text{Pd(0) Catalyst}
\end{align*}
\]

Scheme 37: Retrosynthesis of 5-membered heterocycles.\[45,47,48\]

The success of this methodology relies on the ability of the transition metal to add to the strained cyclopropane ring and regenerates itself upon formation of the less strained 5-membered ring. This was initially thought to be comparable to the Baylis-Hillman reaction (Scheme 38).\[45\]
Early work in this area by Tang\textsuperscript{45} recognised the similarity between the activated vinylcyclopropanes substituted with electron withdrawing groups and the addition of aldehydes to acrylates catalysed by tertiary amines which undergo the Baylis-Hillman reaction. It was thought the activated vinylcyclopropanes would undergo an analogous nucleophilic catalysed reaction, enabling an electrophile to be trapped by the activated vinylcyclopropane.\textsuperscript{51} It was believed the initial adduct would undergo an intramolecular $S_N2'$ substitution reaction and subsequently form a 5-membered ring regenerating the catalyst. Although tertiary amines proved successful in the Baylis-Hillman reaction it proved fruitless for activated vinylcyclopropanes (Scheme 39).
Scheme 39: Proposed intramolecular $S_N2'$ substitution reaction to form 5-membered heterocycles.  

As we have previously discussed, it has since been reported that $\pi$-allyl palladium complexes generated in the presence of palladium(0) catalysts and activated vinylcyclopropanes can be condensed in situ with electrophilic and nucleophilic substrates to afford the corresponding 5-membered rings.  

2.1.ii. Preparation of activated vinylcyclopropanes

It was thought activated vinylcyclopropanes would facilitate the formation of a tetrahydrofuran in the presence of a palladium(0) catalyst when reacted with an appropriate aldehyde. The most successful reported method of accessing activated vinylcyclopropane derivatives involves the double displacement of a disubstituted but-2-ene precursor (189) with an activated methylene component. This methodology has been successfully adopted within the group in the preparation of a variety of activated vinylcyclopropane derivatives (Scheme 40).
The aim of this part of the study was to design synthetic routes to a range of bicyclic vinylcyclopropanes activated with electron withdrawing groups. We envisioned these precursors would react in a similar fashion to the simpler analogous activated vinylcyclopropanes. It was thought addition of a palladium(0) catalyst would facilitate ring opening of the strained cyclopropane via an $S_N2'$ type reaction affording a stabilised malonate anion. Trapping this zwitterionic moiety with an aldehyde or ketone and subsequent intra-molecular ring closure would lead to the formation of novel tetrahydrofurans, whereas an imine could afford the pyrrolidine equivalent. If we were able to synthesise a [4.1.0]-bicyclic vinylcyclopropane which was conducive to our palladium(0) catalysed [3+2]-cycloaddition methodology and trap an imine ($X = NR^1$), it would allow us access to the hydroindole core of the \textit{Stemona} alkaloids (Scheme 41).

\begin{align*}
\text{Scheme 40: General synthesis into a variety of activated vinylcyclopropanes.}^{39,40}
\end{align*}

\begin{align*}
\text{Scheme 41: Retrosynthesis of hydroindole core of the \textit{Stemona} alkaloids.}
\end{align*}
If a general route to these activated bicyclic vinyl cyclopropanes could be facilitated, we hoped to investigate the effect of varying ring size with our palladium(0) catalysed [3+2]-cycloaddition methodology. However, in order to explore our palladium(0) catalysed methodology it was essential to access the activated bicyclic vinylcyclopropanes with relative ease and efficiency.

2.1.iii. Proposed construction of activated bicyclic cyclopropanes

We considered three different routes which we believed would allow us to access the activated bicyclic cyclopropanes and ultimately the desired [4.1.0]-activated bicyclic vinylcyclopropane which we hoped would allow us access the hydroindole core of the Stemona alkaloids. The first route followed had been developed by Bäckvall. It outlined the formation of activated bicyclic vinylcyclopropanes using a completely catalysed palladium route. He accessed the activated bicyclic vinylcyclopropane derivates utilising a similar double displacement that has been previously discussed in the formation of the simpler vinylcyclopropane analogue (155) (Scheme 40, pg 47). The appeal of this path installs palladium at the heart of the route and a novel completely palladium catalysed synthesis would be very interesting in the formation of the hydroindole core. It would also show the diversity of palladium catalysed chemistry, as this particular route portrays complete regio- and stereoselectivity (Scheme 42).

Scheme 42: Bäckvall’s preparation of activated bicyclic vinylcyclopropanes.

The second potential approach followed work outlined by Georgakopoulou. They proposed using an iodonium ylide derived from dimethyl malonate and 1,3-
cyclodienes in a thermally activated rhodium(II) acetate ($\text{Rh}_2(\text{OAc})_4$) catalysed
cycloaddition to form the corresponding bicyclic vinylcyclopropanes (Scheme 43).

$$\text{(198)} \xrightarrow{\text{MeO} \text{Phl(OAc)}_2, \text{KOH, MeOH,} \ -10^\circ \text{C}, \ 4 \text{h}, (50\%)} \text{(199)}$$

Scheme 43: Georgakopoulou’s preparation of activated bicyclic
vinylcyclopropanes.$^{53}$

The final proposed route towards synthesising our desired activated bicyclic
vinylcyclopropanes employed the use of rhodium(I1) catalysed cyclopropanation of a
diazo-carbonyl compound with 1,3-cyclodienes. Aromatic cyclopropanes can be
prepared by a reaction between a vinylaromatic and diazo dimethylmalonate in the
presence of a catalytic amount of rhodium acetate$^{54}$ (Scheme 44).

$$\text{(204)} + \text{(205)} \xrightarrow{\text{MeCN, 24h, (82\%)}} \text{(161)}$$

Scheme 44: Synthesis of an aromatic cyclopropane.$^{54}$

It was thought 1,3-cyclodienes would undergo an analogous reaction to furnish the
desired activated bicyclic vinylcyclopropanes. Livant$^{55}$ has reported utilising this facet
of rhodium-stabilised carbenoid chemistry albeit for the multiple cyclopropanation of
benzene with diazo dimethylmalonate (Scheme 45).
We believed adaptation of this rhodium-stabilised carbenoid chemistry with diazo-carbonyl compounds and 1,3-cyclodienes of varying ring size could allow us access to the desired activated bicyclic vinylcyclopropanes. It also presents the opportunity to vary the electron withdrawing substituents (Scheme 46).

This may further facilitate the palladium(0) catalysed ring opening of the cyclopropane as well as increasing the stability of the resultant malonic species.
If our palladium(0) catalysed cycloaddition chemistry proved successful, it would give us a valuable insight into the reactivity of these activated bicyclic vinylcyclopropanes with differing electron withdrawing groups. It might be possible to extend our investigation to determine whether the various bicyclic vinylcyclopropanes required activation by a singularly or doubly substituted electron withdrawing group to facilitate ring opening of the cyclopropane. As well as determine whether a single electron withdrawing group would sufficiently stabilise the resultant malonic species generated upon addition of the palladium(0) catalyst. Our proposed methodology hinges on the ability of this intermediate to be sufficiently stable so it may trap an electrophile.

The preparation of [4.1.0]-ethylester mono-substituted vinylcyclopropane\(^{56}\) has been reported using rhodium-stabilised carbenoid chemistry with diazo-carbonyl compounds and may prove to be an ideal precursor for our palladium(0) catalysed [3+2]-cycloaddition chemistry (Scheme 47).

\[
\text{[188]} + \text{[212]} \xrightarrow{\text{Rh}_2(\text{OAc})_4, \text{RT, 4h, (90\%)} } \text{[213]}
\]

**Scheme 47: Cyclopropanation of 1,3-cyclohexadiene.\(^{56}\)**

If this line of investigation proved successful it would allow us the potential to expand the scope of our palladium(0) catalysed cycloaddition methodology. As previously mentioned we could explore varying the ring size as well as probing the reactivity of these mono-activated bicyclic vinylcyclopropanes with differing electron withdrawing groups (Scheme 48).
2.2. Preparation of dimethyl bicyclo[4.1.0]hept-2-ene-7,7-dicarboxylate

Our initial attempts to synthesise dimethyl bicyclo[4.1.0]hept-2-ene-7,7-dicarboxylate followed work by Bäckvall. The first step was to stereoselectively oxidise 1,3-cyclohexadiene (188) to the chloro-acetate (193) using catalytic palladium and quinone. Initially the reaction only afforded a 60-65% yield. However, improvements in the extraction of the aqueous phase with Et₂O:pentane (1:9) gave a significantly increased yield (90%). The compound was also shown by ¹H NMR to be sufficiently pure to carry forward to the next synthetic step without further purification. Displacement of the chloride by sodium dimethyl malonate using a palladium(0) catalyst proved problematic. Although the reaction was successful, isolation of the desired compound proved difficult due to the presence of unreacted dimethyl malonate. Careful optimisation of the temperature and pressure while using bulb to bulb distillation removed the unwanted dimethyl malonate affording a 60% yield. We also found reducing the amount of sodium dimethyl malonate from 1.1 to 1.0 equivalent increased the yield to 91%, furnishing the desired compound without the need for further purification (Scheme 49).
Scheme 49: Preparation of the required vinylcyclopropane.$^{52}$

It was particularly disappointing in the final step to recover dimethyl (cis-4-acetoxyhex-2-en-1-yl) malonate (195) after attempting the palladium(0) catalysed cyclisation to form the [4.1.0]-moiety. Numerous attempts directly repeating the conditions outlined by Bäckvall$^{52}$ even prolonging the reaction failed to isolate the desired [4.1.0]-activated bicyclic vinylcyclopropane. We are at a loss to explain why the final step afforded solely starting material. Undeterred, we felt that following the work reported by Georgakopoulou$^{53}$ may prove more successful.

Georgakopoulou$^{53}$ reported utilising Rh(II) catalysed thermal cyclopropanations of dienes with phenyliodonium bis(carbomethoxy)methylide. The reaction of dimethyl malonate (198) with diacetoxyiodobenzene lead to the formation of the iodonium ylide (199) which was used immediately. Although they report cyclopropanating 1,3-cyclohexadiene (188) with the iodinium ylide (199) in an excellent yield (99%), replication of this reaction proved completely fruitless and we were only able to recover starting material. We tried heating the suspension of the iodonium ylide (199) and 1,3-cyclohexadiene (188) in the presence of the rhodium(II) catalyst for slightly longer due to the particularly short reaction durations reported (Scheme 50).
Scheme 50: Proposed route to the synthesis of the required vinylcyclopropane.\textsuperscript{53}

This proved fruitless, furnishing starting material. It was particularly disheartening as the construction of the activated bicyclic cyclopropanes were essential to our investigation.

Our final area of investigation explored the rhodium(II) catalysed thermal decomposition of diazo-carbonyls. Rhodium catalysts have become the catalyst of choice for intramolecular cyclopropanations enjoying a certain popularity due to the regio- and stereoselectivity that can now be achieved.\textsuperscript{57} A thermal rhodium(II) catalysed reaction between diazo dimethylmalonate (205) and 1,3-cyclohexadiene (188) was thought could afford the desired [4.1.0] activated bicyclic cyclopropane (186).

A diazo group transfer was proposed for the synthesis of dimethyl diazomalonate.\textsuperscript{58} The preparation of diazo compound introduced both nitrogen atoms, i.e. the entire diazo group, in a single reaction step. The diazo group is transferred by a donor (azide) to an acceptor (CH-acidic compounds). Tosyl azide (216), which is easily synthesised, has been widely used as a diazo-transfer reagent and was prepared by reacting tosyl chloride (214) with stoichiometric amounts of sodium azide (215). The reaction was monitored by TLC until complete consumption of the starting materials had been observed (Scheme 51).
The reaction was found to be a simple, quick procedure affording excellent yields (99%) up to a 10 g scale and allowed the tosyl azide (216) to be carried forward without further purification. The reaction partner for the tosyl azide (216) is the malonate anion rather than the malonate itself. For this reason, the diazo transfer reaction is carried out in the presence of a base. The strength of the base is determined by the stabilising effects within the neighbouring substituents. These substituents are variable as long as they have stabilising characteristics. This could be advantageous in expanding the investigation into our palladium(0) catalysed [3+2]-methodology.

Our first attempted synthesis of diazo dimethylmalonate (205) followed work by Vandewalle.\(^{59}\) The diazo transfer was carried out in a solution of THF/benzene in the presence of NaH over 12h. Although the reaction was successful, the yield was poor (41%). To furnish a significant quantity of our bicyclic cyclopropane we needed to achieve reasonable yield of the diazo transfer (Scheme 52; Method A).

In our desire to increase the yield of the diazo dimethylmalonate (205) we turned our attention towards work reported by Regitz.\(^{58}\) The procedure used Et\(_3\)N in acetonitrile to facilitate the diazo transfer over longer reaction duration (32h). Initially the procedure afforded a low yield (20-40%) on a 5 g scale, in part due to the extraction.

\(^{58}\) Scheme 51: Preparation of tosyl-azide.

\(^{59}\) Scheme 52: Method A, preparation of dimethyl diazo malonate.
of the diazo dimethylmalonate by trituration. The solvent was removed from the reaction mixture under reduced pressure to afford a white solid. Trituration of the solid with Et₂O lead to the extraction of diazo dimethylmalonate (205) leaving the undesired tosyl-amine (217) solid. After repeating the reaction a number of times we were able to master the trituration and increase the yield significantly (50-70%), although it proved problematic when utilising this procedure on a larger 10 g scale (Scheme 53; Method B).

![Scheme 53: Method B, preparation of dimethyl diazo malonate](image)

Peace also reported the synthesis of dimethyl diazomalonate (205) following Regitz's procedure albeit using benzene as the solvent. He reported the undesired tosyl amine (217) precipitated out of solution allowing the diazo dimethylmalonate (205) to be isolated by filtration. This was particularly appealing as it would eliminate the previous problematic trituration. Although the reaction was initially favoured due to its simplicity it afforded a moderate yield (50%) on a 5 g scale. The inherent problem lay with the sheer amount of the tosyl amide by-product which partially precipitated out of solution. Perseverance led to the discovery that the by-product readily precipitated out of solution when carefully washed with cold benzene (40 mL) and a little hexane (5 mL). This increased the yield dramatically (70-80%) on the smaller 5 g scale, although the separation still proved difficult on a larger 10 g scale (Method C).

Finally, it was proposed a mesyl analogue would undergo an analogous reaction to the tosyl derivative previously outlined. The reaction proved particularly successful affording the mesyl azide (219) in an excellent yield (99%). The diazo transfer also proved particularly rewarding. We were able to wash the undesired mesyl amide (219) cleanly out of solution with 10% NaOH, furnishing diazo dimethylmalonate (205) in a reasonable repeatable yield (70-80%) (Scheme 54; Method D).
Scheme 54: Method D, preparation of dimethyl diazomalonate using mesyl-azide.\textsuperscript{61}

The excellent overall yield using the mesyl moiety allowed us access to dimethyl diazomalonate (205) on a larger scale (10-11 g). This was essential to facilitate the investigation into accessing the desired [4.1.0]-activated bicyclic vinylcyclopropane through rhodium(II) catalysed thermal decomposition on a reasonable scale.

With the dimethyl diazomalonate (205) in hand we were able to begin our exploration into the rhodium(II) catalysed thermal decomposition with 1,3-cyclohexadiene (188). It was hoped this would prove an efficient route to the [4.1.0]-activated bicyclic vinylcyclopropane. Which in turn would be conducive to our palladium catalysed [3+2]-cycloaddition chemistry as has been demonstrated within our group with the simpler vinylcyclopropane analogue.\textsuperscript{47,48}

The rate determining step of the cyclopropanation reactions involving diazo carbonyl compounds is the diazo decomposition.\textsuperscript{62} Both the diazo compound and the catalyst influence the rate of the reaction. Increasing the substitution at the diazo-carbon decreases the nucleophilic reactivity of the diazo carbonyl compounds (Figure 9).
Figure 9: Reactivity for diazo decomposition.\textsuperscript{62}

Decreasing reactivity is seen in the series; amide<ester<ketone, requiring elevated temperatures for diazo decomposition and the resultant cyclopropanation. It has been widely reported that rhodium acetate dimer has catalysed these types of cyclopropanations with other olefins.\textsuperscript{54}

Due the relative stability of our diazo compound we believed the reaction with 1,3-cyclohexadiene (188) would need to be thermally activated in conjunction with our rhodium(II) catalyst (Rh\textsubscript{2}(OAc)\textsubscript{4}) (1 mol%). We decided to carefully monitor the reaction over 3h using a solvent which refluxed at approximately the same temperature as the diene (CH\textsubscript{3}CN). Aware that diazo carbonyl compounds can be potentially explosive we guarded against this by ensuring the reaction mixture was reasonably dilute (0.1 M of diazo dimethylmalonate (205) in CH\textsubscript{3}CN, 5mL) and limiting the small scale of the reaction (0.100g of 1,3-cyclohexadiene (188)). We used a slight excess of diazo dimethylmalonate (205) (1.1 equiv.) in respect to the diene in the hope of ensuring complete cyclopropanation of the diene. A large excess might facilitate an unwanted second cyclopropanation. To our relief we successfully isolated the crucial [4.1.0]-activated bicyclic vinylcyclopropane (186) from a viscous brown reaction mixture by column chromatography albeit in a relatively low yield (28%) (Scheme 55).

As well as isolating the desired [4.1.0]-activated bicyclic vinylcyclopropane we recovered a small amount of each of the starting materials (10-15%). We decided to increase the concentration of the diazo dimethylmalonate (205) in respect to the diene to try and ensure full consumption of the starting materials. It was hoped it would bring the components of the reaction closer in proximity therefore increasing the probability of the desired cyclopropanation. We kept all other reaction parameters constant; 1,3-cyclohexadiene (188) (0.100 g), diazo dimethylmalonate (205) (1.1 equiv.), of Rh₂(OAc)₄ (1 mol%) with the appropriate volume of CH₃CN (Table 2).
Table 2: Cyclopropanation of 1,3-cyclohexadiene with increasing diene concentration.

We were particularly pleased to furnish a moderate yield (57%) when the reaction was performed in the absence of the solvent. Although we saw a pleasant increase in yield we encountered problems upon purification. The absence of a solvent afforded an increase in viscosity of the brown reaction mixture. Purification was only possible by slowly loading the mixture directly onto a column. It was thought the reaction mixture maybe more amenable for purification if a solvent could be found that maintained the yield. We chose a concentration of 1.0 M in respect to the solvent and diazo dimethyl malonate which had previously afforded a reasonable yield with CH₃CN, whilst controlling the other parameters; 1,3-cyclohexadiene (188) (0.100 g), diazo dimethylmalonate (205) (1.1 equiv.), of Rh₂(OAc)₄ (1 mol%) under reflux for 3h (Table 3).

Table 3: Solvent effect on cyclopropanation.

Unfortunately the mixture remained viscous with no appreciable increase in yield. In the hope of optimising conditions to achieve the best possible yield we turned towards work reported with the more reactive mono-substituted ethyl diazoacetate (212). A large excess of 1,3-cyclohexadiene (188) was used to afford an excellent yield (90%) of the corresponding [4.1.0]-mono-activated bicyclic vinylcyclopropane (213). We set the parameters of our investigation to where we had obtained our most successful
yield thus far; (0.100 g), diazo dimethylmalonate (205) (1.1 equiv.), of Rh$_2$(OAc)$_4$ (1 mol%) without solvent under reflux for 3h and varied the equivalence of the diene (Table 4).

<table>
<thead>
<tr>
<th>Equiv. of diene</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>38</td>
</tr>
<tr>
<td>1.1</td>
<td>46</td>
</tr>
<tr>
<td>2.0</td>
<td>42</td>
</tr>
<tr>
<td>3.0</td>
<td>32</td>
</tr>
<tr>
<td>5.0</td>
<td>29</td>
</tr>
</tbody>
</table>

Table 4: Cyclopropanation with increasing equivalence of diene.

We were able to recover the excess diene which was particularly advantageous due to its cost. However, we also recovered a trace of the dimethyl diazomalonate (205) (~5%). This led us to believe the diazo dimethylmalonate (205) might not undergo full diazo decomposition under these conditions and this factor may subsequently restrict the overall yield. If we used an increasing amount of diazo dimethylmalonate (205) it may afford full conversion of the diene to the cyclopropane. We therefore set the parameters of the experiment to; diene (188) (0.100g), Rh$_2$(OAc)$_4$ (1 mol%) without solvent under reflux for 3h and varied the equivalence of diazo dimethylmalonate (205) (Table 5).

<table>
<thead>
<tr>
<th>Equiv. of diazo dimethylmalonate</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>58</td>
</tr>
<tr>
<td>2.0</td>
<td>51</td>
</tr>
<tr>
<td>3.0</td>
<td>42</td>
</tr>
<tr>
<td>5.0</td>
<td>27</td>
</tr>
</tbody>
</table>

Table 5: Cyclopropanation with increasing equivalence of diazo dimethylmalonate.

Although we didn't see an increase in yield we did see the presence of a trace of starting materials along with desired [4.1.0]-activate bicyclic vinlylcyclopropane (186) after purification by column chromatography. It was interesting to note we didn't afford any of the corresponding doubly cyclopropanated product.
As previously mentioned the diazo decomposition can be a limiting factor of the cyclopropanation. Temperature is one factor that may affect the rate of decomposition. We were aware that decomposition must be occurring as we have isolated the desired [4.1.0]-activate bicyclic vinylcyclopropane. However, it maybe the reaction requires a specific reflux duration for the diazo dimethylmalonate (205) to achieve total thermal decomposition. A study was conducted varying only the reflux duration. The other parameters were set to our optimum conditions thus far; diene (188) (0.100g), diazo dimethylmalonate (205) (1.1 equiv.), Rh$_2$(OAc)$_4$ (1 mol%) without solvent (Table 6).

<table>
<thead>
<tr>
<th>Reflux duration/h</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>26</td>
</tr>
<tr>
<td>3</td>
<td>59</td>
</tr>
<tr>
<td>4</td>
<td>56</td>
</tr>
<tr>
<td>5</td>
<td>31</td>
</tr>
</tbody>
</table>

Table 6: Cyclopropanation whilst increasing the reflux duration.

This showed the reflux duration appeared optimal at 3h. Our final train of thought was to increase the amount of catalyst in the hope of aiding diazo decomposition, whilst keeping all other variables constant at our optimum conditions; diene (188) (0.100g), diazo dimethylmalonate (205) (1.1 equiv.), without solvent under reflux for 3h. It was believed there may also be an optimum catalytic amount of Rh$_2$(OAc)$_4$ required to form the singularly cyclopropanated product (Table 7).

<table>
<thead>
<tr>
<th>Catalyst/mol%</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>59</td>
</tr>
<tr>
<td>2</td>
<td>52</td>
</tr>
<tr>
<td>5</td>
<td>51</td>
</tr>
<tr>
<td>10</td>
<td>49</td>
</tr>
</tbody>
</table>

Table 7: Cyclopropanation whilst increasing the amount of catalyst.
Although there was a slight increase in yield it was negligible. However, it helped define the optimum parameters for the cyclopropanation. The nature of the project required the development of a cyclopropanation procedure which would be clean, efficient and reproducible on a reasonable scale. This would enable us to investigate its ability to undergo palladium(0) [3+2]-catalysed cycloadditions. We believed we had adhered to the first constraints therefore, we just had to scale up the reaction using our most successful conditions; diene (188) (1.0 equiv.), diazo dimethyl malonate (205) (1.1 equiv.), Rh$_2$(OAc)$_4$ (1 mol%) without solvent under reflux for 3h, in the hope of ascertaining the desired cyclopropane in reasonable quantities (Table 8).

<table>
<thead>
<tr>
<th>Diene/g</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.10</td>
<td>59</td>
</tr>
<tr>
<td>0.50</td>
<td>54</td>
</tr>
<tr>
<td>1.00</td>
<td>52</td>
</tr>
<tr>
<td>1.50</td>
<td>51</td>
</tr>
<tr>
<td>2.00</td>
<td>39</td>
</tr>
<tr>
<td>3.00</td>
<td>21</td>
</tr>
</tbody>
</table>

**Table 8**: Increasing the scale of the cyclopropanation reaction.

Increasing the scale of the reaction had a detrimental effect on the yield. However, the yield remained reasonable when using the diene on a 1-1.5 g scale, affording the desired [4.1.0]-activated bicyclic vinylcyclopropane (186) on an acceptable scale with which to investigate the susceptibility of this moiety to undergo our palladium(0) [3+2]-catalysed chemistry.

After looking into the cyclopropanation of 1,3-cyclohexadiene (188) it seemed feasible we had developed a method which could be used to singly cyclopropanate a selection of 1,3-cyclodienes of varying size.

The next logical bicyclic ring system to construct seemed to be the cyclopropanation of 1,3-cycloheptadiene (200), which could possibly open the door to a range of biologically active scaffolds following the same methodology as proposed for the construction of the [4.3.0]-hydroindole system of the *Stemona* alkaloids.
2.3. Preparation of dimethyl bicyclo[3.1.0]hept-2-ene-7,7-dicarboxylate

It was decided to use the optimum condition of cyclopropanating 1,3-cyclohexadiene (188) as the initial parameters for other cyclodienes, in this case it was hoped we would facilitate the [3.1.0]-activated bicyclic vinylcyclopropane. The desired 1,3-cyclopentadiene (200) was commercially available as its dimer (221). Therefore, it had to be freshly cracked (a retro Diels-Alder reaction) to obtain the corresponding 1,3-cyclopentadiene (200) (Scheme 56).^64^  

![Scheme 56: Synthesis of 1,3-cyclopentadiene.]  

We synthesised diazo dimethylmalonate (205) from the diazo transfer of mesyl azide (219) to dimethylmalonate (198) as previously shown (Scheme 53, pg 57). We were able to attempt a comparable rhodium catalysed intramolecular cyclopropanation under the conditions previously optimised for the 6-membered analogue; 0.500g diene (200) (1.0 equiv.), diazo dimethylmalonate (205) (1.1 equiv.), Rh$_2$(OAc)$_4$ (1 mol%) without solvent under reflux for 3h (Scheme 57).  

![Scheme 57: Preparation of dimethyl bicyclo[3.1.0]hept-2-ene-7,7-dicarboxylate.]  

As well as isolating the desired [3.1.0]-activated bicyclic vinylcyclopropane (202) (43%), we isolated 1,3-dicyclopentadiene (221) (~10-15%) and a small amount of diazo dimethylmalonate (205) (~5%). This observation led us to believe the cyclopropanation maybe problematic. The 1,3-cyclopentadiene (200) underwent a
Diels-Alder reaction reforming the 1,3-dicyclopentadiene (221) as well as the desired cyclopropanation, inferring these reactions were in competition and would therefore limit the overall yield. It was hoped further investigation into the reaction parameters may help us optimise the yield.

We thought the reflux duration may have a bearing on the overall yield. If the two reactions were in direct competition there may just be a point where the 1,3-cyclopentadiene (200) had been fully consumed and there would be no further increase in yield of the desired cyclopropane. The parameters were set to; 0.500g of diene (200) (1.0 equiv.), diazo dimethylmalonate (205) (1.1 equiv.), Rh₂(OAc)₄ (1 mol%) without solvent whilst varying the reflux duration (Table 9).

<table>
<thead>
<tr>
<th>Reflux duration/h</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>29</td>
</tr>
<tr>
<td>3</td>
<td>37</td>
</tr>
<tr>
<td>4</td>
<td>35</td>
</tr>
</tbody>
</table>

Table 9: Cyclopropanation of 1,3-cyclohexadiene whilst increasing reflux duration.

As anticipated the yield seemed to be consistent after refluxing for 3/4h. Our train of thought was that the cyclopropanation was proceeding at a slower rate to the competing Diels-Alder reaction with the 1,3-diene starting material. We proposed that heating the reaction mixture using a low boiling solvent may facilitate the desired reaction. We chose a concentration of 1.0 M in respect to the solvent and diazo dimethylmalonate (205), 0.500g of diene (200) (1.0 equiv.), diazo dimethylmalonate (205) (1.1 equiv.), Rh₂(OAc)₄ (1 mol%) under reflux for 3h (Table 10).

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₂Cl₂</td>
<td>51</td>
</tr>
<tr>
<td>CH₃CN</td>
<td>21</td>
</tr>
<tr>
<td>DCE</td>
<td>19</td>
</tr>
</tbody>
</table>

Table 10: Solvent effect on cyclopropanation.
Chapter 2

A minimal variance in yield of the higher boiling solvents could, in part, be due to the
cycloaddition taking place prior to the solvent boiling.

We then increased the amount of diazo dimethylmalonate (205) assuming that the
mono cyclopropanated product wouldn't undergo an additional cyclopropanation
before the retro Diels-Alder reaction of the 1,3-cyclopentadiene (200). Hoping that
with an excess of the diazo carbonyl we would increase the probability of the
cyclopropanation occurring. The parameters of the experiment were set to; 0.500g
diene (200) (1.0 equiv.), Rh2(OAc)4 (1 mol%) without solvent under reflux for 3h
whilst the equivalents of diazo dimethylmalonate (205) were varied (Table 11).

<table>
<thead>
<tr>
<th>Equiv. of diazo dimethylmalonate</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>58</td>
</tr>
<tr>
<td>2.0</td>
<td>51</td>
</tr>
<tr>
<td>3.0</td>
<td>42</td>
</tr>
<tr>
<td>5.0</td>
<td>27</td>
</tr>
</tbody>
</table>

Table 11: Cyclopropanation with increasing equivalence of diazo dimethylmalonate.

It looked as though we wouldn't be able to improve the yield above 58% which
maybe because the diazo decomposition required more energy. However, due to the
low boiling point of the 1,3-cyclopentadiene (200) (50°C) and the competing Diels-
Alder reaction we felt this may not be possible.

We required the desired cyclopropane in reasonable quantities. Therefore we
increased the scale of the reaction using our optimum conditions; diene (200) (1.0
equiv.), diazo dimethyl malonate (205) (1.1 equiv.), Rh2(OAc)4 (1 mol%) without
solvent under reflux for 3h (Table 12).
Table 12: Increasing the scale of the cyclopropanation reaction.

As seen for the 6-membered cyclopropane the yield decreased when scaling up the reaction. The major product obtained on a larger scale was 1,3-dicyclopentadiene (221). To date we have only managed to successfully repeat reasonable yields on a small scale.

We were delighted we had utilised this methodology to synthesise the corresponding [3.1.0]-activated bicyclic vinylcyclopropane (202). We thought it would be possible to further explore this avenue by increasing the diene ring size to a 7-membered ring.

2.4. Preparation of bicyclo[5.1.0]oct-2-ene-8,8-dicarboxylic acid dimethyl ester

A cyclopropanation of 1,3-cycloheptadiene (192) was also attempted. Again our optimal starting parameters obtained whilst investigating the 5/6-membered cyclopropane were used. The reaction was initially tried on a small scale and afforded a very clean reaction using; diene (192) (1.0 equiv.), diazo dimethylmalonate (205) (1.1 equiv.), Rh2(OAc)4 (1 mol%) without solvent under reflux for 3h (Scheme 58).
Chapter 2

An increase in scale showed the cyclopropanation followed the same trend as the 5 and 6-membered system where there was a decrease in the formation of desired cyclopropane and the recovery of a small amount of starting material. It was interesting to note that cyclopropanation was the simplest to purify by column chromatography, compared to the other successful cyclopropanations.

Further work continues in this area to optimise the reaction conditions.

2.5. Preparation of bicyclo[6.1.0]non-2-ene-9,9-dicarboxylic acid dimethyl ester

Finally, an attempt to cyclopropanate 1,3-octadiene (201) was pursued. We hoped this would show the range of ring sizes which could be cyclopropanated under this type of methodology. To our delight we managed to isolate the desired cyclopropane using; diene (201) (1.0 equiv.), diazo dimethylmalonate (205) (1.1 equiv.), Rh₂(OAc)₄ (1 mol%) without solvent under reflux for 3h (Scheme 59).

<table>
<thead>
<tr>
<th>Diene/g</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.10</td>
<td>39</td>
</tr>
<tr>
<td>0.50</td>
<td>28</td>
</tr>
</tbody>
</table>

Scheme 58: Cyclopropanation of 1,3-cycloheptadiene.

Scheme 59: Cyclopropanation of 1,3-cyclooctadiene.
We also thought of preparing mono-substituted bicyclic cyclopropanes in the hope of utilising these moieties in the exploration of our palladium(0) [3+2]-catalysed cycloadditions.

2.6. Preparation of mono-ester bicyclic cyclopropanes

Room temperature decomposition of α-diazoesters by rhodium(II) acetate promotes the formation of electrophilic species that are very efficient for the cyclopropanation of unsaturated bonds. Demonceau has reported the reaction between 1,3-cyclohexadiene (188) (4.0 equiv), ethyl diazoacetate (212) (1.0 equiv.) catalysed by Rh2(OAc)4 (1 mol%) at room temperature over 4h to afford the corresponding [4.1.0]-mono-activated vinylcyclopropane (213) (90%). We repeated this reaction with the 5 and 6-membered 1,3-cycloadienes (Scheme 60).

\[
\text{Scheme 60: Cyclopropanation of 1,3-cycloadienes.}^{65}
\]

The reaction proved problematic due to it being extremely exothermic, and potentially explosive. Although a syringe pump was initially used the reaction proved most successful by careful and slow addition of the α-diazoester (212) using a syringe. After careful attention during the reaction, the method was found to be repeatable in a consistently high yield. It also served to demonstrate the notable difference in reactivity of the α-diazo carbonyl compound compared to diazo dimethylmalonate (205).
2.7. Preparation of bis(benzylsulfonyl)methane cyclopropanes

As we have previously discussed, work within the group has synthesised a vinylcyclopropane (191) from the double displacement of a but-2-ene precursor with bis(benzylsulfonyl)methane (190) (Scheme 40, pg 47). It was thought bis(benzylsulfonyl)methane (190) may provide a useful electron withdrawing substituent to facilitate our palladium(0) catalysed chemistry. Research into the literature failed to report the synthesis of this diazo sulfonyl using a diazo transfer. Using our tested synthesis to generate mesyl azide (219) we attempted a comparable diazo transfer. Although this reaction wasn’t as clean as the preceding reaction we were happy to report formation of the corresponding diazo compound (223), albeit in a relatively low yield (20-30%) (Scheme 61).

\[
\begin{align*}
\text{SOCl}_2 &\xrightarrow{\text{Acetone}} \text{SO} &\xrightarrow{\text{Acetone}} \text{N} = \text{N} = \text{N} + \text{SO} \\
(218) &\xrightarrow{\text{RT, 2h, (99\%)}} (219) &\xrightarrow{\text{RT, 2h, (20-30\%)}} (223)
\end{align*}
\]

Scheme 61: Preparation of diazo bis(benzylsulfonyl)methane.

Although various methods have been reported in the literature in forming the corresponding 1,1-diphenylsulfonyl-2-cyclopropanes (191) involving a double displacement of a disubstituted but-2-ene precursor with an activated methylene component,\textsuperscript{40} we believed this type of methodology had yet to be utilised. It was decided to test the substrate on a simple alkene. Styrene had proved successful in previous cyclopropanation studies within the group with the diazo dimethylmalonate analogue (Scheme 62).\textsuperscript{48}

\[
\begin{align*}
\text{N} = \text{N} = \text{N} + \text{N} = \text{N} = \text{N} &\xrightarrow{\text{Rh}_2(OAc)_4 (1 \text{ mol\%)}} \xrightarrow{\text{RT, 12h}} \\
(224) &\xrightarrow{5 \text{ equiv.}} (204) &\xrightarrow{\text{RT, 12h}} (225)
\end{align*}
\]

Scheme 62: Cyclopropanation of styrene.
However, on this occasion the reaction proved fruitless. Although disheartened we thought we would attempt a cyclopropanation onto a 1,3-cyclic diene in the vain hope of emulating the analogous reaction with diazo dimethylmalonate (205); of diene (188) (1.0 equiv.), diazo dimethylmalonate (205) (1.1 equiv.) along with our two optimal reaction conditions to date (Scheme 63).

![Reaction Scheme](image)


Our initial exploration thus far into this area has proved ineffective. At present we have left this avenue open which maybe pursued at a later date.

2.8. Conclusion

The selective cyclopropanation of 1,3-cyclodienes has been achieved by development of rhodium-stabilised carbenoid chemistry. We have shown a new synthetic route to singly cyclopropanate 1,3-cyclodienes of varying ring size. Although it has shown to reveal teething problems, yields have proved acceptable. Conditions have had to be time consumingly fine tuned, even though only minor improvements in productivity have been achieved. It is however an efficient, repeatable preparation to afford these types of compounds.

Further investigation into this field continues alongside ongoing research to increase the reactions productivity. However, it has provided a useful synthetic pathway towards a number of activated bicyclic vinylcyclopropanes of varying ring size which may undergo our palladium(0) [3+2]-catalysed cycloaddition methodology. Ultimately, we hope this will provide a doorway towards the construction of the
[4.3.0]-hydroindole system of the *Stemona* alkaloids and a stepping stone to a number of structurally interesting heterocyclic scaffolds.
Chapter 3- Reactions of [4.1.0]-activated cyclopropanes

3.1.i. Synthesis of heterocycles using palladium(0) catalysis

When work started in this area there were a limited number of examples reporting palladium(0) catalysed [3+2]-cycloadditions involving activated vinylcyclopropanes that afforded the corresponding heterocycle. Although Tsuji initially provided a synthesis of heterocycles using palladium(0) catalysed [3+2]-cycloaddition chemistry, there were two major drawbacks; the use of a highly toxic solvent, hexamethylphosphoramide (HMPA) and two equivalence of the isocyanate (Scheme 64).

![Scheme 64: Synthesis of 5-membered heterocycles under palladium(0) catalysed conditions.](image)

As previously discussed π-allyl palladium complexes can be generated in the presence of palladium(0) catalysts and reacted \textit{in situ} with an electrophilic\textsuperscript{26} or nucleophilic\textsuperscript{27} substrate in order to give condensation products. We believed further work using activated vinylcyclopropanes under palladium catalysed conditions employing alternative electrophiles and solvents would provide access to a range of heterocycles. It was hoped we could facilitate a strategy more applicable to general heterocyclic ring construction than the original synthesis outlined by Tsuji. We believed once a general strategy could be synthesised further manipulation would lead to compounds of biological interest.
3.1.ii. Proposed route to the heterocyclic compounds

We have developed a facile palladium(0) catalysed route employing the use of a number of aldehydes, ketones and imines to form a variety of heterocyclic scaffolds. It has allowed us to outline a general set of conditions to facilitate these reactions; stoichiometric amounts of cyclopropane and electrophile, Lewis acid (ZnBr$_2$) (2 equiv.), tetrakis(triphenylphosphine) palladium(0) catalyst (Pd(PPh$_3$)$_4$) (10 mol%) in THF at RT for 12h. The reaction is high yielding and occurs under very mild conditions in contrast to the conditions of Tsuji’s earlier endeavours (Scheme 65).\textsuperscript{45,47,48}

![Scheme 65: Preparation of heterocyclic scaffolds.\textsuperscript{45,47,48}]

Exploration within our group\textsuperscript{45,47,48} into the diversity of this type of reaction has found Pd(PPh$_3$)$_4$ to be an excellent catalyst and that in general Lewis acids enhance the yield. It was also discovered a large range of solvents including some protic solvents were compatible with this reaction even though at first it was thought they may quench the intermediate π-allyl palladium(II) zwitterion. In one particular example the heterocycle proceeded in a solvent system of water and MeOH (1:1). It is not clear why the reaction was so successful but it demonstrates how robust this type of reaction can be (Table 13).
It was hoped our [4.1.0]-activated bicyclic vinylcyclopropane would exhibit a similar ability to react with a variety of trapping agents as have been reported with the simpler vinylcyclopropane using our general palladium(0) catalysed conditions.\textsuperscript{45,47,48} The major distinguishing factor between the cyclopropanes is the conformationally locked vinyl substituent within the 6-membered ring in the [4.1.0]-moiety. We believed the two vinylcyclopropanes should react in an analogous manor as they both exhibit an identical doubly activated cyclopropane ring. Oxidative addition of the palladium(0) catalyst to the vinyl substituent should facilitate ring opening of the cyclopropane to form a zwitterionic 1π'-allyl palladium(II) complex. It was thought the presence of the two electron withdrawing methyl esters would stabilise the negative charge. The malonic centre could then undergo nucleophilic addition to the electrophilic trapping agent forming a second transient zwitterionic species. It was hoped this would undergo an intramolecular cyclisation with simultaneous reductive elimination of the palladium species to afford the desired [4.3.0]-bicyclic heterocycle. As only a catalytic amount of palladium would be utilised it is assumed the catalyst is regenerated upon formation of the heterocyclic product (Scheme 66).
**Scheme 66:** Proposed mechanism for the palladium(0) catalysed [3+2]-cycloaddition.

Previously work within the group believed the reaction may be promoted by the use of a Lewis acid (ZnBr$_2$).$^{45,47,48}$ It was proposed the Lewis acid may facilitate the ring opening of the cyclopropane by coordination to the electron withdrawing groups. The Lewis acid may also increase the electrophilicity of the electrophile which would in turn enhance its susceptibility to nucleophilic attack from the malonic centre of the zwitterionic $\pi$-allyl palladium(II) complex (Figure 10).

**Figure 10:** Proposed Lewis acid chelation.
We wished to utilise our general palladium(0) methodology to facilitate a variety of [4.3.0]-bicyclic tetrahydrofuran and pyrrolidine scaffolds with our newly acquired [4.1.0]-activated bicyclic vinylcyclopropane. It was hoped using an imine (X = NR₁, Scheme 66, pg 77) in conjunction with our palladium(0) catalysed [3+2]-cycloadDITION chemistry would afford the [4.3.0]-hydroindole core of the Stemona alkaloids.

3.2. Palladium(0) mediated cycloaditions of the dimethyl bicycle[4.1.0]hex-2-ene-7,7-dicarboxylate with a range of aldehydes

With our desired [4.1.0]-activated bicyclic vinylcyclopropane in hand we were eager to test its ability to undergo our proposed palladium(0) mediated [3+2]-cycloadDITION. It was thought that aldehydes with an electron withdrawing group would favour this type of reaction. Their electrophilic character had proved successful in reactions with the simpler vinylcyclopropane, although it must be mentioned that electron rich aldehydes have also been productive with this substrate.⁴⁵,⁴⁶,⁴⁸ It was expected a strong electrophile used in conjunction with a Lewis acid, would induce nucleophilic attack from the malonic centre of the zwitterionic π-allyl palladium(II) complex. The resultant alkoxide would in turn eliminate the palladium upon formation of the bicyclic tetrahydrofuran.

A small, activated aldehyde was thought to be an ideal initial trapping agent. An aldehyde furnishing an electron withdrawing group such as an ester or phenyl substituent was thought to fit these requirements. It was thought an activated phenyl substituent may further activate the carbonyl. We also selected a hetero-aromatic aldehyde as it was envisaged it could be converted to the corresponding carboxylic acid, offering a site for potential functionalisation. Finally, we selected an aldehyde furnishing an electron donating group (PMB), and a small aliphatic aldehyde to explore the potential scope of the reaction. The cycloaditions were initially performed using our general palladium catalysed conditions;⁴⁵ stoichiometric amounts of the cyclopropane and aldehyde, ZnBr₂ (2 equiv.), Pd(PPh₃)₄ (10 mol%) in THF at RT for 12h (Scheme 67).
Scheme 67: Palladium(0) mediated cycloadditions with a selection of aldehydes.

Our first cycloaddition using ethyl glyoxylate proved an exceptionally clean reaction. It was particularly interesting to note that the reaction afforded a single isomer by spectroscopic analysis (Figure 11).

**Figure 11:** $^1$H NMR of 3aR,4,5,7aR-tetrahydro-benzofuran-2,3,3-tricarboxylic acid 2S-ethyl ester 3,3-dimethyl ester.
Analysis by $^1$H, $^{13}$C, COSY and HMQC NMR techniques allowed us to tentatively assign the substituents around the bicyclic tetrahydrofuran. However, we were unable to confidently assign the stereochemistry around the ethyl ester substituent and across the bridged 3a-CH and 7a-CH hydrogens. It was thought nOe data may provide a greater insight into the stereochemistry around these substituents. Although we saw an enhancement of the bridged 3a-CH and 7a-CH protons upon their sequential irradiation, indicating they were aligned on the same face, we had hoped we might see an enhancement of the 2-CH proton if it was also on the same face. This was not the case and to our dismay no enhancement of the surrounding protons were seen upon irradiation of the 2-CH proton. We are therefore unable to categorically state whether we have isolated the trans (233a) or cis (233b) isomer (Figure 12).

![Figure 12: nOe effects of 3aR,4,5,7aR-tetrahydro-benzofuran-2,3,3-tricarboxylic acid 2S-ethyl ester 3,3-dimethyl ester.](image)

We believed the palladium catalysed [3+2]-cycloaddition of the [4.1.0]-activated vinyl cyclopropane with ethyl glyoxolate followed a similar mechanism to that of the simpler vinylcyclopropane. We believe that the trans isomer (233a) would be the sterically favoured configuration (Scheme 68). We will discuss this further in Chapter 4.
Scheme 68: Proposed mechanism for the palladium(0) catalysed [3+2]-cycloaddition with ethyl glyoxolate.

The other aldehydes proved less successful affording the aldehyde and traces of the [4.1.0]-bicyclic cyclopropane in a complex mixture. Alongside our cycloadditions with our [4.1.0]-moiety we attempted [3+2]-cycloadditions of the simpler vinylcyclopropane analogue (155) with the same range of aldehydes using our general palladium(0) catalysed conditions; stoichiometric amounts of the cyclopropane and aldehyde, ZnBr₂ (2 equiv.), Pd(PPh₃)₄ (10 mol%) in THF at RT for 12h.⁴⁷,⁴⁸ It allowed us to compare the reactivity of the cyclopropanes as well as ensuring the sensitive tetrakis (triphenylphosphine) palladium(0) catalyst was active (Table 14).
Table 14: Palladium(0) mediated cycloadditions with a selection of aldehydes.

We were unclear why the [4.1.0]-bicyclic vinylcyclopropane only underwent the desired [3+2]-cycloaddition with ethyl glyoxolate (228). The test reactions indicated the catalyst was active and the simpler vinylcyclopropane underwent the desired [3+2]-cycloaddition with a range of the selected aldehydes under our general palladium(0) catalysed conditions. It was hoped further investigation into the reaction conditions would afford similar success with the [4.1.0]-bicyclic vinylcyclopropane with the selection of aldehydes. The unsuccessful attempt to afford the desired tetrahydrofuran with the aliphatic aldehyde (232) served as a useful indication that this aldehyde was not electrophilic enough to participate in this type of reaction.

The formation of tetrahydrofuran (233a) from the reaction of the [4.1.0]-bicyclic vinylcyclopropane with ethyl glyoxolate suggests that a zwitterionic \( \pi \)-allyl species
was formed. However, it may be that the 1,3-dipolar synthon reacts to form other compounds which we have been unable to isolate. The size and polarity of ethyl glyoxolate may allow it to adopt the correct orientation for a successful cycloaddition. Adjusting the source of palladium(0) may facilitate the lifetime of the 1,3-dipolar synthon.

Sometimes, Pd(PPh\(_3\))\(_4\) can be less reactive as a catalyst. It is a co-ordinatively saturated palladium(0) complex and because it is overligated it has too many ligands to allow the coordination of some reactants. It was believed the catalyst maybe a cause of interference to our desired cycloaddition. An alternative commercially available palladium(0) source is Pd\(_2\)(dba)\(_3\) where the dibenzylideneacetone (dba) behaves as two monodentate ligands and each palladium is coordinated with three double bonds of the three molecules of dba. As a ligand dba is comparable to, or better than monodentate phosphines (Figure 13).\(^66\)

\begin{figure}
\centering
\includegraphics[width=\textwidth]{ligands.png}
\caption{Palladium(0) catalyst ligands.}
\end{figure}

It was hoped using stoichiometric amounts of the cyclopropane and aldehyde in conjunction with two equivalence of Lewis acid (ZnBr\(_2\)) and Pd\(_2\)(dba)\(_3\) (10 mol\%) in CH\(_2\)Cl\(_2\) would facilitate the desired palladium(0) catalysed [3+2]-cycloaddition. A report in the literature suggested CH\(_2\)Cl\(_2\) used in preference to THF may have an effect on the yield.\(^67\) We decided to repeat the range of aldehydes previously tested under these unproven conditions to see if we could isolate the desired bicyclic tetrahydrofurans (Scheme 69).
Scheme 69: Palladium(0) mediated cycloadditions with a selection of aldehydes.

Utilising ethyl glyoxolate (228) as the trapping agent afforded a single isomer of the desired tetrahydrofuran (233a) in an excellent yield (82%). Spectroscopic analysis showed it to be identical to the tetrahydrofuran isolated using the previous catalytic conditions (Scheme 67, pg 79). Although we were pleased the conditions afforded the tetrahydrofuran, we were particularly disappointed that the scope of the trapping agents seemed limited to ethyl glyoxolate. The other aldehydes proved less successful affording the aldehyde and traces of the [4.1.0]-bicyclic cyclopropane in a complex mixture. We are at a loss to explain the apparent reactivity solely towards this trapping agent.

Our next attempt at synthesising these tetrahydrofuran scaffolds followed work by Wyatt and occurred as a result of investigating the reactivity of a variety of appropriate trapping agents which might undergo a Heck reaction after our palladium catalysed [3+2]-cycloaddition which we will discuss later in our investigation. She found using stoichiometric amounts of the cyclopropane and aldehydes with Pd(PPh₃)₄ (10 mol%) in MeOH in the absence of Lewis acid afforded the desired tetrahydrofurans when investigating the simple vinylcyclopropane analogues (Table 12). We hoped that these conditions may help our cause (Scheme 70).
Scheme 70: Palladium(0) mediated cycloadditions with a selection of aldehydes.

It was disappointing not even to afford tetrahydrofuran (233) as in our previous conditions. It was very disheartening to discover that yet again our investigation into these aldehydes failed to furnish the corresponding tetrahydrofurans affording the aldehyde and a complex mixture. We are at a loss to explain this apparent lack of reactivity, especially after ascertaining an excellent yield with ethyl glyoxolate using two different palladium(0) catalytic conditions.

Slightly disappointed we turned our attention towards palladium(0) catalysed [3+2]-cycloadditions of ketones.

3.3. Palladium(0) mediated cycloadditions of the dimethyl bicyclo[4.1.0]hex-2-ene-7,7-dicarboxylate with a selection of activated ketones

Previous work within the group has afforded the desired tetrahydrofuran from the simpler vinylcyclopropane analogue (155) and activated ketones in reasonable yields. This work showed ketones would require activation by an electron withdrawing group to further activate the electrophilicity of the carbonyl. The electron withdrawing group would in turn encourage nucleophilic attack of the malonate centre of the palladium π-allyl zwitterionic species. It was anticipated that α-keto esters could be a suitable precursor for the palladium catalysed cycloaddition. The presence of the electrophilic ketone moiety, activated by the adjacent electron withdrawing group could make this a suitable electrophile for a [3+2]-cycloaddition.
The first substrate we chose to investigate was ethyl pyruvate (238). It was chosen due to its similarity to ethyl glyoxolate (228). We hoped the electron withdrawing ethyl ester would increase the electrophilicity of the carbonyl to demonstrate that this \(\alpha\)-keto ester was indeed a suitable substrate. If successful it would serve as a useful indication to the type of electrophiles which were suitable to participate in this type of \([3+2]\)-cycloaddition.

We utilised the three sets of reaction conditions that had previously been successful when investigating the \([3+2]\)-cycloaddition of the \([4.1.0]\)-bicyclic activated cyclopropane with ethyl glyoxolate (Scheme 71).

\[
\begin{align*}
\text{(186)} & \quad + \quad \text{(238)} \quad \rightarrow \quad \text{(187)} \\
\text{i) } & \text{Pd(PPh}_3\text{)}_4 \text{ (10 mol%), ZnBr}_2 \text{ (2 equiv.), THF, RT, 12h} \\
\text{ii) } & \text{Pd}_2\text{(dba)}_3 \text{ (10 mol%), ZnBr}_2 \text{ (2 equiv.), CH}_2\text{Cl}_2 \text{, RT, 12h} \\
\text{iii) } & \text{Pd(PPh}_3\text{)}_4 \text{ (10 mol%), MeOH, RT, 12h}
\end{align*}
\]

Scheme 71: Palladium(0) mediated cycloadditions with ethyl pyruvate.

It was particularly disappointing to afford a complex mixture and not the desired tetrahydrofuran. It could be reasoned that the ketone moiety was not electrophilic enough to participate in the nucleophilic addition of the zwitterionic \(\pi\)-allyl palladium(I) complex. This could be attributed to the electron donating methyl group and hence the ketone moiety was slightly less electrophilic than the aldehyde moiety of ethyl glyoxolate.

Work within the group with the simple vinyl cyclopropane analogue had also shown ethyl 4-nitrophenylglyoxolate (239) to be a particularly effective trapping agent. It was thought the phenyl ring, activated by a nitro group adjacent to the ketone, in conjunction with the electron withdrawing ethyl ester group would increase the electrophilicity of the ketone and hence encourage attack from the \(\pi\)-allyl palladium (II) complex. Similarly, we have found isatin derivatives to be particularly susceptible
to [3+2]-cycloadditions with the simpler vinlycyclopropane. It was believed the presence of the aromatic ring and the adjacent amide electron withdrawing group would increase the electrophilicity of the ketone moiety. It was hoped these trapping agents would be sufficiently reactive to undergo a [3+2]-cycloaddition. The selected ketones were subjected to the general palladium catalysed conditions optimised within the group using stoichiometric amounts of cyclopropane and ketone (Scheme 72).

Scheme 72: Palladium(0) mediated cycloadditions with a selection of α-ketones.

The reactions proved fruitless furnishing the ketones and traces of the [4.1.0]-bicyclic cyclopropane in a complex mixture. It was particularly disappointing to furnish the corresponding heterocycles in reasonable yields when we subjected these selected ketones to our general palladium catalysed conditions using the simpler vinlycyclopropane analogue (151) (Table 15).
There seemed to be little correlation between the reactivity of the simpler vinylcyclopropane and the [4.1.0]-bicyclic vinylcyclopropane with these ketones. These reactions only served to indicate the simpler vinylcyclopropane (155) was far more conducive to our palladium catalysed conditions that the [4.1.0]-bicyclic vinylcyclopropane with the ketones that we had investigated.

It was hoped that we may fair more successfully when we turned our attention towards utilising imines as trapping agents and the construction of pyrrolidine skeletons.
3.4. Palladium(0) mediated cycloadditions of dimethyl bicyclo[4.1.0]hex-2-ene-7,7-dicarboxylate with a selection of imines

In the pursuit to construct the hydroindole sub-unit towards the preparation of the azepinoindole core of the *Stemona* alkaloids, it was envisaged a one pot cycloaddition of the [4.1.0]-bicyclic vinylcyclopropane with a suitability functionalised imine would provide a quick, clean, efficient and simple strategy. Imines in organic synthesis have been well documented and reviewed by Hart.\(^6^8\) Our preferred synthesis was to react the amines with the corresponding aldehyde, at room temperature in the presence of Et\(_2\)O and molecular sieves over 8h, unless otherwise stated (Scheme 73).

\[
\begin{align*}
\text{(228)} & \quad \text{HCO}_2\text{Et} \\
\text{(244)} & \quad \text{NH}_2 \\
\text{4 A molecular sieves, Et}_2\text{O}, \\ 
\text{RT, 12h, (94%)} & \quad \text{NCO}_2\text{Et} \\
\end{align*}
\]

**Scheme 73: General synthesis of imines**

Based on the success of the palladium(0) [3+2]-catalysed cycloaddition of the [4.1.0]-activated bicyclic cyclopropane with ethyl glyoxolate (228). We thought an imine derived from ethyl glyoxolate would be an ideal precursor. A strong electron withdrawing ethyl ester substituent adjacent to the carbon and a powerful para-methoxybenzyl (PMB) electron rich group attached to the nitrogen was thought to be most likely to trap the \(\pi\)-allyl palladium(II) zwitterion and afford the desired bicyclic pyrrolidine. This imine was particularly attractive as removal of the PMB group using ceric ammonium nitrate (CAN)\(^6^9\) would furnish the hydroindole core of the *Stemona* alkaloids. With the long term aim of the total synthesis of a *Stemona* alkaloid the ester also offered a site for potential functionalisation (Scheme 74).
We began by performing a direct repeat of the work initially performed by Tandy; using stoichiometric amounts of cyclopropane (155) and the imine (245), ZnBr₂ (2 equiv.), Pd(PPh₃)₄ (10 mol%) in THF at RT for 12h. The reaction was performed in order to see whether 4-methoxybenzene ethylester imine (245) would undergo a palladium(0) catalysed [3+2]-cycloaddition. It was also thought it may aid characterisation should the analogous reaction with our desired bicyclic heterocycle prove successful (Scheme 75).

However, we were not sure how the imine would react under our Pd(PPh₃)₄, MeOH conditions. It was expected that the imine may decompose under these protic conditions (Scheme 76).
Scheme 76: Palladium catalysed [3+2]-cycloaddition with vinylcyclopropane.

We were particularly pleased afforded the desired pyrrolidine using MeOH as a solvent. Spectroscopic analysis showed that the ethyl ester group had been converted to the methyl ester presumably via ester exchange with the solvent. We will discuss these conditions at greater length, later in our investigation (Chapter 5). The two test reactions had proceeded smoothly and it was hoped our [4.1.0]-activated cyclopropane would undergo the [3+2]-cycloaddition under our general conditions (Scheme 77).

Scheme 77: Palladium catalysed [3+2]-cycloaddition with 4-methoxybenzene ethylester imine.

It was disappointing to discover that the reaction was unsuccessful with recovery of the imine and a complex mixture. If we assume from our previous success using ethyl glyoxolate that the zwitterionic π-allyl species is formed, a plausible explanation could be that the 1,3-dipolar synthon forms but reacts to form other compounds which we have been unable to isolate. It maybe the imine moiety was too bulky or not electrophilic enough to participate in the nucleophilic addition to the zwitterionic π-
allyl palladium(II) complex. It was thought altering the reaction conditions may encourage the reaction. We believed increasing the equivalents of the imine may react with any of the zwitterion even if it was formed in small quantities to afford the desired [3+2]-cycloaddition. The reactions were carried out as before with increasing equivalents of the 4-methoxybenzene ethylester imine (245) (Table 16).

<table>
<thead>
<tr>
<th>Equiv. of imine</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>S.M.</td>
</tr>
<tr>
<td>1.1</td>
<td>S.M.</td>
</tr>
<tr>
<td>1.5</td>
<td>S.M.</td>
</tr>
<tr>
<td>2.0</td>
<td>S.M.</td>
</tr>
<tr>
<td>3.0</td>
<td>S.M.</td>
</tr>
<tr>
<td>5.0</td>
<td>S.M.</td>
</tr>
</tbody>
</table>

Table 16: Cycloaddition with varying equivalence of imine.

It was hoped that the increase in thermal energy may promote the desired reaction. We briefly explored the effect of increasing the temperature of the reaction whilst keeping the other reaction parameters fixed to our general conditions; stoichiometric amounts of cyclopropane and the imine, ZnBr₂ (2 equiv.), Pd(PPh₃)₄ (10 mol%) in THF at RT for 12h (Table 17).

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Temp/°C</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>THF</td>
<td>20</td>
<td>S.M.</td>
</tr>
<tr>
<td>THF</td>
<td>50</td>
<td>S.M.</td>
</tr>
<tr>
<td>THF</td>
<td>reflux</td>
<td>S.M.</td>
</tr>
</tbody>
</table>

Table 17: Increase in temperature of the [3+2]-cycloaddition with 4-methoxybenzene ethylester imine.

This proved unsuccessful and has led to further investigation into the reaction parameters. It maybe the imine was just not conducive to a [3+2]-cycloaddition under these palladium catalysed conditions. We decided to explore the conditions we had previously investigated utilising ethyl glyoxolate (228) as a trapping agent using stoichiometric amounts of cyclopropane and imine (Scheme 78).
We were slightly dismayed that our attempts thus far had yet to afford a productive route to form this pyrrolidine scaffold. It was decided to attempt the formation of a pyrrolidine from N-benzyl imines. The advantage of this group was that the aromatic group was spaced away from the nitrogen by a CH₂ group. We believed this spacer group may relieve any steric bulk experienced when using the PMB group which may have been preventing the reaction. It was also thought the benzyl group could be removed by hydrogenation or other reducing reactions. We believed an ester substituent adjacent to the carbon of the imine moiety may activate the carbon as previously seen with the successfully [3+2]-cycloaddition of ethyl glyoxolate (228). However, we were unable to synthesise the corresponding benzyl imine. We therefore prepared benzyl imines furnishing a phenyl or activated phenyl substituent which we thought may activate the carbon of the imine moiety sufficiently for it to undergo a [3+2]-cycloaddition. We also prepared another two benzyl imines in reasonable yields to explore the potential scope of the reaction. The first furnishing a hetero-aromatic group which we thought could be converted to the corresponding carboxylic acid offering a site for potential functionalisation and the other furnishing electron donating groups (PMB) (Scheme 79).

**Scheme 78:** Palladium(0) mediated cycloadditions with 4-methoxybenzene ethylester imine.
These imines were subjected to our general palladium(0) catalysed [3+2]-cycloaddition conditions; using a stoichiometric amount of cyclopropane and imine (Scheme 80).

We failed to afford even a trace of the desired bicyclic pyrrolidines observing the presence of the imine and a complex mixture. We also performed the corresponding reactions with the simpler vinylcyclopropane analogue (155) under analogous conditions. The reactions only served to indicate that these substrates appeared conducive to a palladium catalysed [3+2]-cycloaddition. Indicating a stark contrast in reactivity compared to the [4,1,0]-bicyclic cyclopropane analogue under these conditions (Table 18).
Chapter 3

![Chemical reaction diagram]

**Table 18: Preparation of pyrrolidine scaffolds from benzyl imines.**

It was unfortunate not to isolate the desired bicyclic pyrrolidine using our general palladium(0) catalysed conditions with these imines. Nevertheless, it was thought it was worthwhile to explore the other reaction parameters we had previously investigated to be successful with the [3+2]-cycloaddition using stoichiometric amounts of ethyl glyoxolate (228) and the [4.1.0]-activated bicyclic cyclopropane (Scheme 81).
Chapter 3

We were understandably disappointed with the productivity of this line of the investigation. It was hoped we would be able to prepare a bicyclic pyrrolidine skeleton which had the potential to undergo a Heck reaction to form a fused tricyclic structure. Due to the ease in synthesising the benzyl imines it was thought a selection of 2-bromobenzyl imines would be ideal trapping agents with which to attempt a [3+2]-cycloaddition. A selection of 2-bromobenzyl imines were prepared in reasonable yields, exhibiting the same substituents adjacent to the carbon as the benzyl imines (Scheme 82).

It was thought we may be able to fortuitously afford the corresponding pyrrolidine scaffold. This would in turn provide an excellent precursor with which to attempt a Heck reaction, possibly affording a tricyclic scaffold (Scheme 83).

Scheme 81: Preparation of bicyclic pyrrolidine scaffolds from benzyl imines.

Scheme 82: Preparation of 2-bromobenzyl imines.
Scheme 83: Preparation of bicyclic pyrrolidine scaffolds from 2-bromobenzyl imines.

Unfortunately this proved fruitless and we were unable to afford the corresponding bicyclic pyrrolidine with which to attempt a Heck reaction (Scheme 84).

Scheme 84: Proposed Heck reaction.

We did furnish the corresponding heterocycles in reasonable yields when we subjected the selected 2-bromobenzyl imines to our general palladium catalysed conditions using the simpler vinylcyclopropane analogue (155) (Table 19).
It was thought these would be ideal precursors with which to attempt model Heck reactions. We will discuss our efforts towards the Heck reaction later in our investigation (Chapter 5).

3.5. Palladium(0) mediated cycloadditions of bicyclo[4.1.0]hex-2-ene-7-carboxylic acid ethyl ester

During our exploration into the preparation of bicyclic cyclopropane we also synthesised the equivalent [4.1.0]-singly activated vinylcyclopropane (213). We were not sure whether the cyclopropane would be sufficiently activated to ring open or whether the single electron withdrawing ethyl ester would stabilise the resulting malonic zwitterionic charge under our palladium(0) catalysed conditions to undergo a [3+2]-cycloaddition. We decided to briefly investigate whether this moiety would
undergo the desired [3+2]-cycloaddition with our only successful trapping agent in
the analogous reaction with the [4.1.0]-doubly activated vinyl cyclopropane, ethyl
glyoxolate (Scheme 85).

\[
\begin{align*}
\text{H} & \quad \text{+} \quad \text{O} \quad \text{H} \\
\text{CO,ET} & \quad \text{H} & \quad \text{0}
\end{align*}
\]

(213) (228)

\[i, ii, iii)\]

\[
\begin{align*}
\text{H} & \quad \text{Pd(pPh3)4 (10 mol%), ZnBr2 (2 equiv.), THF, RT, 12h} \\
\text{H} & \quad \text{Pd2(dba)3 (10 mol%), ZnBr2 (2 equiv.), CH2Cl2, RT, 12h} \\
\text{H} & \quad \text{Pd(PPh3)4 (10 mol%), MeOH, RT, 12h}
\end{align*}
\]

**Scheme 85:** Preparation of a bicyclic tetrahydrofuran scaffold from ethyl glyoxolate.

The reactions proved fruitless with recovery of the starting materials. It maybe
reasoned that the mono-substituted cyclopropane was not sufficiently activated to
facilitate ring opening under these palladium(0) catalysed conditions and may require
activation by two electron withdrawing groups to undergo a [3+2]-cycloaddition
reaction.

It was believed the doubly activated 7 and 8-membered bicyclic vinylcyclopropanes
maybe more susceptible to undergo the desired palladium(0) catalysed cycloaddition.

3.6. Palladium(0) mediated cycloadditions of dimethyl bicyclo[5.1.0]hex-2-ene-7,7-
dicarboxylate and dimethyl bicyclo[6.1.0]hex-2-ene-7,7-dicarboxylate

In our preparation of bicyclic cyclopropanes of varying in ring size, we reported the
preparation of the corresponding 7 and 8-membered doubly activated bicyclic
vinylcyclopropanes. With the knowledge that these moieties seemed particularly
susceptible to undergo the required palladium(0) catalysed [3+2]-cycloaddition with
the small, electrophilic ethyl glyoxolate (228), we subjected these two moieties to our
palladium(0) catalysed conditions that had been productive for the [4.1.0]-activated
bicyclic vinylcyclopropane (Scheme 86).
Scheme 86: Cycloadditions of [4.1.0] and [5.1.0]-activated bicyclic cyclopropanes with ethyl glyoxolate.

To our delight we managed to isolate the corresponding [5.3.0]-tetrahydrofuran (266a) in an acceptable yield (48%). Although we only managed to isolate starting material with the analogous reaction with 8-membered bicyclic vinylcyclopropanes. Analysis of the successful cycloaddition by $^1$H, $^{13}$C, COSY and HMQC NMR techniques indicated the hydrogens across the bridge of the bicycle were cis and we have been able to assign the majority of the stereochemistry. Although, we have yet to gain conclusive evidence of the stereochemistry around the ethoxy substituent. We thought NOe data may give us a greater insight. Although, we saw an enhancement of the bridged cis protons it failed to enlighten us any further.

This further fuelled speculation that the bicyclic cyclopropanes maybe only susceptible to certain types of electrophiles.

3.7. Proposed mechanism of bicyclic tetrahydrofuran ring formation

Based on work within the group and the success of the [3+2]-cycloaddition of the 6 and 7-membered bicyclic cyclopropanes with ethyl glyoxolate (228), it is possible to propose an appropriate reaction mechanism. The first feature to be noted is that the reaction only requires a catalytic amount of palladium(0) reagent (10 mol%), which implies that a catalytic cycle is set up whereby the palladium species must be regenerated on formation of the 5-membered heterocyclic product. It follows that oxidative addition of the palladium(0) catalyst to the activated bicyclic cyclopropane generates a π-allyl zwitterion that subsequently undergoes nucleophilic attack onto the
electrophilic substrate affording a second transient zwitterion. The resultant alkoxide displaces the palladium reagent from the π-allyl site. The transition metal catalyst also undergoes simultaneous reductive elimination to afford the corresponding bicyclic tetrahydrofuran. If the reaction was to proceed with an imine moiety, we postulate the same methodology might apply and displacement would occur in an analogous fashion to that of the alkoxide. We will discuss our efforts towards establishing a mechanism later in our investigation (Chapter 4).

As we only have one confirmed example of a trapping agent that has undergone the [3+2]-cycloaddition, we cannot determine the contribution of the Lewis acid, solvent and temperature to the stereochemistry or yield on a range of substrates. It has been proposed by previous work within the group that the Lewis acid promotes the cycloaddition by activation and co-ordination between the metal ion and the carbonyl groups of the cyclopropane and the electron rich moiety of the electrophile. It is also possible that the π-allyl palladium complex is affected by varying the solvent's polarity. It is hoped further investigation will shed light into how these factors may effect the palladium(0) catalysed [3+2]-cycloadditions of the bicyclic vinylcyclopropanes.

3.8. Conclusion

Our investigation into palladium(0) [3+2]-catalysed cycloadditions of the [4.1.0]-activated bicyclic vinylcyclopropane has been very disappointing. We have at least begun to explore the initial stages of a novel methodology for the construction of highly functionalised bicyclic ring systems using a mild and efficient procedure based on a parallel strategy developed within our group. The tolerance of this reaction towards a variety of functionalised trapping agents has proved limited, although we have only begun to test the reaction parameters. The most encouraging result is that even though we only have limited examples, we can facilitate ring opening the activated bicyclic cyclopropane under the conditions we have developed. This formed the corresponding bicyclic tetrahydrofuran when reacted in situ with ethyl glyoxolate (228). This leads us to believe the reaction follows our proposed catalytic cycle.
We believe further manipulation of the reaction parameters may facilitate the desired hydroindole core of the *Stemona* alkaloids and allow an insight into how we may increase the scope of this methodology. Investigation into the use of different palladium(0) catalysts, ligands and Lewis acids may prove worthwhile.

It was hoped the [3.1.0]-activated bicyclic vinylcyclopropane would increase the scope of our palladium(0) catalysed [3+2]-cycloaddition methodology, allowing us to gain a greater understanding into the reactivity of these bicyclic cyclopropanes. In the next chapter we describe our initial studies in the application of this methodology towards the synthesis of [3.3.0]-bicyclic heterocycles.
Chapter 4- Reactions of [3.1.0]-activated cyclopropanes

4.1.1. Synthesis of heterocycles using palladium(0) catalysis

Trost\textsuperscript{67} has reported the cyclisation of a 5-membered ring substrate. He used a palladium(0) catalyst to promote ring closure generating a π-allyl complex which subsequently formed the bicyclic lactone (Scheme 87).

\[
\text{H}_2\text{COCO-} \quad \text{(267)} \quad \text{H}_2\text{COCOCH}_3 \quad \text{(268)} \quad \text{H}_2\text{COCOCH}_3 \quad \text{(269)}
\]

\[
\begin{array}{cc}
\text{[n}_3\text{-C}_3\text{H}_2\text{PdCl}]_2 (1\text{mol%}), & \text{NaOMe, MeOH, -20}^\circ\text{C-RT, dppp (2.5mol%), 1h, (54%)}
\end{array}
\]

\textbf{Scheme 87: Synthesis of bicyclic lactone.}\textsuperscript{67}

The reaction parameters have led to the formation of a fused bicyclic lactone system setting a precedent towards work in this area.

Several simple olefinic tosylamide cyclisations using a palladium(II) catalyst have been reported by Larock\textsuperscript{70}. The formation of a π-allyl palladium complex followed by intramolecular nucleophilic displacement of the palladium by the nitrogen generates the desired allylic nitrogen moiety (Scheme 88).

\[
\begin{array}{cc}
\text{Pd(OAc)}_2 (5 \text{ mol%}) & \text{(270)} \quad \text{(271)}
\end{array}
\]

\[
\begin{array}{cc}
\text{NaOAc (2 equiv.),} & \text{DMSO, RT, 72h, (86%)}
\end{array}
\]

\textbf{Scheme 88: Synthesis of [3.3.0]-allylic nitrogen bicycle.}\textsuperscript{70}

Mori\textsuperscript{71} has also reported work into asymmetric alkylations employing a π-allyl palladium complex in the presence of chiral ligands. They report a catalytic asymmetric synthesis of cyclopentanoids from cyclopentenediol derivatives and the corresponding allylic nitrogen moieties (Scheme 89).
We believed utilising our palladium(0) catalysed [3+2]-cycloaddition methodology and the [3.1.0]-bicyclic cyclopropane with a variety of electrophiles would provide access to a range of similar [3.3.0]-fused heterocycles. It was plausible the synthesis would follow that of the [4.1.0] and [5.1.0]-bicyclic cyclopropanes that we have previously outlined. Addition of a Lewis acid (ZnBr$_2$) and a catalytic amount of palladium would facilitate the ring opening of the cyclopropane, forming a zwitterionic $\pi$-allyl palladium(II) complex. Subsequent addition of an aldehyde, ketone or imine to the zwitterionic moiety would furnish a second transient zwitterionic species. We thought this would undergo intramolecular ring closure and provide access to a range of fused heterocyclic scaffolds. It was hoped we could facilitate a strategy which could be applicable for general heterocyclic ring construction. Once a general strategy could be facilitated further manipulation could lead to compounds of biological interest (Scheme 90).
Scheme 90: Proposed mechanism for the palladium(0) catalysed [3+2]-cycloaddition.

We hoped to draw on our experience working with the analogous [4.1.0] and [5.1.0]-bicyclic vinylcyclopropanes as well as the simpler vinylcyclopropane to further develop our palladium catalysed [3+2]-cycloadditions with the [3.1.0]-bicyclic vinylcyclopropane. It was thought work in this area could improve our knowledge into the reactivity of the bicyclic vinylcyclopropanes. This in turn would increase the scope of our cycloaddition methodology toward affording bicyclic heterocycles of varying size.

4.2. Palladium(0) mediated cycloadditions of the dimethyl bicyclo[3.1.0]hex-2-ene-7,7-dicarboxylate with a selection of aldehydes

As with the [4.1.0]-analogue it was thought aldehydes with an electron withdrawing group would favour a [3+2]-cycloaddition reaction. Our only success achieved prior to this point in forming these types of heterocycles was using the [4.1.0] and [5.1.0]-bicyclic vinylcyclopropane with ethyl glyoxolate. It was therefore expected a small electrophilic aldehyde used in conjunction with a Lewis acid and a palladium catalyst, would induce nucleophilic attack from the malonic centre of the zwitterionic π-allyl palladium(II) complex. The resultant alkoxide would in turn displace the palladium upon formation of the bicyclic tetrahydrofuran.
Our line of investigation followed that which we had previously adopted with the [4.1.0]-bicyclic vinylcyclopropane. It was thought a small, polar, activated aldehyde furnishing an electron withdrawing group such as an ester, phenyl or activated phenyl substituent, would be an ideal electrophile. We also hoped to explore the scope of our methodology by investigating the feasibility of a hetero-aromatic aldehyde which offered a site for potential functionalisation. As well as an electron rich aldehyde (PMB) which we thought would show the scope of the reaction, it would also allow us to directly compare the reactivity of the [3.1.0] and [4.1.0]-bicyclic vinylcyclopropanes utilising our palladium catalysed methodology. The cycloadditions were initially performed using our general palladium catalysed conditions, stoichiometric amounts of the cyclopropane and aldehyde, ZnBr₂ (2 equiv.), Pd(PPh₃)₄ (10 mol%) in THF at RT for 12h (Scheme 91).

Scheme 91: Palladium(0) mediated cycloadditions with a selection of aldehydes.

It was pleasing to find that ethyl glyoxolate (228) cyclised efficiently under our general palladium(0) conditions. This was not unexpected due to its reactivity in the analogous reaction with the [4.1.0] and [5.1.0]-bicyclic vinylcyclopropanes. The cycloaddition proved to be an exceptionally clean reaction, affording a single isomer by spectroscopic analysis (Figure 14).
Figure 14: $^1$H NMR of 4,6aR-dihydro-3aHR-cyclopenta[b]furan-2,3,3-tricarboxylic acid 2S-ethyl ester 3,3-dimethyl ester.

Analysis by $^1$H, $^{13}$C, COSY and HMOC NMR techniques as with the analogous cycloaddition of the [4.1.0] and [5.1.0]-bicyclic vinylcyclopropane allowed us to tentatively assign the arrangement around the bicyclic tetrahydrofuran. However, we were unable to confidently assign the stereochemistry around the ethyl ester substituent and across the bridged 3a-CH and 6a-CH hydrogens. It was thought NOe data may provide a greater insight into the stereochemistry around these substituents. To our delight it indicated the hydrogen next to the ethyl ester substituent was on the opposite face to the cis bridged 3a-CH and 6a-CH hydrogens. Although as seen with the larger [4.1.0] and [5.1.0]-heterocycles no enhancement of the 2-CH proton was seen when irradiating the cis bridged hydrogens. We did however see an enhancement of one of the 4-C(H)H upon irradiation of the 2-CH proton indicating it was on the opposite face to the bridged hydrogens. This was confirmed by an enhancement of the other 4-C(H)H with the cis 3a-CH bridged proton (Figure 15).
Chapter 4

Figure 15: nOe effects of 4,6aR-dihydro-3aHR-cyclopenta[b]furan-2,3,3-tricarboxylic acid 2S-ethyl ester 3,3-dimethyl ester.

It was very encouraging to discover the reaction also proved successful with a phenyl activated by an electron withdrawing 4-nitro substituent. Although it appeared the desired tetrahydrofuran had been formed, a significant proportion of aldehyde remained even after purification by column chromatography. A bisulfite wash was found to remove the excess aldehyde leaving the desired tetrahydrofuran albeit in a low yield (18%), which we were able to analyse (Figure 16).

Figure 16: $^1$H NMR of 2R-(4-nitro-phenyl)-4,6aR-dihydro-3aHR-cyclopenta[b]furan-3,3-dicarboxylic acid dimethyl ester.
Using analogous spectroscopic techniques that had helped us assign the bicyclic tetrahydrofuran afforded with ethyl glyoxolate (228), we were able to ascertain the stereochemistry around this tetrahydrofuran was identical to that exhibited in our previous example (Figure 17).

![Figure 17: nOe effects of 2R-(4-nitro-phenyl)-4,6aR-dihydro-3aHR-cyclopenta[b]furan-3,3-dicarboxylic acid dimethyl ester.](image)

Unfortunately the reactions with 2-furaldehyde and 4-methoxybenzaldehyde proved unsuccessful and saw the recovery of a significant amount of the corresponding aldehyde. We were also unable to recover the [3.1.0]-bicyclic vinylcyclopropane from what appeared to be a complex mixture. It may be that the 1,3-dipolar synthon reacts to form other compounds which we have been unable to isolate. As can be seen with the examples which afford the desired tetrahydrofuran, the characteristic 2-CH, 6a-CH, 5-CH and 6-CH were easily recognisable by $^1$H NMR analysis which corresponded to a successful [3+2]-cycloaddition. This was particularly advantageous in recognising whether a cycloaddition had been successful.

We also carried out the corresponding reactions with simpler vinylcyclopropane analogue (155) under the general palladium catalysed conditions. Their isolation were reported in Chapter 3 (Table 14, pg 82).

As previously discussed, Pd(PPh$_3$)$_4$ can be a less reactive catalyst.$^{66}$ It was decided that another palladium(0) catalyst may furnish improved results. As a ligand dba is comparable to, or better than monodentate phosphines as well as being relatively
cheap and commercially available. We decided to see whether using Pd$_2$(dba)$_3$ as the palladium(0) catalyst would have any bearing on the reaction. The general cycloaddition procedure remained the same; using stoichiometric amounts of the cyclopropane and aldehyde in conjunction with Lewis acid (ZnBr$_2$) (2 equiv.) and Pd$_2$(dba)$_3$ (10 mol%) in CH$_2$Cl$_2$. We repeated the range of aldehydes previously tested under our general conditions as a direct comparison to see if we could isolate the desired bicyclic tetrahydrofurans (Scheme 92).

![Scheme 92: Palladium(0) mediated cycloadditions with a selection of aldehydes.](image)

The unsuccessful reactions saw the recovery of a significant amount of the corresponding aldehyde, but we were unable to recover the [3.1.0]-bicyclic vinylcyclopropane from the complex mixture. We were pleased to note an increase in yield when using 4-nitrobenzaldehyde (229). Although we had been able to fully assign the stereochemistry it was hoped that an increase in yield may afford crystalline compound due to the ionic nature of nitro group. This would provide full and conclusive data on the stereochemistry of these types of heterocyclic compounds. Unfortunately we have not been successful in affording a crystalline compound thus far. However, this result gave us renewed vigour to unlock the door to a vast array of bicyclic heterocycles.

We did afford a particularly interesting result when using propionaldehyde (232) as the trapping agent. Instead of recovering the desired bicyclic heterocycle, we afforded a small amount of an unexpected [3.3.0]-bicyclic lactone (Scheme 93).
It was thought one of the methyl esters of the [3.1.0]-bicyclic cyclopropane had been converted to a carboxylic acid due to the presence of water, which subsequently cyclised to form the bicyclic lactone.

Our final attempt at synthesising these tetrahydrofuran scaffolds followed work outlined by Wyatt\(^47\) using stoichiometric amounts of the cyclopropane and aldehydes with \(\text{Pd(PPh}_3\text{)}_4\) (10 mol\%) in MeOH, which afforded the desired tetrahydrofurans when investigating the simple vinylcyclopropane analogues (Chapter 3, Table 13, pg 76). We hoped that these conditions may help our cause although they proved unsuccessful with the [4.1.0]-bicyclic vinylcyclopropane (Scheme 94).

The attempted palladium catalysed [3+2]-cycloadditions using \(\text{Pd(PPh}_3\text{)}_4\) in MeOH has yet to afford the desired bicyclic tetrahydrofuran furnishing a complex mixture and traces of the corresponding aldehydes, even though these conditions had
previously worked with simpler vinylcyclopropane analogue (155) and selected trapping agents.\textsuperscript{47} It may be that the 1,3-dipolar synthon forms on addition of the palladium(0) catalyst but reacts to form other compounds which we have been unable to isolate.

Although we have had limited success with aldehydes it was hoped that we could promote the cycloaddition of a bromo-substituted aromatic aldehyde which may be susceptible to a Heck cyclisation. General Heck reactions coupling an alkene with a halide have been well documented in the literature.\textsuperscript{72} If successful this would lead to the formation of a fused tricyclic compound containing a 5-membered heterocycle.

A commercially available aldehyde which adhered to these constrains was chosen as a suitable precursor with which to attempt this line of enquiry. Our previous success using our Pd(PPh\textsubscript{3})\textsubscript{4} and Pd\textsubscript{2}(dba)\textsubscript{3} catalytic conditions with 4-nitrobenzaldehyde (229) led us to believe we might be able to afford the corresponding bicyclic heterocycle with 2-bromobenzaldehyde (277). This in turn might set up a suitable precursor, providing we ascertained the suitable stereochemistry, which might allow us to try and construct a tricycle compound under Heck conditions (Scheme 95).

\begin{center}
\vspace{0.5cm}
\begin{tikzpicture}
  \node (1) at (0,0) {CO\textsubscript{2}Me} ;
  \node (2) at (1,0) {H} ;
  \node (3) at (2,0) {Br} ;
  \node (4) at (3,0) {H} ;
  \node (5) at (4,0) {CO\textsubscript{2}Me} ;
  \node (6) at (5,0) {H} ;
  \node (7) at (6,0) {CO\textsubscript{2}Me} ;
  \node (8) at (7,0) {Br} ;
  \node (9) at (8,0) {H} ;
  \node (10) at (9,0) {CO\textsubscript{2}Me} ;

  \node (a) at (0.5,1.5) {H} ;
  \node (b) at (1.5,1.5) {O} ;
  \node (c) at (2.5,1.5) {H} ;
  \node (d) at (3.5,1.5) {Br} ;

  \draw[->,thick] (1) -- (2) -- (3) -- (4) -- (5) -- (6) -- (7) -- (8) -- (9) -- (10) ;
  \draw[->,thick] (a) -- (b) -- (c) -- (d) ;

  \node at (1.5,2.5) {i) and ii) \rightarrow} ;
  \node at (4.5,2.5) {X} ;

  \node (11) at (12,0) {CO\textsubscript{2}Me} ;
  \node (12) at (13,0) {H} ;
  \node (13) at (14,0) {CO\textsubscript{2}Me} ;
  \node (14) at (15,0) {Br} ;
  \node (15) at (16,0) {H} ;
  \node (16) at (17,0) {CO\textsubscript{2}Me} ;

  \node (17) at (12.5,1.5) {H} ;
  \node (18) at (13.5,1.5) {O} ;
  \node (19) at (14.5,1.5) {H} ;

  \node at (13,2.5) {\textsuperscript{1}Pd(PPh\textsubscript{3})\textsubscript{4} (10 mol\%), ZnBr\textsubscript{2} (2 equiv.), THF, RT, 12h} ;
  \node at (16,2.5) {\textsuperscript{2}Pd\textsubscript{2}(dba)\textsubscript{3} (10 mol\%), ZnBr\textsubscript{2} (2 equiv.), CH\textsubscript{2}Cl\textsubscript{2}, RT, 12h} ;

\end{tikzpicture}
\end{center}

\textbf{Scheme 95: Preparation of bicyclic Heck precursor.}

Our efforts provided little encouragement and it was decided to try to develop this methodology using the simpler vinylcyclopropane analogue (155). It was hoped we could prepare a variety of heterocyclic Heck precursors through our general [3+2]-methodology. We will discuss our efforts towards the construction of the heterocyclic Heck precursors later in our investigation (Chapter 5).
It appeared changing the palladium(0) source to Pd₂(dba)₃ may have increased the potency of the [3+2]-cycloaddition reaction. We hoped we would see an upturn in fortunes with a wider selection of trapping agents which had proved unsuccessful thus far. Our attention turned back to a selection of ketones that had previously been probed by the group with the simpler vinylcyclopropane analogue (155) and work looking into the reactivity of the [4.1.0]-bicyclic vinylcyclopropane.

4.3. Palladium(0) mediated cycloadditions of the dimethyl bicyclo[3.1.0]hex-2-ene-7,7-dicarboxylate with a selection of activated ketones

We thought ketones would require activation by an electron withdrawing group to further increase the electrophilicity of the carbonyl. The electron withdrawing group would in turn encourage nucleophilic attack of the malonic centre of the palladium π-allyl zwitterionic species. It was anticipated that α-keto esters would be a suitable precursor for the palladium catalysed cycloaddition. The presence of the electrophilic ketone moiety, activated by the adjacent electron withdrawing group could make this a suitable electrophile for a [3+2]-cycloaddition.

A selection of substrates were chosen which we thought may prove successful and afford interesting bicyclic scaffolds. Due to the unsuccessful reaction of ethyl pyruvate with the [4.1.0]-bicyclic cyclopropane, we chose two α-keto esters which were activated by two electron withdrawing groups. If successful it may serve as a useful indication of which functional groups were required to participate in this type of cycloaddition. We utilised the two sets of reaction conditions that had previously been successful when investigating the [3+2]-cycloaddition of the [3.1.0]-bicyclic activate cyclopropane with ethyl glyoxolate and 4-nitrobenzaldehyde (Scheme 96).
We also tried two $\alpha,\beta$-unsaturated cyclic carbonyls as trapping agents. If the reaction was successful we would form a novel tricyclic ring structure (Scheme 97).

The reactions with $\alpha$-keto esters and $\alpha,\beta$-unsaturated cyclic carbonyls proved fruitless furnishing traces of the corresponding ketone. Regrettably we were unable to recover the [3.1.0]-bicyclic vinylcyclopropane from the complex mixture.

Alongside our cycloadditions with our [3.1.0]-moiety we attempted [3+2]-cycloadditions of the simpler vinylcyclopropane analogue (155) with the same range of ketones using our general palladium(0) catalysed conditions (Table 20).
Chapter 4

We afforded the tetrahydrofurans corresponding to the α-keto esters with the vinylcyclopropane analogue (155). However, it was particularly disappointing to furnish the vinylcyclopropane (155) when we subjected the α,β-unsaturated cyclic carbonyls to these conditions.

It was envisaged the activated α-ketones (239 and 278) would emulate the success we had previously found when using ethyl glyoxolate (228) with the [3.1.0]-moiety. Their polarised nature led us to believe they may react to form the desired heterocycle. It was with great disillusionment that we did not afford the desired bicyclic tetrahydrofurans with either. However, it maybe reasoned that the α,β-unsaturated cyclic carbonyls were not sufficiently electrophilic to undergo a palladium(0) catalysed [3+2]-cycloaddition under our conditions as they proved...
completely unsuccessful with the [3.1.0]-bicyclic vinyl cyclopropanes and the simple vinylcyclopropane analogue (155).

To our dismay little progress has been made utilising ketones as trapping agents with our [3.1.0]-bicyclic vinylcyclopropane. It was hoped we may fair more successfully when we turned our attention towards utilising imines as trapping agents and the construction of bicyclic pyrrolidine skeletons.

4.4. Palladium(O) mediated cycloadditions of dimethyl bicyclo[3.1.0]hex-2-ene-7,7-dicarboxylate with a selection of imines

Based on our limited success with our [3.1.0]-bicyclic vinylcyclopropane with a selection of aldehydes. We thought an imine derived from ethyl glyoxolate (228) would be an ideal precursor. It was decided to utilise the imine derived from ethyl glyoxolate and p-anisidine that had previously been unsuccessful with the [4.1.0]-bicyclic vinylcyclopropane. Our reasoning followed that outlined with the [4.1.0]-moiety, we believed an imine with strong electron withdrawing groups adjacent to the carbon and an electron rich group attached to the nitrogen would be most likely to trap the π-allyl palladium(II) zwitterion and afford the desired bicyclic pyrrolidine. The PMB group also offered a site for potential functionalisation if it could be removed using CAN (Scheme 98).
Scheme 98: Palladium catalysed [3+2]-cycloaddition with 4-methoxybenzene ethylester imine.

It was disappointing to discover that the reaction was unsuccessful with recovery of the imine and a complex mixture. However we did manage to isolate a compound using the second conditions (Scheme 98) which we very tentatively assigned as the desired pyrrolidine.

However, we were unable to assign the stereochemistry with any degree of certainty using $^1\text{H}$, $^{13}\text{C}$, COSY and HMQC NMR analysis. Our only indication that it was the desired pyrrolidine was by mass spectrometry. To date we have been unable to repeat the reaction to isolate this compound.

If we assume from our previous success using ethyl glyoxolate (228) and 4-nitrobenzaldehyde (229) that the zwitterionic $\pi$-allyl species is formed, a plausible explanation could be that the 1,3-dipolar synthon forms but reacts to form other compounds which we have been unable to isolate. It maybe the imine moiety was too bulky or not electrophilic enough to participate in the nucleophilic addition of the zwitterionic $\pi$-allyl palladium(II) complex. We thought if we could increase the distance of the substituent attached to the nitrogen of the imine we may facilitate the desired reaction. We had already prepared a selection of N-benzyl imines whilst investigating analogous reactions with the [4.1.0]-bicyclic vinylcyclopropane (Chapter 3, Scheme 79, pg 94). We believed this CH$_2$ spacer group may relieve any
steric bulk experienced when using the PMB group which may have been preventing the reaction. It was also thought the benzyl group could be removed by hydrogenation or other reducing reactions. These imines were subjected to our general palladium(0) catalysed [3+2]-cycloaddition conditions; using a stoichiometric amount of cyclopropane and imine (Scheme 99).

![Scheme 99: Preparation of pyrrolidine scaffold from benzyl imines.](image)

The unsuccessful reactions saw the recovery of a significant amount of the corresponding imine although we were unable to recover the [3.1.0]-bicyclic vinylcyclopropane from the resulting complex mixture. It was pleasing to find the phenyl and 4-nitrophenyl benzyl imines cyclised under our general palladium(0) conditions. This was unexpected due to their lack of reactivity in the analogous reaction with the [4.1.0]-bicyclic vinylcyclopropanes. The cycloadditions were not as clean by NMR analysis as the reactions with the successful aldehydes. Although, it was particularly interesting to note the reaction also afforded a single isomer by spectroscopic analysis (Figure 18).
Analysis by $^1$H, $^{13}$C, COSY and HMQC NMR techniques as with the analogous cycloaddition with the successful aldehydes allowed us to tentatively assign the substituents around the bicyclic pyrrolidine. However, we were unable to confidently assign the stereochemistry around the phenyl or 4-nitrophenyl substituent and across the bridged 3a-CH and 6a-CH hydrogens. As with our previous successful [3.3.0]-bicyclic tetrahydrofurans nOe data indicated the hydrogen next to the phenyl and 4-nitrophenyl substituent was on the opposite face to the cis bridged 3a-CH and 6a-CH hydrogens. An analogous pattern to that of the [3.3.0]-bicyclic tetrahydrofuran was seen. An enhancement of the 4-C(H)H proton was observed upon irradiation of the 2-CH proton indicating it was on the opposite face to the bridged hydrogens. This was confirmed by an enhancement of the other 4-C(H)H with the cis 3a-CH proton (Figure 19).
Figure 19: nOe effects indicating the formation of trans [3.3.0]-benzyl derived bicyclic pyrrolidines.

It was very exciting to discover we had afforded the bicyclic pyrrolidines utilising our general palladium(0) catalysed conditions. We have already shown changing the palladium(0) source to Pd$_2$(dba)$_3$ increased the yield with the [3.3.0]-bicyclic tetrahydrofurans. We hoped we could emulate this success with the benzyl imines (Scheme 100).

Scheme 100: Preparation of [3.3.0]-bicyclic pyrrolidine scaffolds from benzyl imines.
To our delight we managed to isolate the two bicyclic pyrrolidines in slightly better yields. Spectroscopic analysis indicated they were identical to the pyrrolidines isolated with our first set of palladium(0) catalysed conditions. Although we have had little success using stoichiometric amounts of the cyclopropane and aldehydes with Pd(PPh₃)₄ (10 mol%) in MeOH, which had previously been successful when investigating the simple vinylcyclopropane analogues. We thought we would explore this route as it might show how robust the reaction conditions could be (Scheme 101).

Scheme 101: Preparation of [3.3.0]-bicyclic pyrrolidine scaffolds from benzyl imines.

It was unfortunate that these conditions have yet to afford the corresponding bicyclic scaffold with any of the electrophiles we have investigated thus far with the [3.1.0]-bicyclic vinylcyclopropane. We managed to isolate the imine starting material and a complex mixture which we were unable to purify.

With an upturn in fortunes we thought the key to the reactivity of these [3.1.0]-moieties maybe due to the CH₂ spacer group. We therefore decided to prepare a selection of tosyl imines. It was thought the slightly longer N-S bond of the tosyl imine may facilitate the reaction as well as provide a possible site for functionalisation. Unfortunately our efforts to prepare these imines using molecular sieves in Et₂O, proved fruitless. However, Chemla⁷² reported the condensation of the aldehyde, sulfonamides and arenesulfinic acid to the corresponding sulphonamide sulfone. Due to our previous success with aldehydes and benzyl imines we thought an
ethylester, phenyl and 4-nitrophenyl \( N \)-sulfonyl aldimines would give us the best chance of affording the corresponding bicyclic pyrrolidine (Scheme 102).

\[
\text{Scheme 102: Preparation of } N \text{-sulfonyl aldimines.}^{72}
\]

Unfortunately we only managed to furnish the \( N \)-sulfonyl aldimine derived from benzaldehyde (32%), recovering starting material in the unsuccessful reactions. We nevertheless attempted a palladium(0) catalysed [3+2]-cycloaddition using our three catalytic conditions with the phenyl derivative (Scheme 103).

\[
\text{Scheme 103: Preparation of pyrrolidine scaffold from } N \text{-benzylidene-benzenesulfonamide.}
\]

We were disheartened not to afford the corresponding bicyclic pyrrolidine, it may have been the sulfonyl moiety was too bulky for the reaction to proceed. Our attention turned towards work conducted with the [4.1.0]-bicyclic vinylcyclopropane. Due to
our success with benzyl substituted imines and the commercial availability of 2-bromobenzyl amine, we prepared a similar set of 2-bromobenzyl imines to those we have already eluded to whilst investigating the [4.1.0]-bicyclic vinylcyclopropane (Chapter 3, Scheme 82, pg 96). The substrates were screened due to our previous success with benzyl substituted imines under our palladium(0) catalysed methodology. If successful these bicyclic compounds could then potentially allow us to form the third ring and a fused tricyclic structure under Heck conditions. The cycloadditions were initially performed using our general palladium catalysed conditions; stoichiometric amounts of the cyclopropane and aldehyde, ZnBr₂ (2 equiv.), Pd(PPh₃)₄ (10 mol%) in THF at RT for 12h (Scheme 104).

Scheme 104: Preparation of bicyclic pyrrolidine scaffolds from 2-bromobenzyl imines

It was very disheartening not to afford even a trace of the desired bicyclic pyrrolidine. We decided to explore the conditions which had proved most successful with the benzyl imines, in the hope we might increase the scope of the trapping agents and the potency of the reactions (Scheme 105).
Scheme 105: Preparation of bicyclic pyrrolidine scaffolds from 2-bromobenzyl imines.

It was with great relief that we had managed to isolate a bicyclic pyrrolidine which had the potential to undergo a Heck cyclisation. As can be seen with the examples which afford the desired tetrahydrofurans and benzyl derived pyrrolidines, the characteristic 2-CH, 6a-CH, 5-CH and 6-CH were easily recognisable by $^1$H NMR analysis which corresponded to a successful [3+2]-cycloaddition (Figure 20).

Figure 20: $^1$H NMR of 1-(2-bromo-benzyl)-2R-(4-nitro-phenyl)-1,3aR,4,6aR-tetrahydro-2H-cyclopenta[b]pyrrole-3,3-dicarboxylic acid dimethyl ester.
Using analogous spectroscopic techniques that helped us assign the bicyclic tetrahydrofuran and benzyl derived pyrrolidines, we were able to ascertain the stereochemistry around this tetrahydrofuran was identical to that exhibited in our previous [3.3.0]-bicyclic examples (Figure 21).

![Diagram](image)

**Figure 21:** nOe effects indicating the formation of *trans* [3.3.0]-bromo-benzyl derived bicyclic pyrrolidines.

It was extremely encouraging to see that changing the catalyst did afford the desired bicyclic pyrrolidine. However, it was unfortunate that the success of the reaction was still limited to one substrate. It seemed at last we had make some progress. Our final attempt at synthesising these pyrrolidine scaffolds followed work outlined by Wyatt using stoichiometric amounts of the cyclopropane and aldehydes with Pd(PPh₃)₄ (10 mol%) in MeOH which had afforded the desired tetrahydrofurans when investigating the simple vinylcyclopropane analogues (Chapter 3, Table 13, pg 76). We hoped that these conditions may help our cause (Scheme 106).
Scheme 106: Preparation of bicyclic pyrrolidine scaffolds from 2-bromobenzyl imines.

It was not unexpected that these conditions failed to afford the corresponding bicyclic scaffold as this approach has proved unproductive with any of the electrophiles we have investigated thus far with the [3.1.0]-bicyclic vinylcyclopropane. We did however see the presence of the imine starting material and a complex mixture.

4.5. Palladium(0) mediated cycloadditions of bicyclo[3.1.0]hex-2-ene-7-carboxylic acid ethyl ester

During our exploration into the preparation of bicyclic cyclopropane we also synthesised the equivalent [3.1.0]-singularly activated vinylcyclopropane (222). We were not sure whether the cyclopropane would be sufficiently activated to ring open or whether the single electron withdrawing ethyl ester would stabilise the resulting malonic zwitterionic charge under our palladium(0) catalysed conditions to undergo a [3+2]-cycloaddition. We decided to briefly investigate whether this moiety would undergo the desired cycloaddition with our most successful trapping agent in the analogous reaction with the [3.1.0]-doubly activated vinylcyclopropane and ethyl glyoxolate (Scheme 107).
Scheme 107: Preparation of a bicyclic tetrahydrofuran scaffold from ethyl glyoxolate.

The reactions proved fruitless with recovery of the starting materials. It maybe reasoned that the mono-substituted cyclopropane was not sufficiently activated to facilitate ring opening under these palladium(0) catalysed conditions and may require activation by two electron withdrawing groups to undergo a [3+2]-cycloaddition reaction.

4.6. Proposed mechanism of bicyclic tetrahydrofuran ring formation

Through the extensive work within the group it has been proposed that Lewis acids, solvents and temperature all contribute to the eventual yield and stereochemical outcome of the reaction. This indicates the diastereoselectivity is reliant on the precise coordination of the zwitterion, electrophile, Lewis acid and catalyst. It can therefore be rationalised that in Lewis acid promoted cycloadditions, there is activation and coordination between the metal ion and carbonyl groups of the electrophile and the π–allyl palladium complex. In non-polar solvents it may be assumed an additional tighter coordination between the Lewis acid and palladium metal is present in order to minimise charge distribution to form the lowest energy conformer (Scheme 108).
Unlike the vinylcyclopropanes where we see a mixture of diastereoisomers, the vinyl substituent is conformationally locked within the bicyclic system. For this reason the ring opening of the cyclopropane may only afford a single isomer as there is no rotation of the vinyl group. It was interesting to note we didn’t see any isomerism around the 2C portion of the bicycle which suggests a set orientation upon generating the zwitterion or the second transient zwitterion species. With this in mind we can propose an appropriate general palladium catalysed [3+2]-reaction mechanism with the [3.1.0]-bicyclic vinylcyclopropane (Scheme 109).

Scheme 109: A general [3+2]-cycloaddition route to the [3.3.0]-bicyclic system.

This mechanism has been tentatively proposed based on initial experimental observations. Further work continues in order to fully establish the precise nature and sequence of events that take place.
If we look at the bicyclic cyclopropanes as a whole, it is possible to propose a general mechanism based on varying ring size with our successful palladium(0) [3+2]-cycloadditions when using ethyl glyoxolate (228) as a trapping agent (Scheme 110).

Based on nOe evidence with the successful [3+2]-cycloaddition reactions of the [3.1.0]-bicyclic cyclopropane, we believe the larger [4.1.0] and [5.1.0]-tetrahydrofuran skeletons also exhibit identical stereochemistry. This places the proton next to the ethyl ester substituent on the opposite face to the bridged cis protons. Our results also indicate that the yield of the reaction decreases with increasing ring size. Based on these findings we would speculate an analogous reaction with larger bicyclic cyclopropanes than those we have reported would not afford the desired tetrahydrofuran.
4.7. Conclusion

In this chapter we have delved deeper into the development of a general method to construct novel highly functionalised bicyclic ring systems (Table 21).

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="274a.png" alt="Image" /></td>
<td>82(\text{a})</td>
</tr>
<tr>
<td><img src="275a.png" alt="Image" /></td>
<td>18(\text{a})</td>
</tr>
<tr>
<td><img src="283a.png" alt="Image" /></td>
<td>9(\text{a, b}), 16(\text{b})</td>
</tr>
<tr>
<td><img src="284a.png" alt="Image" /></td>
<td>15(\text{a, b}), 63(\text{b})</td>
</tr>
<tr>
<td><img src="286a.png" alt="Image" /></td>
<td>49(\text{b})</td>
</tr>
</tbody>
</table>

\(\text{a} \) Pd\((\text{PPh}_3)_4\) (10 mol%), ZnBr\(_2\) (2 equiv.), THF, 12h, RT; \(\text{b} \) Pd\(_2\)(dba)\(_3\) (10 mol%), ZnBr\(_2\) (2 equiv.), CH\(_2\)Cl\(_2\), 12h, RT.

Table 21: [3.3.0]-heterocyclic scaffolds.
Our exploration into this area has discovered a small selection of [3.3.0]-bicyclic skeletons. After initial success using aldehydes we were disillusioned to discover the scope of the desired imine trapping agents was low at best. Characterisation proved particularly successful even with low amounts of the desired compounds. Thus far the stereochemistry of all the cycloadditions has been identical with the hydrogen next to the R substituent on the opposite endo-face to the bridged hydrogens of the ring junction.

We are uncertain why ethyl glyoxolate (228) was such an efficient trapping agent and we have not had the same level of success with other trapping agents. One train of thought was that the ring opening maybe happening very fast and it maybe in part due to the small nature and reactivity of ethyl glyoxolate that the reaction is so successful. The other trapping agents cannot adopt the correct orientation to undergo the [3+2]-cycloaddition and instead of trapping our desired substrate the cyclopropane underwent other undetermined reactions. It is possible that the CH2 link in the imines plays an important steric effect, this does bare further research as well as the observed increase in productivity when changing the palladium(0) catalyst.

There are many variables which have yet to be explored. Further investigation of the reaction parameters may induce further stereochemical preferences. Areas of interest include variation of palladium(0) reagent, solvents, Lewis acid and temperature. Our main priority remains to optimise our general conditions.

We have managed to isolate a [3.3.0]-pyrrolidine which we believed would be a suitable precursor to undergo a Heck cyclisation. It was thought it wise to investigate Heck conditions on a selection of model precursors prepared from the simpler vinylcyclopropane (155) in the hope of optimising a set of conditions that would readily afford the desired fused tricyclic skeleton from our [3.3.0]-bicyclic pyrrolidine moiety.
Chapter 5 - Heck mediated coupling

5.1.i. The Heck reaction

The Heck reaction typically couples an alkene with a halide or a triflate to form a new alkene. The \( R^1 \) group in \( R^1X \) can be aryl or vinyl, and the \( X \) group can be a halide (Br or I) or triflate (\( \text{OSO}_2\text{CF}_3 \)). The alkene can be mono- or disubstituted and can be electron-rich, -poor, or -neutral. A mild base; \( \text{Et}_3\text{N}, \text{NaOAc} \) or aqueous \( \text{Na}_2\text{CO}_3 \) is commonly used in this very accommodating reaction (Scheme 111).

\[
\begin{array}{c}
\text{R}^1\text{X} + \text{H} = \text{R}\text{R'} \xrightarrow{\text{Pd(0) cat. Base}} \text{R}^1\text{R'} + \text{H} = \text{X}
\end{array}
\]

**Scheme 111**: General depiction of the Heck reaction.

The palladium catalysed addition of aryl, vinyl or substituted vinyl groups to organic halides or triflates is one of the most synthetically useful palladium catalysed reactions. The mechanism involves the oxidative addition into the halide bond, addition to the olefin and elimination of the product by a \( \beta \)-hydride elimination process. A base then regenerates the palladium(0) catalyst. The whole process is catalytic in palladium (Scheme 112).

**Scheme 112**: The Heck reaction.
The reaction tolerates a variety of functional groups, and works well with both electron-withdrawing and electron-donating groups on either substrate. We hoped we would be able to construct a selection of heterocyclic Heck precursors using our palladium(0) catalysed methodology with the simpler vinylcyclopropane (155). This would enable us to investigate the conditions required to facilitate a Heck mediated cyclisation as we hoped to establish a general method which we could try with our [3.3.0]-bicyclic pyrrolidine scaffold.

5.1.ii. Synthesis of vinyl cyclopropane

Work within the group has shown the versatility of vinylcyclopropane (155) towards our [3+2]-cycloaddition methodology. It has been reacted with an extensive range of electrophiles to afford a variety of heterocycles.\(^{45,47,48}\) It was prepared by a double displacement of a disubstituted but-2-ene precursor with an activated methylene component on a reasonably large scale (10g) in a repeatable yield (71%) (Scheme 113).

![Scheme 113: Synthesis of vinylcyclopropane.\(^{45}\)](image)

5.1.iii. Proposed route to bicyclic pyrrolidines and tetrahydrofuran using an intramolecular Heck cyclisation

We have already eluded to work within the group with this vinylcyclopropane involving an array of aldehydes, ketones and imines.\(^{45,47,48}\) The results have allowed us to formulate a general palladium(0) [3+2]-catalysed methodology towards the construction of tetrahydrofuran and pyrrolidine skeletons (Scheme 114).
Using the knowledge from these reactions it was hoped we would be able to construct heterocyclic analogues which could undergo a Heck cyclisation to form the corresponding heterocyclic scaffolds. It was believed we would be able to prepare a selection of cis tetrahydrofuran and pyrrolidine skeletons which may undergo this type of reaction (Scheme 115).

Scheme 114: Preparation of heterocyclic scaffolds.\(^{45,47,48}\)

Scheme 115: General preparation of bicyclic tetrahydrofuran and pyrrolidine scaffolds.

Preparation of these novel tetrahydrofurans and pyrrolidines would allow us to see whether an intramolecular Heck reaction would be possible. Further functionalisation may lead to compounds which are synthetically and biologically interesting. Work within this area would provide valuable information towards a Heck cyclisation with our [3.3.0]-bicyclic 2-bromobenzyl pyrrolidine, which we had prepared in Chapter 4, to form a fused tricyclic skeleton. It would also indicate whether this route would
prove feasible, if at a later date it was possible to prepare an appropriate [4.3.0]-bicyclic pyrrolidine. A successful Heck reaction would in turn afford a tricyclic skeleton resembling the tricyclic core within the *Stemona* alkaloids (Chapter 1, Scheme 36, pg 44).

5.2. Palladium(0) mediated cycloadditions of vinylcyclopropane with phenyl isocyanate

Initial work in this area developed by Tsuji set a precedent for these types of palladium(0) catalysed reactions, with what we believe to be the only reported examples of a [3+2]-cycloaddition involving activated vinylcyclopropanes and an isocyanate (Chapter 3, Scheme 64, pg 74). We thought by utilising the methodology developed within our group we maybe able to repeat Tsuji's work.\(^{43}\) Therefore, making it an extremely attractive synthesis with the potential for further functionalisation under our facile palladium(0) catalysed conditions; stoichiometric amounts of the cyclopropane and aldehyde, ZnBr\(_2\) (2 equiv.), Pd(PPh\(_3\))\(_4\) (10 mol\%) in THF at RT for 12h (Table 22).

![Reaction scheme](image)

<table>
<thead>
<tr>
<th>Pd(0) cat.</th>
<th>Lewis Acid</th>
<th>Yield / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pd(PPh(_3))(_4)</td>
<td>ZnBr(_2)</td>
<td>S.M.</td>
</tr>
<tr>
<td>Pd(PPh(_3))(_4)</td>
<td>-</td>
<td>S.M.</td>
</tr>
<tr>
<td>Pd(_2)(dba)(_3)</td>
<td>ZnBr(_2)</td>
<td>S.M.</td>
</tr>
<tr>
<td>Pd(_2)(dba)(_3)</td>
<td>-</td>
<td>S.M.</td>
</tr>
</tbody>
</table>

**Table 22:** Preparation of a pyrrolidine scaffold using an isocyanate trapping agent

Unfortunately, our attempt to prepare a similar heterocycle was unsuccessful. We had hoped due to our success with a multitude of aldehydes, ketones and imines that this
would be a relatively straightforward reaction. Unfortunately this didn’t seem to be the case. Work within this area postulated that the Lewis acid may sometimes hinder this type of reaction.\textsuperscript{47} However, although this is substrate dependant it didn’t appear to have any profitable effect in this reaction. After this brief fruitless intersection we moved quickly towards preparing a variety of heterocycles which had the potential to undergo an intramolecular Heck reaction.

5.3. Palladium(0) mediated cycloadditions of vinylcyclopropane with a range of 2-bromo substituted aldehydes

Our experience with vinylcyclopropanes had revealed aldehydes faired successfully as trapping agents.\textsuperscript{45,47} It was here we began our investigation into plausible precursors which after formation of the subsequent tetrahydrofuran would have the potential to undergo intermolecular Heck cyclisations.

Exploration into this area began with an aromatic halide, 2-bromobenzaldehyde. It was cheap and commercially available. We had already attempted a [3+2]-cycloaddition with the [3.1.0]-bicyclic vinylcyclopropane without success. However, our test reactions, whilst investigating the bicyclic cyclopropanes indicated that the simpler vinylcyclopropane (155) may be more susceptible to a wider range of trapping agents. Work with benzaldehyde and 4-nitrobenzaldehyde had shown simple aromatic aldehydes to be particularly successful.\textsuperscript{45,47} A small study was undertaken to find the optimum conditions for the yield and diastereoselectivity of this reaction (Table 23).
Pd(0) cat. | Lewis Acid | Solvent | Yield /% | Diastereomeric Ratio*<br>Trans:Cis
---|---|---|---|---
Pd(PPh₃)₄ | ZnBr₂ | THF | S.M. | - -
Pd(PPh₃)₄ | ZnBr₂ | CH₂Cl₂ | S.M. | - -
Pd(PPh₃)₄ | - | THF | S.M. | - -
Pd₂(dba)₃ | ZnBr₂ | THF | S.M. | - -
Pd₂(dba)₃ | ZnBr₂ | CH₂Cl₂ | S.M. | - -
Pd₂(dba)₃ | - | THF | S.M. | - -
- | ZnBr₂ | CH₂Cl₂ | 5 | 3 2

* Diastereomeric ratio based on ¹H NMR peak integrations.

Table 23: Palladium(0) mediated cycloaddition with 2-bromobenzaldehyde.

It was very disheartening that our general palladium(0) catalysed conditions using Pd(PPh₃)₄, and the conditions utilising Pd₂(dba)₃ that had been successful with our bicyclic cyclopropanes, appeared ineffective. Undeterred, we turned towards a set of conditions that had proved unexpectedly successful whilst investigating benzaldehyde as a trapping agent. Work in this area highlighted the unlikely use of MeOH as a solvent which afforded interesting results.⁴⁷ We had found benzaldehyde to be slightly temperamental with our general conditions and it was thought we would test the effectiveness of these conditions using 4-nitrobenzaldehyde which had proved an exceptional trapping agent forming the desired tetrahydrofuran in a very reasonable yield (86%) under our general Pd(PPh₃)₄ conditions (Scheme 116).
Scheme 116: Palladium(0) catalysed [3+2]-cycloaddition of 4-nitrobenzaldehyde in MeOH.

The reaction proceeded efficiently, with the diastereoselectivity shifting slightly towards the trans isomer (3:2) unlike the analogous reaction with our general Pd(PPh₃)₄ conditions, which favoured the cis isomer (1:1.7) although there was a slight decrease in yield (86 to 80%). We therefore hoped for a successful reaction with 2-bromobenzaldehyde under analogous conditions (Table 24).

Table 24: Palladium(0) mediated cycloaddition with 2-bromobenzaldehyde.
Finally, we had afforded the desired heterocycle in an excellent yield (96%), although it was a little disappointing that we were unable to separate the isomers by column chromatography. We hoped this would not prove to be too problematic and the desired Heck reaction would proceed in the presence of the trans isomer, which might be separated from the bicyclic tetrahydrofuran by column chromatography. We were intrigued to see whether the reaction would afford the desired tetrahydrofuran with another alcohol. We repeated the reaction using Pd(PPh₃)₄ in EtOH and found the reaction was successful (36%) although it was not as clean as with MeOH with a slight shift in diastereoselectivity (trans:cis, 1:1.3).

It was interesting to discover that the reaction proceeded efficiently in MeOH as it was expected a SN₂' addition of MeOH to the vinylcyclopropane might occur. The final result in the table showed that this was the case in the absence of the aldehyde. If we reacted the vinylcyclopropane and palladium(0) catalyst in MeOH we afforded the corresponding SN₂' product (Scheme 117).

\[
\begin{array}{c}
\text{CO}_2\text{Me} \\
\text{CO}_2\text{Me}
\end{array}
\overset{\text{Pd(PPh}₃\text{)}₄, \text{MeOH, RT, 12h, (99\%)}\text{}}{\longrightarrow}
\begin{array}{c}
\text{MeO} \\
\text{MeO}
\end{array}
\]

Scheme 117: Addition of MeOH to vinylcyclopropane.

This seemed to indicate that the trapping of the substrate proceeds quicker than the addition of the MeOH. Therefore, it maybe reasoned the addition of the trapping agent to the vinylcyclopropane is sufficiently fast as to negate the competing nucleophilic addition of the MeOH and the formation of the undesired SN₂' product.

We had successfully isolated our first tetrahydrofuran which we believed was an ideal precursor to undergo an intra-molecular Heck cyclisation. Albeit, with a lot more effort than anticipated.

We had also highlighted two further aldehydes which we thought may undergo our desired Heck cyclisation. The first was a tri-methoxy bromo-substituted aldehyde which had been prepared in our group by Wyatt whilst looking to synthesise
monocerin (164) (Chapter 1, Scheme 29, pg 39). We set about preparing the aldehyde in analogous fashion by brominating the corresponding tri-methoxy aldehyde (171) (Scheme 118).47

![Scheme 118: Preparation of 2-bromo-3,4,5-trimethoxy-benzaldehyde.47](image)

Wyatt had shown this aldehyde to afford the desired tetrahydrofuran with a substituted vinylecyclopropane. We therefore briefly explored the reaction conditions as we wished to afford, if possible, predominantly the cis tetrahydrofuran. This was the desired stereochemistry for the substrate to undergo a Heck cyclisation (Table 25).
The final aldehyde we thought would undergo a palladium(0) catalysed [3+2]-cycloaddition was the commercially available α-bromocinnamaldehyde (291). We investigated the preparation of the desired tetrahydrofuran skeleton initially with the conditions we had found to be successful thus far with this type of reaction, as well as using Pd(PPh₃)₄ in MeOH (Table 26).
Table 26: Palladium(O) mediated cycloadditions with α-bromocinnamaldehyde.

The results indicated how the catalytic conditions effect the reaction, most interestingly the variation in diastereoselectivity. It was also a little bewildering to isolate starting material when using MeOH as a solvent. We thought we may have afforded the SN2' product, as seen when we reacted just the palladium(O) catalyst and vinylcyclopropane in MeOH in the absence of the trapping agent (Scheme 117, pg 139).

It was pleasing to obtain the desired tetrahydrofuran in a reasonable yield (86%). More importantly we were able to separate the two isomers by column chromatography with the higher yielding reactions. It was hoped the isolation of the cis isomer would increase the likelihood of a successful Heck cyclisation negating the possibility of unwanted side reactions with the corresponding trans isomer.

We were intrigued to see if the reaction with Pd(PPh3)4 and MeOH would proceed more efficiently under reflux. We hoped to lower the reaction duration and increase the yield (Scheme 119).
Scheme 119: Palladium(0) [3+2]-cycloadditions with α-bromocinnamaldehyde.

The reaction proceeded smoothly in a reasonable yield, which enables us to separate the isomers by column chromatography. We had thought the S_N2' product observed when we tried the reaction without the presence of the trapping agent, may have been more predominant at elevated temperature. This was not the case and we can only reason that the rate of the [3+2]-cycloaddition must be faster than the corresponding S_N2' addition of MeOH to the vinylcyclopropane.

Although we had prepared three tetrahydrofuran scaffolds, which we believed had the potential to undergo a Heck cyclisation, we also wished to prepare a selection of pyrrolidine scaffolds with the appropriate 2-bromobenzyl functionality. It was hoped they would give us an indication of the potential reactivity of our [3.3.0]-bicyclic pyrrolidine.

5.4. Palladium(0) mediated cycloadditions of vinylcyclopropane with a range of 2-bromobenzyl substituted imines

During our investigation into the palladium(0) catalysed [3+2]-cycloadditions with [4.1.0] and [3.1.0]-bicyclic vinylcyclopropanes, we had prepared a selection of 2-bromobenzyl imines (Chapter 3, Scheme 79, pg 94). They had been successfully cyclised as test reactions under our general palladium(0) conditions with the simpler vinylcyclopropane analogue (155), to afford a selection of pyrrolidine scaffolds which incorporated a halide substituent similar to that of our [3.3.0]-bicyclic pyrrolidine (Chapter 4, Scheme 105, pg 124). We believed these would act as ideal model substrates helping us gain knowledge into intra-molecular Heck conditions. It was
thought this insight could be used in conjunction with the [3.3.0]-bicyclic pyrrolidine
Heck precursor to successfully afford a fused tricyclic skeleton.

It was believed further study into these original test reactions would help optimise the
yields and diastereoselectivity to help us selectively isolate the cis or trans pyrrolidine
skeleton for the Heck cyclisation. The first 2-bromobenzyl imine selected was the
very first imine we prepared whilst investigating the [4.1.0]-bicyclic vinylcyclopropane, incorporating a phenyl substituent adjacent to the carbon of the
imine. We subjected the imine to the three palladium(0) catalysed conditions that had
previously been investigated with the [3+2]-cycloaddition reactions of the [3.1.0] and
[4.1.0]-bicyclic cyclopropanes in the hope of isolating one of the pyrrolidine isomers
in a reasonable yield (Table 27).

![Diagram](image)

**Table 27: Palladium(0) [3+2]-cycloaddition with benzylidene-(2-bromobenzyl)-
amine.**

The three sets of palladium catalysed conditions afforded the desired pyrrolidine with
the cis stereochemistry albeit in varying yields. The optimum yield was achieved
using our general palladium conditions (82%), but it served as an example of how the reaction conditions could affect the overall yield. Due to our experience with these types of reactions within the group we had expected a mixture of diastereoisomers, however we were very pleased to exclusively afford the \textit{cis} isomer (Figure 22).

The next 2-bromobenzyl imine selected incorporated a 4-nitrophenyl substituent adjacent to the carbon of the imine, and was the only imine that successfully underwent a \([3+2]\)-cycloaddition with the \([3.1.0]\)-bicyclic vinylcyclopropane. We subjected the imine to the three palladium(0) catalysed conditions that had been investigated with the first imine. This would serve as a comparison, to see if the palladium(0) catalysed conditions indicated there was a general trend in respect to the yield and diastereoselectivity or whether it was substrate dependent (Table 28).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure22}
\caption{\(^1\)H NMR of 1-(2-bromo-benzyl)-2-phenyl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester.}
\end{figure}
We managed to isolate the desired pyrrolidine in a reasonable yield (71%) using our general palladium(0) catalysed conditions and purification by column chromatography led to the separation the *trans* isomer. The imine in this [3+2]-cycloaddition seemed particularly prone to hydrolysis, as we also afforded the tetrahydrofuran corresponding to a [3+2]-cycloaddition with 4-nitrobenzaldehyde under our general palladium catalysed conditions (10%). It was therefore not unexpected to afford the undesired tetrahydrofuran under the protic, MeOH conditions. The results indicated these types of reactions had certain limitations with respect to yield and diastereoselectivity, which appeared to be substrate specific.

An imine with a hetero-aromatic substituent adjacent to the carbon, was thought would be particularly useful whilst investigating the bicyclic vinylcyclopropanes with these 2-bromobenzyl imines. The hetero-aromatic offered a site for potential functionalisation should it be possible to conveniently convert it to the corresponding carboxylic acid. These advantages were also inherent with the analogous reaction of

---

<table>
<thead>
<tr>
<th>Pd(0) cat.</th>
<th>Lewis Acid</th>
<th>Solvent</th>
<th>Yield/%</th>
<th>Diastereomeric Ratio*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pd(PPh₃)₄</td>
<td>ZnBr₂</td>
<td>THF</td>
<td>71</td>
<td>1.1 Trans:Cis 1</td>
</tr>
<tr>
<td>Pd₂(dbah)</td>
<td>ZnBr₂</td>
<td>CH₂Cl₂</td>
<td>6</td>
<td>1.1 Trans:Cis 1</td>
</tr>
<tr>
<td>Pd(PPh₃)₄</td>
<td>-</td>
<td>MeOH</td>
<td>48b</td>
<td>3b Trans:Cis 2b</td>
</tr>
</tbody>
</table>

* Diastereomeric ratio based on $^1$H NMR peak integrations. b Yield of tetrahydrofuran corresponding to a [3+2]-cycloaddition with 4-nitrobenzaldehyde. Diastereoisomers were not separated unless stated.

**Table 28:** Palladium(0) [3+2]-cycloaddition with (2-bromobenzyl)-(4-nitrobenzylidene)-amine.
the simpler vinylcyclopropane (155). We investigated our three palladium(0) conditions as with the previous two substituted 2-bromobenzyl imines that had provided such an interesting selection of results (Table 29).

![Chemical Structures](image)

**Table 29: Palladium(0) [3+2]-cycloaddition with (2-bromobenzyl)-furan-2-ylmethylene-amine.**

<table>
<thead>
<tr>
<th>Pd(0) cat.</th>
<th>Lewis Acid</th>
<th>Solvent</th>
<th>Yield/%</th>
<th>Diastereomeric Ratio* Trans:Cis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pd(PPh₃)₄</td>
<td>ZnBr₂</td>
<td>THF</td>
<td>38</td>
<td>1:1</td>
</tr>
<tr>
<td>Pd₂(dba)₃</td>
<td>ZnBr₂</td>
<td>CH₂Cl₂</td>
<td>40</td>
<td>1:3.8</td>
</tr>
<tr>
<td>Pd(PPh₃)₄</td>
<td>-</td>
<td>MeOH</td>
<td>26</td>
<td>1:1</td>
</tr>
</tbody>
</table>

* Diastereomeric ratio based on ¹H NMR peak integrations. Diastereoisomers were not separated unless stated.

The palladium(0) catalysed conditions afforded the desired pyrrolidine albeit in relatively low yields. Again the palladium(0) conditions using MeOH appeared to induce hydrolysis of the imine. It initially appeared we had isolated the tetrahydrofuran corresponding to the [3+2]-cycloaddition with 2-furanaldehyde but on closer inspection this was not the case. Comparison of an earlier test reaction with 2-furanaldehyde (Chapter 3, Table 14, pg 82) uncovered we had managed to isolate an unknown compound which exhibited similar characteristic features as the proposed tetrahydrofuran skeleton. We have as yet been unable to determine its structure. Column chromatography failed to separate the diastereomers, although we felt the diastereoselectivity sufficiently favoured the cis isomer when the reaction was performed in conjunction with Pd₂(dba)₃ to test under Heck conditions. It was hoped
if the cyclisation afforded the tricyclic structures of both the pyrrolidine diastereomers we maybe able to separate them by column chromatography.

Our final imine selected to undergo our three palladium(0) catalysed conditions furnished a 4-methoxybenzyl substituent adjacent to the carbon. It was felt that an electron rich group would show the range of imines that could potentially undergo this type of palladium(0) catalysed [3+2]-cycloaddition chemistry (Table 30).

![Reaction Scheme](image)

<table>
<thead>
<tr>
<th>Pd(0) cat.</th>
<th>Lewis Acid</th>
<th>Solvent</th>
<th>Yield/%</th>
<th>Diastereomeric Ratio$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pd(PPh$_3$)$_4$</td>
<td>ZnBr$_2$</td>
<td>THF</td>
<td>41</td>
<td>0:1</td>
</tr>
<tr>
<td>Pd$_2$(dba)$_3$</td>
<td>ZnBr$_2$</td>
<td>CH$_2$Cl$_2$</td>
<td>49</td>
<td>0:1</td>
</tr>
<tr>
<td>Pd(PPh$_3$)$_4$</td>
<td>-</td>
<td>MeOH</td>
<td>61</td>
<td>1.2:1</td>
</tr>
</tbody>
</table>

$^a$ Diastereomeric ratio based on $^1$H NMR peak integrations. Diastereoisomers were not separated unless stated.

**Table 30**: Palladium(0) [3+2]-cycloaddition with (2-bromobenzyl)- (4-methoxybenzylidene)-amine.

It was very encouraging to afford the desired pyrrolidine. We felt this showed the scope of the substituents that could be incorporated with these types of imines. The diastereoselectivity of the reaction appeared dependant on the reaction conditions, and we observed a complete change in preference from almost exclusively cis using our general palladium(0) conditions, to predominantly trans isomer when using MeOH.
Our investigation into the preparation of a selection of Heck precursors proved successful, although we have shown conditions appear to have a certain amount of substrate specificity with respect to yield and diastereoselectivity. We had in hand a range of tetrahydrofuran and pyrrolidine skeletons which we believed would undergo a Heck cyclisation to afford the corresponding bicyclic heterocycles.

5.5. Intramolecular Heck cyclisations with tetrahydrofurans

The intramolecular Heck reaction has been widely used for the synthesis of cyclic ring systems. We hoped the intramolecular Heck cyclisation of our model tetrahydrofuran and pyrrolidine components would prove equally successful forming a variety of functionalised bicyclic compounds and in the case of the [3.3.0]-bicyclic pyrrolidine a tricyclic skeleton. We believed this methodology could be further developed in future, ideally, to construct the tricyclic core within the *Stemona* alkaloids providing a suitable [4.3.0]-bicyclic pyrrolidine could be prepared.

Our initial attempts within this area began with our tetrahydrofuran precursors. Conditions for Heck cyclisations between aryl halide and an alkene have been well documented in the literature. Although the synthetic potential of this transformation was largely unappreciated for a number of years, the application of this powerful reaction in natural product synthesis has flourished recently. A variety of palladium(0) complexes serve as effective precatalysts, or precursors to the active palladium(0) catalyst. The most common used in Heck chemistry are Pd(OAc)$_2$ and Pd$_2$(dba)$_3$, both are air stable and commercially available. Typical catalyst loading range from 5-10 mol% palladium employing phosphine ligands. A base is required in Heck reactions to neutralise the acid (HX) that is produced when the hydridopalladium(II) species is reduced to regenerate the active palladium(0) catalyst. A stoichiometric amount of base is needed but in practice 3-5 molar equivalents or an excess are often used. A variety of inorganic bases have been used in Heck reactions, with K$_2$CO$_3$, NaOAc and CaCO$_3$ reported most frequently. Tertiary amine bases such as Et$_3$N, t-Pr$_2$NEt are also commonly employed. Solvent such as CH$_3$CN, THF and DMF are typically used although in some cases an excess of base is used instead of a solvent. The choice of ligand can also enhance the reactivity of the catalyst. Phosphine ligands are most commonly used in this type of reaction.
study in this area employed the α-bromocinnamaldehyde derived tetrahydrofuran where we had successfully isolated the cis isomer (Table 31).

![Chemical structure](image)

(291b) Cis Isomer

<table>
<thead>
<tr>
<th>Pd(0) cat.</th>
<th>Ligand</th>
<th>Base</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pd(OAc)₂</td>
<td>PPh₃</td>
<td>Et₃N</td>
<td>8</td>
</tr>
<tr>
<td>Pd(OAc)₂</td>
<td>P(o-Tol)₃</td>
<td>Et₃N</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>Pd(OAc)₂</td>
<td>P(p-Tol)₃</td>
<td>Et₃N</td>
<td>Complex mixture</td>
</tr>
</tbody>
</table>

Table 31: Preparation of bicyclic tetrahydrofurans.

To our delight we managed to isolate the desired bicyclic tetrahydrofuran (8%) under our Pd(OAc)₂, PPh₃ conditions. We had thought changing the phosphine ligand may increase the reactivity of the palladium complex. This was not the case and we recovered an undetermined complex mixture.

We hoped we would achieve similar success with the other two 2-bromophenyl tetrahydrofuran precursors. These two substrates would allow us to compare the susceptibility of a 2-bromophenyl ring and a tri-substituted 2-bromophenyl ring to react under our successful Heck conditions (Table 32).
We were unable to isolate any of the desired bicyclic tetrahydrofuran scaffolds, failing to observe peaks of any real significance by $^1$H NMR. It may be reasoned that the presence of the \textit{trans} isomer or steric hindrance may have effected the success of the reaction. We therefore tried varying the conditions of the Heck reaction. This proved fruitless as we failed to isolate even the starting material. Due to the lack of success we left our preliminary studies into these bicyclic tetrahydrofuran scaffolds and turned our attention towards our 2-bromobenzyl pyrrolidine substrates which we hoped would prove to be far more successful.

5.6. Intramolecular Heck cyclisations with pyrrolidines

The successful isolation of the bicyclic tetrahydrofuran scaffold with the \textit{cis} $\alpha$-bromocinnamaldehyde derived tetrahydrofuran led us to believe it would be possible to afford an assortment of bicyclic pyrrolidines with our selection of novel 2-bromobenzyl pyrrolidine scaffolds. Our train of thought followed that outlined with our successful Heck conditions. It was thought the CH$_2$ spacer group between the nitrogen and the 2-bromophenyl substituent may reduce any potential steric hindrance associated with the tetrahydrofuran reaction. We selected the pyrrolidine scaffold with

<table>
<thead>
<tr>
<th>R</th>
<th>Pd((0)) cat.</th>
<th>Ligand</th>
<th>Base</th>
<th>Solvent</th>
<th>Yield/(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Pd((\text{OAc})_2)</td>
<td>PPh$_3$</td>
<td>Et$_3$N</td>
<td>-</td>
<td>N.R.</td>
</tr>
<tr>
<td>OMe</td>
<td>Pd((\text{OAc})_2)</td>
<td>PPh$_3$</td>
<td>Et$_3$N</td>
<td>-</td>
<td>N.R.</td>
</tr>
<tr>
<td>H</td>
<td>Pd((\text{OAc})_2)</td>
<td>PPh$_3$</td>
<td>i-Pr$_2$NEt</td>
<td>DMF</td>
<td>N.R.</td>
</tr>
<tr>
<td>H</td>
<td>Pd((\text{OAc})_2)</td>
<td>PPh$_3$</td>
<td>NaOAc</td>
<td>CH$_3$CN</td>
<td>N.R.</td>
</tr>
</tbody>
</table>

Table 32: Preparation of bicyclic tetrahydrofurans.
a phenyl group at the 2-position as we were able to isolate the cis isomer. We hoped this substrate would undergo a successful Heck reaction as with the cis α-bromocinnamaldehyde derived tetrahydrofuran (Table 33).

We were delighted to isolate the bicyclic scaffold with the Heck conditions. The \(^1\)H NMR spectra clearly showed the characteristic alkene CH\(_2\) and the 2-CH proton next to the phenyl substituent (Figure 23).

Table 33: Preparation of bicyclic tetrahydrofurans.
Figure 23: $^1$H NMR of 10-methylene-3-phenyl-1,5,10,10a-tetrahydro-pyrrolo[1,2-b]isoquinoline-2,2-dicarboxylic acid dimethyl ester.

The stereochemistry was confirmed by nOe analysis which indicated the 2-CH proton next to the phenyl substituent was on the same face as the 5-CH proton. This was expected due to the stereochemical preference of the Heck cyclisation and the cis isomer of the pyrrolidine (Figure 24).

Figure 24: nOe effects indicating the formation of 10-methylene-3-phenyl-1,5,10,10a-tetrahydro-pyrrolo[1,2-b]isoquinoline-2,2-dicarboxylic acid dimethyl ester.
We felt further work in this area utilising different conditions could significantly improve the yield. However, we had highlighted conditions that afforded the desired bicyclic skeletons. It was believed we could prepare a range of bicyclic scaffolds utilising these conditions using our other 2-bromobenzyl substituted pyrrolidines. Unfortunately as we were only able to isolate the selective diastereomers in small amounts the reactions were carried out on a small scale (Table 34).

![Chemical structure](image)

Table 34: Preparation of bicyclic pyrrolidines.

We had mixed success with the 2-bromobenzyl substituted pyrrolidines. It has been possible to isolate the desired bicyclic skeleton with all but the 2-furyl derived 2-
bromobenzyl pyrrolidine. Using the knowledge gained from the 2-bromobenzyl pyrrolidine phenyl derivative, we were able to quickly identify the successful cyclisation with the appearance of the characteristic alkene CH\(_2\) and the 2-CH proton. Although it was only possible to tentatively assign the data, as we only obtained small amounts of the desired compound, in part due to the small scale and low yields. However, we had shown that this selection of substituted 2-bromobenzyl pyrrolidine scaffolds underwent our desired Heck cyclisation. Due to time constraints we have yet to fully explore this area and it was thought repeating these reactions on a larger scale would aid characterisation. They did serve as a good initial indication to the success of the Heck cyclisation with these types of compounds.

Our attention turned towards an analogous Heck cyclisation with the [3.3.0]-bicyclic 2-bromobenzyl pyrrolidine (Chapter 4, Scheme 105, pg 124) which would form a fused tricyclic skeleton. Our most successful conditions utilising the 2-bromobenzyl pyrrolidine Heck precursors used Pd(OAc)\(_2\) with PPh\(_3\) in an excess of Et\(_3\)N. It was thought these conditions would be most likely to afford the desired fused tricycle with our bicyclic pyrrolidine (Scheme 120).

![Scheme 120: Intramolecular Heck cyclisation with [3.3.0]-bicyclic 2-bromobenzyl pyrrolidine.](image)

As yet our attempts with the moiety proved disappointing. Our success with the 2-bromobenzyl pyrrolidine scaffolds led us to believe we could afford the desired fused tricyclic scaffold. We have yet to delve deeper into this area but it was thought varying the palladium(0) source, base and solvent may unlock the key to these synthetically interesting, novel and potentially biologically appealing compounds.
Although it was pleasing to isolate a series of highly functionalised bicyclic
tetrahydrofuran and pyrrolidine scaffolds in a stepwise procedure, to fully explore the
potential of the palladium reactions, we wished to investigate the possibility of
formulating a one-pot procedure.

5.7. Tandem approach to bicyclic tetrahydrofuran and pyrrolidine bicyclic scaffolds

To fully use the power of the palladium reactions, we investigated a one-pot
procedure. Tandem alkylation/Heck reactions have recently been reported\textsuperscript{76} and we
believed it would be possible to initiate a palladium(0) catalytic cascade process
where a single catalytic cycle set up a sequential [3+2]-cycloaddition/Heck
transformation. This would enable a clean, efficient synthesis of the desired
heterocyclic skeletons in a single catalytic cycle. Our stepwise procedure had already
proved successful with a selection of Heck precursors albeit in low yields. We
therefore believed it would be possible to isolate the same tetrahydrofuran and
pyrrolidine scaffolds using a one-pot strategy. This protocol would provide an
exceptionally powerful route to synthesise these types of highly functionalised
tetrahydrofuran and pyrrolidine bicyclic scaffolds.

We began by looking at the tetrahydrofuran precursors. It was decided to test the α-
bromocinnamaldehyde derived tetrahydrofuran, which had been our only successful
tetrahydrofuran precursor to undergo our stepwise cycloaddition/Heck cyclisation. It
was thought we could employ our general palladium catalysed cycloaddition
methodology; stoichiometric amounts of aldehyde and vinylcyclopropane, ZnBr\textsubscript{2} (2
equiv.), Pd(PPh\textsubscript{3})\textsubscript{4} (10 mol\%) in THF at RT for 12h. At which point we would add an
excess of base and heat the reaction to reflux. Thus far our stepwise reactions had
shown Et\textsubscript{3}N to be a successful base. It was thought if we added an excess of Et\textsubscript{3}N and
heated the reaction at reflux for 72h we would increase the likelihood of affording the
desired tetrahydrofuran (Scheme 121).
Scheme 121: One-pot intramolecular Heck cyclisation with α-bromocinnamaldehyde.

Our initial attempt failed to afford the desired bicyclic skeleton. However, in our stepwise Heck reaction we were able to isolate the cis isomer by column chromatography. It may be the mixture of cis and trans isomers underwent a series of undesired reactions, which resulted in the formation of the observed complex mixture.

As we had not been able to isolate the 2-bromoaldehyde tetrahydrofuran under our general palladium(0) catalysed conditions, we decided to test our one-pot conditions with the tri-substituted 2-bromo phenyl tetrahydrofuran derivative (Scheme 122).
Scheme 122: One-pot intramolecular Heck cyclisation with α-bromocinnamaldehyde

We failed to observe peaks of any real significance by $^1$H NMR. There was no trace of either the starting material or the desired bicyclic tetrahydrofuran. As we have suggested this maybe due to the presence of the mixture of cis and trans diastereoisomers.

We have shown it was possible to exclusively afford the cis isomer with the pyrrolidine scaffold from 2-bromobenzyl imines with a phenyl or 4-methoxybenzyl substituent, using our general palladium conditions. It was thought the stereoselectivity of these reactions may allow our desired Heck cyclisation to progress successfully (Scheme 123).
Chapter 5

Scheme 123: One-pot intramolecular Heck cyclisation with 2-bromobenzyl substituted imines.

It was somewhat surprising to afford the desired bicyclic pyrrolidine scaffold in an increased yield (48%) to that observed by the stepwise process (28%) with phenyl substituted 2-bromobenzyl imine. We were particularly pleased to isolate the bicyclic pyrrolidine scaffold in a one-pot strategy, although it was disappointing not to achieve a successful synthesis with the 4-methoxy benzyl imine. Although, if we look at the process stepwise, the [3+2]-cycloaddition using the catalytic conditions to isolate the Heck precursor was relatively low (41%) and the subsequent Heck cyclisation proceeded in a moderate yield (12%). Therefore the overall one-pot procedure may not have proceeded in an appreciable yield.

It may also be reasoned that the presence of a mixture of the diastereomers may lead to unwanted side reactions hindering the desired Heck cyclisation. We decided to see if this was the case using the pyrrolidine scaffold prepared from 2-bromobenzyl imines, with 4-nitrobenzyl or a 2-furyl substituent under our one-pot conditions. These scaffolds had afforded a mixed ratio of isomers with our general palladium(0) cycloaddition conditions (Scheme 124).
We failed to observe either of the bicyclic pyrrolidine skeletons using these conditions. However, we managed to isolate the pyrrolidine derived from the 2-furyl substituted 2-bromobenzyl imine, indicating at least the first step was successful. It was unfortunate but not unexpected to afford the bicyclic scaffolds using these imines. Our stepwise conditions had indicated unless one diastereomer was isolated we did not afford the bicyclic skeleton. This led us to infer that the possible presence of mixed diastereomers may have a detrimental effect on our one-pot Heck conditions.

As yet we have only managed to achieve one successful one pot [3+2]-cycloaddition/Heck reaction. However, we decided it would be worth while testing our one-pot Heck conditions on our [3.3.0]-bicyclic 2-bromobenzyl pyrrolidine (Scheme 125).
Scheme 125: Intramolecular Heck cyclisation with [3.3.0]-bicyclic 2-bromobenzyl pyrrolidine.

Unfortunately we recovered a complex mixture which failed to resemble the desired fused tricyclic compound. We feel that this [3+2]-cycloaddition/Heck methodology would prove successful if the conditions for the stepwise strategy could be successfully mastered.

Whilst embarking upon this section of the project. It was observed that although there were countless examples of intramolecular palladium(0) catalysed Heck cyclisations between an alkene/alkyne substituents and a tethered imine,\textsuperscript{72,75} there had been to date no reported synthesis of intermolecular Heck reactions between imines and a separate untethered component, which seemed on paper plausible. We therefore decided whilst upon this venture, to investigate whether coupling of an imine and aromatic halide would indeed be possible.
5.8. Intermolecular Heck cyclisations with imines

A simple procedure by Harayama\textsuperscript{78} reported a palladium catalysed quinoline synthesis (Scheme 126).

![Scheme 126: Synthesis of Luotonin A.\textsuperscript{78}](image)

An idea was formulated that if an imine was taken, it maybe plausible to couple an aromatic halide along the same lines as the catalytic pathway in the Heck reaction (Scheme 127).

![Scheme 127: Coupling an aromatic halide with an imine.](image)

To satisfy this curiosity we took a substituted imine, which we thought would be relatively easy to identify by \(^1\)H NMR should the reaction proceed successfully, and subjected it to general palladium(0) catalysed Heck conditions\textsuperscript{72,75} (Table 35).
Table 35: Palladium(0) catalysed coupling of an aromatic halide with an imine.

The reaction mixture was divided into two portions in an attempt to purify the resultant viscous reaction mixture. The first portion was dissolved in EtOAc and flushed through a plug of silica. The second was washed with water in an attempt to remove any impurities and then extracted into EtOAc. Unfortunately, both purification techniques failed to yield the desired product. Characterisation of the reaction mixture was particular difficult as \(^1\)H NMR studies showed a complex mixture. However, it was felt the simplest way to determine the presence of any desired compound was by mass spectrometry. Unfortunately, this proved fruitless indicating the desired compound wasn’t present. We decided, due to the lack of any sign of a successful reaction, to lay this line of enquiry to rest. It still provided an interesting insight into the possible manipulation within this type of chemistry.

5.9. Conclusion

In this chapter we have delved deeper into the development of a general method to construct novel highly functionalised heterocyclic ring systems.

Our brief investigation into Heck mediated cyclisations has proved successful. We have prepared the desired tetrahydrofuran and pyrrolidine precursors using our
palladium(0) catalysed [3+2]-methodology. Ideally we hoped to isolate one of the
diastereomers required for the subsequent Heck cyclisation, either by inducing the
stereochemistry by varying the palladium(0) catalytic conditions, or purification of
the diastereomers. This has been achieved with varying success. The subsequent Heck
cyclisation afforded a selection of highly functionalised bicyclic tetrahydrofuran and
pyrrolidine skeletons in a stepwise procedure.

We have then gone on to use the knowledge acquired through our stepwise
methodology to develop a one-pot [3+2]-cycloaddition/Heck cyclisation procedure. It
was very pleasing to isolate a bicyclic pyrrolidine scaffold using this strategy.

There are many variables which have yet to be explored. Further investigation into the
reaction parameters may induce further stereochemical preferences with the
tetrahydrofuran/pyrrolidine scaffolds. Areas of interest include variation of
palladium(0) reagent, solvents, Lewis acid and temperature. Stereochemical control
maybe further induced with employment of chiral reagents i.e. chiral palladium
reagents and chiral Lewis acids. Our main priority remains to optimise our general
conditions, before looking to induce further stereo-control.

We have only touched upon possible conditions which could induce the Heck
cyclisation through a stepwise or one-pot strategy. Variation of the palladium(0)
catalyst, base, solvent and increasing the scale of the reactions could have significant
effects on the overall yield. It is believed optimisation of reaction conditions could
lead to a number of structurally and biologically interesting compounds.

We set out to achieve two main objectives. The first was to form a highly
functionalised bicyclic scaffold from a [3+2]-palladium(0) catalysed cycloaddition
with a suitable trapping agent and a bicyclic cyclopropane. The second was to explore
the viability of a Heck cyclisation establishing a route to form a ring from the tether
on the nitrogen to the vinyl substituent.

We have successfully achieved these two aims. However, the palladium(0) catalysed
[3+2]-methodology offers enormous potential. There are still many variables we have
yet to investigate. We have not had the resources to screen palladium(0) catalysts and
the effects of the ligands. It was felt this might increase the life-time of the \( \pi \)-allyl zwitterionic species, encouraging reactions that had previously been unsuccessful. We also believe further work with the [3.1.0]-bicyclic cyclopropane and imines with a variety of tethers would provide suitable precursors with which to attempt Heck cyclisation. This would allow exploration into precursors for a Heck cyclisation (Scheme 128).

![Scheme 128: Preparation of tricyclic scaffolds.](image)

We successfully prepared a selection of tetrahydrofuran and pyrrolidine precursors in order to investigate whether they would undergo the desired Heck cyclisation in a step-wise procedure. Further work into selectively isolating the diastereomers would provide the opportunity to afford the corresponding fused skeletons stereoselectively. Ideally, inducing preferential formation of the desired diastereomer by subtle changes in solvent or palladium(0) catalyst, which would undergo a Heck cyclisation to form the corresponding fused scaffolds (Scheme 129).
This area of research has only been touched upon and we feel it offers enormous potential. Investigation into a variety of imines with appropriate tethers would afford a range of structurally interesting and novel bicyclic scaffolds (Scheme 130).

Finally, we have begun the initial stages of investigating a one-pot tandem [3+2]-cycloaddition/Heck cyclisation. It was thought that if it was possible to successfully afford a selection of novel bicyclic scaffolds they would have the potential to undergo a one-pot procedure (Scheme 131).
Scheme 131: One-pot preparation of bicyclic scaffolds.

An enthusiastic approach continues within our group towards further progress in this area.
Chapter 6 - Experiment

General information

6.1.i. Solvents and Reagents

All solvents and reagents were purified by standard techniques as reported in Perrin. D.D.; Armarego, W. L. F., Purification of Laboratory Chemicals, 3rd edition. Pergamon Press, Oxford, 1998 or as used as supplied from commercial sources as appropriate.

Reagent chemicals were purchased from Aldrich Chemical Company Ltd., Lancaster Chemical Synthesis Ltd., Acros (Fischer) Chemicals Ltd. and Avocado. Commercially available reagents were used as supplied, without further purification unless otherwise stated. Air- and moisture-sensitive reactions were carried out using glassware that had been dried overnight in an oven at 240°C. The reactions were carried out under a slight positive static pressure of nitrogen unless otherwise stated.

Solvents where necessary, were dried and stored over 4Å molecular sieves prior to use. Molecular sieves were activated at 240°C over a period of 3 days. 40-60 petroleum ether (P.E. 40-60) refers to the fraction of the light petroleum ether which boils between 40-60°C. CH₂Cl₂, Et₂O, MeOH, EtOH and THF refer to dichloromethane, diethyl ether, methanol, ethanol and tetrahydrofuran respectively.

6.1.ii. Chromatographic Procedures

Analytical thin layer chromatography (TLC) was conducted using aluminium backed plates coated with 0.25 mm silica containing fluorescer. Plates were visualised by quenching of UV light (254 nm) as well as through staining with 1% v/v potassium permanganate in aqueous alkaline solution followed by heat where appropriate. Flash chromatography was conducted using Merck Kiesgel (70-230 Mesh ASTM) as the stationary phase unless otherwise stated. Samples were applied as saturated solutions in the appropriate solvent. Pressure was applied to the column by use of hand bellows.
6.1.iii. **FT-IR**

Infra-red spectroscopy (IR) was conducted in the range of 4000-600 cm\(^{-1}\), using a Perkin-Elmer Fourier Transform Paragon 1000 spectrophotometer (with internal calibration). Samples were dissolved in appropriate solvent and applied as thin film to the NaCl plates. Liquid samples were applied neat to the plate and run as thin films. Only major absorbencies have been quoted.

6.1.iv. **\(^1\)H NMR**

Proton magnetic resonance spectra (\(^1\)H NMR) were recorded at 250 and 400 MHz using a Brüker AC-250 or Brüker DPX-400 spectrometer as solutions of deuterated CDCl\(_3\) unless otherwise specified. Chemical shifts (\(\delta_H\)) were quoted as parts per million (ppm) and are referenced to the residual solvent peak tetramethylsilane (TMS) as the internal standard. The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q) multiplet (m), broad (br) and (env.) envelope. Assignment of individual proton signals was assisted by analysis of \(^1\)H COSY spectra and nOe data. Coupling constants (\(J\) values) are reported in Hertz (Hz). Diastereoisomer ratios were calculated from the integration of suitable peaks in the \(^1\)H NMR spectra.

6.1.v. **\(^{13}\)C NMR**

Carbon magnetic resonance spectra (\(^{13}\)C NMR) at 100 MHz using a DPX-400 spectrometer were recorded as solutions of deuterated CDCl\(_3\) unless otherwise specified. (\(\delta_H\)) were quoted as parts per million (ppm) and are referenced to the residual solvent peak tetramethylsilane (TMS) as the internal standard. Assignment of individual carbon signals was assisted by DEPT and HMQC data.

6.1.vi. **Mass Spectra**

Mass spectra (high/low resolution) were recorded using a Fisons VG Quattro II SQ instrument, with modes of ionisation being indicated as electron impact (El) and fast atom bombardment (FAB) and electron spray (ES) with only the molecular ion, molecular ion fragments and major peaks being reported. Accurate masses were
recorded using a Kratos MS-80 instrument. Elemental analysis was performed by Mr J. Kershaw, Department of Chemistry, Loughborough University and by the ESPRC National mass spectrometry service in Swansea.

6.1.vii. Other Data

Melting points where appropriate were determined using an electrical 9100 Thermal Melting point instrument and are uncorrected. Yields (unless otherwise stated) are quoted for isolated pure products.

Dicyclopentadiene was distilled (178°C) into an ice bath and the resulting 1,3-cyclopentadiene was reacted immediately.63
Preparation of 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester (155)\textsuperscript{39}

To a stirred solution of sodium methoxide (prepared from sodium 1.150 g, 50.0 mmol in MeOH (20 mL)) was added dimethylmalonate (198) (5.89 mL, 51.5 mmol) followed by a solution of trans 1,4-dibromobut-2-ene (189) (5.350 g, 25.0 mmol) in MeOH (40 mL). The reaction mixture was refluxed for 3 h and then cooled to room temperature. The white precipitate (NaBr) was filtered off and the solvent removed under reduced pressure to afford a viscous pale yellow oil. The solution was partitioned between Et\textsubscript{2}O (60 mL) and distilled water (60 mL). The organic layer was further washed with distilled water (2 x 30 mL) and dried (MgSO\textsubscript{4}). The solvent was removed under reduced pressure to afford crude 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester (155) (6.743 g) as a pale yellow oil. The oil was purified using column chromatography (SiO\textsubscript{2}, Et\textsubscript{2}O: P.E. 40-60 °C, 1:4) to afford 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester (155) (3.266 g, 17.7 mmol, 71\% yield) as a clear viscous oil. $v_{\text{max}}$/cm$^{-1}$ (neat) 2954 (C-H str.), 1731 (CO\textsubscript{2}R str.), 1438, 1330, 1274, 1210, 1131; $\delta_{\text{H}}$ (CDCl\textsubscript{3}, 250 MHz) 1.58 (1H, dd, $J$ 5.0 and 9.0 Hz, 3-C(H=CH)), 2.59 (1H, m, 2-CH), 3.72 (6H, s, 2 x OCH\textsubscript{3}), 5.12 (1H, dd, $J$ 2.2 and 9.0 Hz, C(H)=CH), 5.27 (1H, dd, $J$ 2.1 and 17.1 Hz, C(H)=CH), 5.40 (1H, m, CH\textsubscript{2}=CH); $\delta_{\text{C}}$ (CDCl\textsubscript{3}, 100 MHz) 20.95 (3-CH\textsubscript{2}), 31.83 (2-CH), 36.06 (1-C), 52.90 (OCH\textsubscript{2}), 53.09 (OCH\textsubscript{3}), 119.07 (CH\textsubscript{2}=CH), 133.32 (CH\textsubscript{2}=CH), 168.13 (C=O), 170.35 (C=O).
Preparation of cis-1-acetocy-4-chloro-2-cyclohexene (193)$^{52}$

To a stirred solution of LiCl (1.300 g, 30.0 mmol), LiOAc.2H$_2$O (3.161 g, 30.0 mmol), p-benzoquinone (3.520 g, 32.0 mmol) and Pd(OAc)$_2$ (0.170 g, 0.78 mmol) in acetic acid (56 mL), was added 1,3-cyclohexadiene (188) (1.240 g, 15.5 mmol) by syringe at room temperature over 15 min. The reaction mixture was stirred at 40$^\circ$C for 3h, allowed to reach room temperature and stirred for a further 2h. At which point sat. NaCl aq. sol. (30 mL) was added to the black solution and the organic layer separated. The aqueous layer was further washed with Et$_2$O:pentane (3 x 100 mL, 1:9). The organic extracts were combined, washed with water (2 x 50 mL), sat. Na$_2$CO$_3$ aq. sol. (50 mL), 2 M NaOH (2 x 40 mL), sat. NaCl aq. sol. (50 mL) and dried (MgSO$_4$). The solvent was removed under reduced pressure furnishing crude cis-1-acetocy-4-chloro-2-cyclohexene (193) (2.731 g) as a yellow oil. Purification by bulb to bulb distillation (80$^\circ$C, 3 mmHg) afforded cis-1-acetocy-4-chloro-2-cyclohexene (193) (2.434 g, 13.9 mmol, 90% yield) as a yellow oil. $\nu_{\max}$/cm$^{-1}$ (neat) 2957, 2360, 2337, 1736 (C=O str.), 1371, 1239, 1033, 993, 875; $\delta_H$ (CDCl$_3$, 400 MHz) 2.09 (3H, s, COCH$_3$), 2.05-2.16 (4H, m, 5-CH$_2$ and 6-CH$_2$), 4.56 (1H, br s, 4-CH), 5.28 (1H, m, 1-CH), 5.80 (1H, ddd, $J = 0.7$, 2.6 and 13.5 Hz, 2-CH), 5.97 (1 H, ddd, $J = 1.6$, 4.0 and 13.5 Hz, 3-CH); $\delta_C$ (CDCl$_3$, 100 MHz) 21.57 (CH$_3$), 22.84 (6-CH$_2$), 29.94 (5-CH$_2$), 53.90 (1-CH), 68.08 (4-CH), 129.72 (2-CH), 132.80 (3-CH), 170.72 (C=O).
Preparation of dimethyl (cis-4-acetoxy-cyclohex-2-en-1-yl) malonate (195)\textsuperscript{52}

A solution of sodium dimethylmalonate (23 mL of a 0.125 M solution in THF, 2.87 mmol) was prepared by the careful addition of dimethyl malonate (0.380 g, 2.87 mmol) to NaH (0.553 g, 3.16 mmol) in THF (23 mL) at 0°C. The yellow solution was stirred for 20 min. at 0°C before being allowed to reach room temperature. This was followed by the addition of Pd(OAc)\textsubscript{2} (0.010 g, 0.06 mmol), PPh\textsubscript{3} (0.070 g, 0.26 mmol) and cis-1-acetoxy-4-chloro-2-cyclohexene (193) (0.500 g, 2.87 mmol). The grey/purple solution was stirred for a further 45 min. The reaction mixture was extracted with sat. NaHCO\textsubscript{3} aq. sol. (30 mL), water (15 mL) and Et\textsubscript{2}O (60 mL). The aqueous layer was washed with Et\textsubscript{2}O (3 x 75 mL). The combined organic extracts were washed with sat. NaCl aq. sol. (50 mL) and dried (MgSO\textsubscript{4}). The solvent was removed under reduced pressure furnishing crude dimethyl (cis-4-acetoxy-cyclohex-2-en-1-yl) malonate (195) (0.530 g) as a yellow oil. Purification by bulb to bulb distillation (60°C, 3 mmHg) afforded dimethyl (cis-4-acetoxy-cyclohex-2-en-1-yl) malonate (195) (0.702 g, 2.61 mmol, 91% yield) as a yellow oil. $\textbf{v}_{\text{max/cm}}^{-1}$ (neat) 2952, 1732 (CO\textsubscript{2}R str.), 1716 (C=O str.), 1455, 1435, 1372, 1243, 1015, 960, 743; $\delta_{\text{H}}$ (CDCl\textsubscript{3}, 250 MHz) 1.53-1.92 (4H, m, 5-CH\textsubscript{2} and 6-CH\textsubscript{2}), 2.01 (3H, s, 1-COCOC.fu), 2.85 (1H, m, 4-CH), 3.32 (1H, d, J 9.5 Hz, CH(CO\textsubscript{2}CH\textsubscript{3})\textsubscript{2}), 3.73 (6H, s, 2 x CO\textsubscript{2}CH\textsubscript{3}), 5.17 (1H, br s, 1-CH), 5.8 (2H, br env., 2-CH and 3-CH); $\delta_{\text{C}}$ (100 MHz) 21.64 (1-COCOCH\textsubscript{3}), 22.64 (5-CH\textsubscript{2}), 27.33 (6-CH\textsubscript{2}), 35.74 (CH(CO\textsubscript{2}CH\textsubscript{3})\textsubscript{2}), 52.86 (CO\textsubscript{2}CH\textsubscript{3}), 52.88 (CO\textsubscript{2}CH\textsubscript{3}), 56.39 (4-CH), 66.64 (1-CH), 127.32 (3-CH), 133.68 (2-CH), 168.81 (C=O), 168.90 (C=O), 170.92 (1-CHCOCH\textsubscript{3}).
Preparation of tosyl-azide (216)\textsuperscript{58}

\[
\begin{align*}
\text{S} & \text{6} \\
\text{3} & \text{2} \\
\text{4} & \text{N} \\
\text{5} & \text{N} \\
\text{6} & \text{N} \\
\text{N} & \text{N} \\
\text{O} & \text{N} \\
\end{align*}
\]

To a solution sodium azide (215) (5.000 g, 77.0 mmol) in acetone (60 mL) and water (40 mL), tosyl chloride (214) (7.000 g, 36.8 mmol) was added portion wise at room temperature over 5 min. The reaction mixture was stirred at room temperature for a further 3h. Water (40 mL) was then added and the organic layer separated. The aqueous layer was further extracted with CH\textsubscript{2}Cl\textsubscript{2} (2 x 100 mL), the organic layers combined and dried (MgSO\textsubscript{4}). The solvent was removed under reduced pressure furnishing tosyl-azide (216) (7.171 g, 36.4 mmol, 99\% yield) as a colourless oil. 

\begin{align*}
\nu_{\text{max}} / \text{cm}^{-1} \text{ (neat)} & \quad 2924, 2345 (N_3 \text{ str.}), 2125 (N_3 \text{ str.}), 1595, 1494, 1448, 1399, 1369, 1120, 1086, 1017, 814; \\
\delta_H \text{ (CDCl}_3, 250 \text{ MHz)} & \quad 2.48 (3H, s, \text{CH}_3), 7.41 (2H, d, J 8.3 \\
\text{Hz, 3-CH and 5-CH arom.}), 7.84 (2H, d, J 8.3 \text{ Hz, 2-CH and 6-CH arom.}).
\end{align*}
Preparation of dimethyl diazomalonate (205); Method A\textsuperscript{59}

![Dimethyl Diazomalonate](image)

To a suspension of sodium hydride (0.070 g, 2.79 mmol) in benzene (12 mL) and THF (2 mL) was added a solution of dimethyl malonate (198) (0.330 g, 2.54 mmol) in benzene (2 mL) by syringe at room temperature over 5 min. The reaction mixture was stirred at room temperature for a further 45 min. A solution of tosyl azide (216) (0.500 g, 2.54 mmol) in benzene (2 mL) was then slowly added to the reaction mixture by syringe at room temperature over 5 min. The reaction mixture was allowed to stand at room temperature for 12 h. The solvent was removed under reduced pressure furnishing a white solid which was triturated with Et\textsubscript{2}O (2 x 100 mL). The solvent was removed under reduced pressure affording dimethyl diazomalonate (205) (0.165 g, 1.04 mmol, 41% yield) as a yellow oil. \( \nu_{\text{max}} \) cm\textsuperscript{-1} (neat) 3032, 2935, 2371, 2345, 2140 (N\textsubscript{2} str.), 1732 (CO\textsubscript{2}R str.), 1363, 1329, 1200, 1166, 967, 778, 729; \( \delta \)\textsubscript{H} (CDCl\textsubscript{3}, 250 MHz) 3.81 (6 H, s, 2 x OCH\textsubscript{3}).

Preparation of dimethyl diazomalonate (205); Method B\textsuperscript{58}

To a solution of tosyl azide (216) (2.390 g, 10.0 mmol) and dimethyl malonate (198) (1.570 g, 10.0 mol) in CH\textsubscript{3}CN (50 mL) was added triethylamine (1.240 g, 0.01 mol) by syringe over 10 min. at room temperature. The reaction mixture was allowed to stand at room temperature for a further 22 h. The solvent was removed under reduced pressure affording a white solid. The solid was triturated with Et\textsubscript{2}O (150 mL) and the Et\textsubscript{2}O extract was washed with KOH (2.700 g) in water (100 mL). The aqueous layer was washed with sat. NaSO\textsubscript{3} aq. sol. and extracted with Et\textsubscript{2}O (100 mL). The combined ethereal extracts were acidified with 6 \textit{N} HCl and dried (Na\textsubscript{2}SO\textsubscript{4}). The solvent was removed under reduced pressure affording dimethyl diazomalonate (205) (0.810 g, 5.10 mmol, 51% yield) as a yellow oil. Data as shown in Method A.
Preparation of dimethyl diazomalonate (205); Method C

To a solution of tosyl azide (216) (4.430 g, 22.5 mmol) in benzene (20 mL) was added dimethyl malonate (198) (3.010 g, 22.8 mol) at room temperature by syringe over 5 min. The reaction mixture was allowed to stand at room temperature for 18h. The reaction mixture was filtered and the solid washed with cold benzene (10 mL). The organic layers were combined and the solvent was removed under reduced pressure affording dimethyl diazomalonate (205) (1.599 g, 10.1 mmol, 45% yield) as a yellow oil. Data as shown in Method A.

Preparation of mesyl azide (219)

To a solution of sodium azide (215) (11.34 g, 170 mmol) in acetone (60 mL) was added methanesulfonyl chloride (218) (13.32 g, 120 mmol) by syringe at room temperature over 5 min. The reaction mixture was stirred at room temperature for a further 3h, filtered and the resultant white residue washed with acetone (3 x 20 mL). The organic extracts were combined and the solvent was removed under reduced pressure to afford mesyl azide (219) (14.14 g, 120 mmol, 99% yield) as a colourless oil. \( \nu_{\text{max/cm}^{-1}} \) (neat) 3032, 2935, 2371, 2345 (N\(_3\) str.), 2125 (N\(_3\) str.), 1595, 1363, 1329, 1200, 1166, 967, 778, 729; \( \delta_{\text{H}} \) (CDCl\(_3\), 250 MHz) 3.33 (3 H, s, CH\(_3\)).
Preparation of dimethyl diazomalonate (205); Method D$^{61}$

![Image](image_url)

To a solution of dimethyl malonate (198) (13.25 g, 100 mmol) and mesyl azide (219) (13.36 g, 110 mmol) in CH$_3$CN (50 ml) was added Et$_3$N (22.34 g, 220 mmol) slowly by syringe at room temperature over 20 min. The reaction mixture was stirred at room temperature for a further 4h at which point 10% NaOH (50 ml) was added. The aqueous layer was washed with CH$_2$Cl$_2$ (3 x 50 mL), the organic extracts combined, dried (MgSO$_4$) and the solvent was removed under reduced pressure affording dimethyl diazomalonate (205) (11.28 g, 71.4 mmol, 71% yield) as a yellow oil. $\nu_{\text{max}}$/cm$^{-1}$ (neat) 3032, 2935, 2371, 2140 (N$_2$ str.), 1732 (CO$_2$R str.), 1363, 1329, 1200, 1166, 967, 778, 729; $\delta_{\text{H}}$ (CDCl$_3$, 250 MHz) 3.81 (3 H, s, OCH$_3$).
Preparation of bicyclo[4.1.0]hept-2-ene-7,7-dicarboxylic acid dimethyl ester (186)\[42]

To a stirred mixture of 1,3-cyclohexadiene (188) (1.000 g, 12.5 mmol) and Rh$_2$(OAc)$_4$ (0.047 g, 0.10 mmol) in CH$_3$CN (10 mL) was added dimethyl diazomalonate (205) (2.172 g, 13.7 mmol) in CH$_3$CN (2 mL) by syringe at room temperature over 5 min. The reaction mixture was then refluxed for 3h, cooled to room temperature and the solvent removed under reduced pressure to afford crude bicyclo[4.1.0]hept-2-ene-7,7-dicarboxylic acid dimethyl ester (186) (1.329 g) a brown oil. The oil was purified using column chromatography (SiO$_2$, Hexane:EtOAc, 4:1) to afford bicyclo[4.1.0]hept-2-ene-7,7-dicarboxylic acid dimethyl ester (186) (1.102 g, 5.25 mmol, 42% yield) as a clear viscous oil. $\nu_{\max}$/cm$^{-1}$ (neat) 3081, 2445, 2121, 1740 (CO$_2$R str.), 1592, 1399, 1301, 1023, 894; $\delta_H$ (CDCl$_3$, 250 MHz) 1.63-2.13 (6H, m, 2-CH, 5-CH$_2$, 6-CH$_2$, 7-CH), 3.69 (3H, s, CO$_2$CH$_3$), 3.71 (3H, s, CO$_2$CH$_3$), 5.69 (1H, m, 3-CH), 5.89 (1H, m, 4-CH); $\delta_C$ (CDCl$_3$, 100 MHz) 16.41 (6-CH$_2$), 20.88 (5-CH$_2$), 24.95 (7-CH), 27.07 (2-CH), 41.18 (1-CH), 52.94 (OCH$_3$), 53.69 (OCH$_3$), 122.20 (3-CH), 128.28 (4-CH), 168.10 (C=O), 170.53 (C=O); ms (EI): $m/z$ 211 (M$^+$, 50%), 150 (12), 52 (100); HRMS calc. for C$_{11}$H$_{14}$O$_4$ 211.0965 found 211.0967.
Preparation of bicyclo[4.1.0]hept-2-ene-7,7-dicarboxylic acid dimethyl ester (186)\textsuperscript{52}

To a stirred mixture of 1,3-cyclohexadiene (188) (1.000 g, 12.5 mmol) and Rh\textsubscript{2}(OAc)\textsubscript{4} (0.047 g, 0.10 mmol) was added dimethyl diazomalonate (205) (2.172 g, 13.7 mmol) by syringe at room temperature over 5 min. The reaction mixture was then refluxed for 3 h, cooled to room temperature and the solvent removed under reduced pressure to afford crude bicyclo[4.1.0]hept-2-ene-7,7-dicarboxylic acid dimethyl ester (186) (1.428 g) as a brown oil. The oil was purified using column chromatography (SiO\textsubscript{2}, Hexane:EtOAc, 4:1) to afford bicyclo[4.1.0]hept-2-ene-7,7-dicarboxylic acid dimethyl ester (186) (1.339 g, 6.34 mmol, 51% yield) as a clear viscous oil. Data as above.

Preparation of bicyclo[4.1.0]hept-2-ene-7,7-dicarboxylic acid dimethyl ester (186)\textsuperscript{52}

To a stirred mixture of 1,3-cyclohexadiene (188) (1.000 g, 12.5 mmol) and Rh\textsubscript{2}(OAc)\textsubscript{4} (0.047 g, 0.10 mmol) in DCE (10 mL) was added dimethyl diazomalonate (205) (2.172 g, 13.7 mmol) in DCE (2.0 mL) by syringe at room temperature over 5 min. The reaction mixture was then refluxed for 3 h, cooled to room temperature and the solvent removed under reduced pressure to afford crude bicyclo[4.1.0]hept-2-ene-7,7-dicarboxylic acid dimethyl ester (186) (1.891 g) as a brown oil. The oil was purified using column chromatography (SiO\textsubscript{2}, Hexane:EtOAc, 4:1) to afford bicyclo[4.1.0]hept-2-ene-7,7-dicarboxylic acid dimethyl ester (186) (1.575 g, 7.50 mmol, 60% yield) as a clear viscous oil. Data as above.
Preparation of bicyclo[4.1.0]hept-2-ene-7,7-dicarboxylic acid dimethyl ester (186)\textsuperscript{52}

To a stirred mixture of 1,3-cyclohexadiene (188) (1.000 g, 12.5 mmol) and Rh\textsubscript{2}(OAc)\textsubscript{4} (0.047 g, 0.10 mmol) in DCE (10 mL) at reflux was added dimethyl diazomalonate (205) (2.172 g, 13.7 mmol) in DCE (2.0 mL) drop wise by syringe over 1h. The reaction mixture was then refluxed for a further 2h, cooled to room temperature and the solvent removed under reduced pressure to afford crude bicyclo[4.1.0]hept-2-ene-7,7-dicarboxylic acid dimethyl ester (186) (1.798 g) as a brown oil. The oil was purified using column chromatography (SiO\textsubscript{2}, Hexane:EtOAc, 4:1) to afford bicyclo[4.1.0]hept-2-ene-7,7-dicarboxylic acid dimethyl ester (186) (1.574 g, 7.50 mmol, 60\% yield) as a clear viscous oil. Data as above.
Preparation of bicyclo[3.1.0]hex-2-ene-6,6-dicarboxylic acid dimethyl ester (202)33

To a stirred mixture of 1,3-cyclopentadiene (200) (1.000 g, 12.5 mmol) and Rh₂(OAc)₄ (0.047 g, 0.10 mmol) in CH₂Cl₂ (10 mL) was added dimethyl diazomalonate (205) (2.172 g, 13.7 mmol) in CH₂Cl₂ (2 mL) by syringe at room temperature over 5 min. The reaction mixture was then refluxed for 3h, cooled to room temperature and the solvent removed under reduced pressure to afford crude bicyclo[3.1.0]hex-2-ene-6,6-dicarboxylic acid dimethyl ester (202) (0.789 g) as a brown oil. The oil was purified using column chromatography (SiO₂, Hexane:EtOAc, 4:1) to afford bicyclo[3.1.0]hex-2-ene-6,6-dicarboxylic acid dimethyl ester (202) (0.172 g, 0.88 mmol, 29% yield) as a clear viscous oil. νmax/cm⁻¹ 3443, 2989, 2953, 2844, 1728 (CO₂R str.), 1436, 1331, 1316, 1290, 1254, 1197, 1163, 1084; δH (CDCl₃, 250 MHz) 2.45 (1H, s, 6-CH), 2.70-2.79 (2H, m, 5-CH₂), 2.84 (1H, s, 2-CH), 3.64 (3H, s, C0₂C₆H₅), 3.72 (3H, s, CO₂CH₃), 5.61 (1H, m, 4-CH), 5.81 (1H, m, 3-CH); δC (CDCl₃, 100 MHz) 31.66 (6-CH), 34.40 (5-CH₂), 38.67 (1-C), 39.41 (2-CH), 52.24 (CO₂CH₃), 52.69 (CO₂CH₃), 129.52 (4-CH), 132.63 (3-CH), 166.57 (C=O), 170.39 (C=O); ms (EI): m/z 196 (M⁺, 56%), 166 (12), 165 (100); HRMS calc. for C₁₀H₁₄O₄ 196.0727 found 196.0725.

Preparation of bicyclo[3.1.0]hex-2-ene-6,6-dicarboxylic acid dimethyl ester (202)33

To a stirred mixture of 1,3-cyclopentadiene (200) (1.000 g, 15.1 mmol) and Rh₂(OAc)₄ (0.048 g, 0.10 mmol) was added dimethyl diazomalonate (205) (0.477 g, 3.02 mmol) slowly by syringe at room temperature over 5 min. The reaction mixture was then refluxed for 3h, cooled to room temperature to afford crude bicyclo[3.1.0]hex-2-ene-6,6-dicarboxylic acid dimethyl ester (202) (0.529 g) as a brown oil. The oil was purified using column chromatography (SiO₂, Hexane:EtOAc, 4:1) to afford bicyclo[3.1.0]hex-2-ene-6,6-dicarboxylic acid dimethyl ester (202) (0.172 g, 0.88 mmol, 29% yield) as a clear viscous oil. νmax/cm⁻¹ 3443, 2989, 2953, 2844, 1728 (CO₂R str.), 1436, 1331, 1316, 1290, 1254, 1197, 1163, 1084; δH (CDCl₃, 250 MHz) 2.45 (1H, s, 6-CH), 2.70-2.79 (2H, m, 5-CH₂), 2.84 (1H, s, 2-CH), 3.64 (3H, s, C0₂C₆H₅), 3.72 (3H, s, CO₂CH₃), 5.61 (1H, m, 4-CH), 5.81 (1H, m, 3-CH); δC (CDCl₃, 100 MHz) 31.66 (6-CH), 34.40 (5-CH₂), 38.67 (1-C), 39.41 (2-CH), 52.24 (CO₂CH₃), 52.69 (CO₂CH₃), 129.52 (4-CH), 132.63 (3-CH), 166.57 (C=O), 170.39 (C=O); ms (EI): m/z 196 (M⁺, 56%), 166 (12), 165 (100); HRMS calc. for C₁₀H₁₄O₄ 196.0727 found 196.0725.
4:1) to afford bicyclo[3.1.0]hex-2-ene-6,6-dicarboxylic acid dimethyl ester (202) (0.307 g, 1.56 mmol, 52% yield) as a clear viscous oil. Data as above.

**Preparation of bicyclo[3.1.0]hex-2-ene-6,6-dicarboxylic acid dimethyl ester (202)**

To a stirred mixture of 1,3-cyclopentadiene (200) (1.000 g, 15.1 mmol) and Rh₂(OAc)₄ (0.048 g, 0.10 mmol) in CH₂Cl₂ (10 mL) at reflux was added dimethyl diazomalonate (202) (0.477 g, 3.02 mmol) in CH₂Cl₂ (2.0 mL) drop wise by syringe over 1h. The reaction mixture was then refluxed for 2h, cooled to room temperature and the solvent removed under reduced pressure to afford crude bicyclo[3.1.0]hex-2-ene-6,6-dicarboxylic acid dimethyl ester (202) (0.512 g) as a brown oil. The oil was purified using column chromatography (SiO₂, Hexane:EtOAc, 4:1) to afford bicyclo[3.1.0]hex-2-ene-6,6-dicarboxylic acid dimethyl ester (202) (0.290 g, 1.48 mmol, 49% yield) as a clear viscous oil. Data as above.
Preparation of bicyclo[5.1.0]oct-2-ene-8,8-dicarboxylic acid dimethyl ester (197)$^{33}$

To a stirred mixture of 1,3-cycloheptadiene (192) (1.000 g, 10.6 mmol) and Rh$_2$(OAc)$_4$ (0.051 g, 0.05 mmol) was added dimethyl diazomalonate (205) (1.850 g, 11.7 mmol) by syringe at room temperature over 5 min. The reaction mixture was then refluxed for 3h, cooled to room temperature to afford crude bicyclo[5.1.0]oct-2-ene-8,8-dicarboxylic acid dimethyl ester (197) (1.354 g) as a brown oil. The oil was purified using column chromatography (SiO$_2$, Hexane:EtOAc, 4:1) to afford bicyclo[5.1.0]oct-2-ene-8,8-dicarboxylic acid dimethyl ester (197) (0.930 g, 4.15 mmol, 39% yield) as a clear viscous oil. $\nu_{\text{max}}$/cm$^{-1}$ 3440, 2982, 2953, 2844, 1730 (CO$_2$ str.), 1438, 1321, 1316, 1290, 1253, 1197, 1163, 1024; $\delta$$_H$ (CDCl$_3$, 400 MHz) 1.26-1.37 (2H, m, 6-CH$_2$), 1.60-1.63 (2H, m, 7-C(H)H), 1.71-1.75 (1H, m, 7-C(H)H), 2.02 (1H, m, 8-CH), 2.10 (1H, m, 5-C(H)H), 2.27 (1H, m, 2-CH), 2.42 (1H, m, 5-C(H)H), 3.73 (3H, s, CO$_2$CH$_3$), 3.74 (3H, s, CO$_2$CH$_3$), 5.60 (1H, m, 4-CH), 5.70 (1H, m, 3-CH); $\delta$$_C$ (CDCl$_3$, 100 MHz) 23.24 (7-CH$_2$), 23.79 (6-CH$_2$), 28.50 (5-CH$_2$), 29.97 (8-CH), 30.92 (2-CH), 38.35 (1-C), 52.22 (CO$_2$CH$_3$), 52.71 (CO$_2$CH$_3$), 123.54 (3-CH), 131.26 (4-CH), 167.27 (C=O), 171.00 (C=O); ms (EI): $m/z$ 225 (M$^+$, 100%); HRMS calc. for C$_{12}$H$_{16}$O$_4$ 225.1121 found 225.1119.
Preparation of bicyclo[6.1.0]non-2-ene-9,9-dicarboxylic acid dimethyl ester (203)\(^{33}\)

To a stirred mixture of 1,3-cyclo-octadiene (201) (1.000 g, 9.26 mmol) and Rh\(_2\)(OAc)_4 (0.024 g, 0.05 mmol) was added dimethyl diazomalonate (205) (1.610 g, 10.2 mmol). The reaction mixture was refluxed for 3h, cooled to room temperature to afford crude bicyclo[6.1.0]non-2-ene-9,9-dicarboxylic acid dimethyl ester (203) (1.231 g) as a brown oil. The oil was purified using column chromatography (SiO\(_2\), Hexane:EtOAc, 4:1) to afford bicyclo[6.1.0]non-2-ene-9,9-dicarboxylic acid dimethyl ester (203) (0.220 g, 0.93 mmol, 10\% yield) as a clear viscous oil. \(\nu_{\text{max}}/\text{cm}^{-1}\) 3440, 2982, 2953, 2844, 1730 (CO\(_2\)R str.), 1438, 1321, 1316, 1290, 1253, 1197, 1163, 1024; \(\delta_{\text{H}}\) (CDCl\(_3\), 400 MHz) 1.14 (1H, m, 8-CH(H)H), 1.46 (1H, m, 6-C(H)H), 1.63 (1H, m, 7-C(H)H), 1.74 (1H, m, 7-C(H)H), 1.82 (1H, m, 9-CH), 1.93-1.99 (2H, m, 5-C(H)H and 6-C(H)H), 2.05 (1H, m, 8-C(H)H), 2.39 (1H, m, 5-C(H)H), 2.44 (1H, m, 2-CH), 3.75 (3H, s, CO\(_2\)C), 3.77 (3H, s, CO\(_2\)C), 5.57 (1H, m, 4-CH), 5.80 (1H, m, 3-CH); \(\delta_{\text{C}}\) (CDCl\(_3\), 100 MHz) 24.05 (8-CH\(_2\)), 24.76 (6-CH\(_2\)), 29.62 (5-CH\(_2\)), 29.75 (7-CH\(_2\)), 30.24 (2-CH), 32.94 (9-CH), 36.14 (1-CH), 52.13 (CO\(_2\)C\(_3\)), 52.74 (CO\(_2\)C\(_3\)), 120.60 (3-CH), 136.33 (4-CH), 167.15 (C=O), 171.29 (C=O); ms (El): \(m/z\) 238 (M\(^+\), 19\%), 207 (15), 206 (15), 179 (28), 178 (48), 177 (12), 175 (22), 174 (53), 150 (12), 147 (20), 146 (32), 139 (11), 133 (24), 119 (90), 117 (25), 107 (26), 106 (100); HRMS calc. for C\(_{13}\)H\(_{18}\)O\(_4\) 238.1205 found 238.1208.
Preparation of bicyclo[3.1.0]hex-2-ene-6-carboxylic acid ethyl ester (222) (trans:cis; 3:2)\(^{65}\)

To a stirred mixture of 1,3-cyclopentadiene (200) (6.000 g, 91.0 mmol) and Rh\(_2\)(OAc)\(_4\) (0.050 g, 0.12 mmol) was added ethyl diazoacetate (212) (0.310 g, 27.2 mmol) drop wise by syringe at room temperature over 4h. The reaction mixture was stirred at room temperature for a further 2h, cooled to room temperature to afford crude bicyclo[3.1.0]hex-2-ene-6-carboxylic acid ethyl ester (222) (2.061 g) as a light yellow/brown oil. The oil was purified using column chromatography (SiO\(_2\), Hexane:EtOAc, 5:1) to afford bicyclo[3.1.0]hex-2-ene-6-carboxylic acid ethyl ester (222) (2.976 g, 19.6 mmol, 72% yield) as a colourless oil. \(v_{\text{max/cm}}^{-1}\) 3059, 2979, 2904, 1732 (CO\(_2\)R str.), 1399, 1350, 1301, 1264; \(\delta_\text{H}\) (CDCl\(_3\), 400 MHz) 0.91 (1H, m, 6-C'H), 1.23 (3H, t, \(J\ 7.1\) Hz, CH\(_2\)CH\(_3\)), 1.27 (3H, t, \(J\ 7.1\) Hz, C'H\(_2\)C'H\(_3\)), 1.64 (1H, br s, 6-CH), 1.81 (1H, m, 1-CH), 1.99 (1H, m, 2-CH), 2.43-2.49 (3H, m, 2-C'H and 5-C'(H)H), 2.58 (1H, m, 5-C'(H)H), 2.69 (1H, m, 5-C'(H)H), 2.82 (1H, m, 5-C(H)H), 4.03-4.09 (2H, m, CH\(_2\)CH\(_3\)), 4.12 (2H, q, \(J\ 7.1\) and 14.2 Hz, C'H\(_2\)C'H\(_3\)), 5.56 (1H, m, 4-CH), 5.67 (1H, m, 4-C'H), 5.69 (1H, m, 3-C'H), 5.95 (1H, m, 3-CH); \(\delta_\text{C}\) (CDCl\(_3\), 100 MHz) 14.29 (CH\(_2\)CH\(_3\) and C'H\(_2\)C'H\(_3\)), 22.01 (1-CH), 23.26 (2-CH), 26.08 (1-C'H), 30.27 (6-C'H), 31.33 (6-CH), 32.97 (5-C'H), 34.37 (2-C'H), 36.16 (5-C'H), 59.88 (CH\(_2\)CH\(_3\)), 60.31 (C'H\(_2\)C'H\(_3\)), 127.02 (4-CH), 130.38 (4-C'H), 132.09 (3-C'H), 132.46 (3-CH), 169.59 (C=O), 173.41 (C=O); ms (FAB): \(m/z\) 152 (M\(^+\), 39%), 219 (100); HRMS calc. for C\(_9\)H\(_{12}\)O\(_2\) 152.0837 found 152.0840.
Preparation of bicyclo[4.1.0]hex-2-ene-7-carboxylic acid ethyl ester (213) (trans:cis; 2:1)

To a stirred mixture of 1,3-cyclohexadiene (188) (2.000 g, 25.0 mmol) and Rh2(OAc)4 (0.050 g, 0.12 mmol) was added ethyl diazoacetate (212) (0.570 g, 5.00 mmol) drop wise by syringe at room temperature over 1h. The reaction mixture was stirred at room temperature for a further 2h, cooled to room temperature to afford crude bicyclo[4.1.0]hex-2-ene-7-carboxylic acid ethyl ester (213) (2.567 g) as a light yellow/brown oil. The oil was purified using column chromatography (SiO2, Hexane:EtOAc, 5:1) to afford bicyclo[4.1.0]hex-2-ene-7-carboxylic acid ethyl ester (213) (0.598 g, 3.62 mmol, 72% yield) as a colourless oil. v_max/cm⁻¹ 3059, 2979, 2904, 1732 (CO₂R str.), 1399, 1350, 1301, 1264; δH (CDCl₃, 400 MHz) 1.16-1.21 (6H, m, CH₂CH₃ and C’H₂C’H₃), 1.54-1.93 (12H, m, 1-CH, 1-C’H, 2-CH, 2-C’H, 5-CH₂, 5-C’H₂, 6-CH₂, 6-C’H₂), 4.00-4.07 (4H, m, C’H₂C’H₃ and CH₂CH₃), 5.48 (1H, m, 4-CH), 5.72 (1H, m, 4-C’H), 5.76 (1H, m, 3-C’H), 5.92 (1H, m, 3-CH); δ_c (CDCl₃, 100 MHz) 14.29 (C’H₂C’H₃ and CH₂CH₃), 15.91 (6-C’H), 16.77 (6-CH), 20.55 (5-CH₂), 20.95 (2-CH), 21.61 (5-C’H₂), 24.05 (1-CH and 1-C’H), 25.03 (7-CH and 7-C’H), 26.85 (2-C’H), 59.93 (C’H₂C’H₃), 60.40 (CH₂CH₃), 121.20 (4-C’H), 125.19 (4-CH), 125.48 (3-CH), 129.30 (3-C’H), 173.39 (C=O and C’=O); ms (FAB): m/z 167 (M⁺, 16%), 166 (13), 165 (20), 155 (27), 154 (100); HRMS calc. for C₁₀H₁₄O₂ 167.1072 found 167.1075.
Preparation of diazo bis(phenylsulphonyl)methane (223)

To a solution of bis(phenylsulphonyl)methane (190) (0.500 g, 1.69 mmol) and mesyl azide (219) (0.997 g, 8.45 mmol) in CH₃CN (20 ml) was added Et₃N (3.43 g, 0.034 mol) by syringe at room temperature over 10 min. The reaction mixture was stirred at room temperature for a further 4 h at which point 10 % NaOH (50 ml) was added. The aqueous layer was washed with CH₂Cl₂ (3 x 50 mL) and the organic extracts were combined, dried (MgSO₄) and the solvent was removed under reduced pressure affording diazo bis(phenylsulphonyl)methane (223) (0.103 g, 0.32 mmol, 19% yield) as an orange oil. \( \nu_{\text{max}}/\text{cm}^{-1} \) (neat) 3029, 2933, 2377, 2346, 2132 (N₂ str.), 1617, 1476, 1448, 1359, 1166, 1083, 966, 782, 725; \( \delta_H \) (CDCl₃, 400 MHz) 7.59-7.65 (4H, m, 4 x CH arom.), 7.71-7.77 (2H, m, 2 x CH arom.), 7.94-7.99 (4H, m, 4 x CH arom.). \( \delta_C \) (CDCl₃, 100 MHz) 127.48 (4 x CH arom.), 129.76 (4 x CH arom.), 134.91 (2 x CH arom.), 138.42 (2 x C arom. and CN₂); ms (EI): \( m/z \) 322 (M⁺, 6%), 141 (36), 125 (18), 86 (12), 78 (11), 77 (100); HRMS calc. for C₁₃H₁₀N₂O₄S₂ 322.0082 found 322.0081.
Preparation of 3aR,4,5,7aR-tetrahydro-benzofuran-2,3,3-tricarboxylic acid 2S-ethyl ester 3,3-dimethyl ester (233a)

To a stirred solution of ethyl glyoxolate (228) (0.049 g, 0.48 mmol) in anhydrous THF (5 mL) was added zinc bromide (0.216 g, 0.96 mmol). The reaction mixture was left to stir for 10 min before bicyclo[4.1.0]hex-2-ene-6,6-dicarboxylic acid dimethyl ester (186) (0.100 g, 0.48 mmol) was added. The reaction mixture was stirred for a further 5 min before a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.058 g, 0.05 mmol) was added. The resulting mixture was stirred at room temperature for 12h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica to afford crude 3aR,4,5,7aR-tetrahydro-benzofuran-2,3,3-tricarboxylic acid 2S-ethyl ester 3,3-dimethyl ester (233a) (0.178 g). The oil was purified using column chromatography (SiO2, EtOAc:P.E. 40-60, 6:1) to afford 3aR,4,5,7aR-tetrahydro-benzofuran-2,3,3-tricarboxylic acid 2S-ethyl ester 3,3-dimethyl ester (233a) (0.121 g, 0.38 mmol, 81% yield) as a yellow oil. νmax/cm⁻¹ (neat) 2952, 2358, 1731 (C02R str.), 1682, 1575, 1539, 1506, 1489, 1434, 1270, 1156, 1090, 932, 695; δH (CDCl3, 400 MHz) 1.22 (3H, t, J7.2 Hz, CH2Cfu), 1.28 (1H, m, 4-C(H)H), 1.37 (1H, m, 4-C(H)H), 1.90 (1H, m, 5-C(H)H), 2.07 (1H, m, 5-C(H)H), 2.91 (1H, apparent dt, J 4.8, 13.2 Hz, 3a-CH), 3.64 (3H, s, CO2CH3), 3.73 (3H, s, CO2CH3), 4.07-4.18 (2H, m, CH2CH3), 4.69 (1H, m, 7a-CH), 5.85 (1H, s, 2-CH), 5.86 (1H, m, 6-CH), 5.98 (1H, m, 7-CH); δC (CDCl3, 100 MHz) 14.12 (CH2CH3), 20.46 (4-CH2), 24.27 (5-CH2), 43.87 (3a-CH), 52.91 (CO2CH3), 53.10 (CO2CH3), 61.61 (CH2CH3), 68.61 (3-C), 75.88 (2-CH), 79.56 (7a-CH), 124.13 (6-CH), 132.31 (7-CH), 166.41 (2 x C=O), 167.61 (C=O).
Preparation of 3a,4,5,7a-tetrahydro-benzofuran-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (233a)

To a stirred solution of ethyl glyoxolate (228) (0.049 g, 0.48 mmol) in anhydrous CH₂Cl₂ (5 mL) was added zinc bromide (0.216 g, 0.96 mmol). The reaction mixture was left to stir for 10 min before bicyclo[4.1.0]hex-2-ene-6,6-dicarboxylic acid dimethyl ester (186) (0.100 g, 0.48 mmol) was added. The reaction mixture was stirred for a further 5 min before a catalytic amount of bis(dibenzylideneacetone) palladium(0) (0.045 g, 0.05 mmol) was added. The resulting mixture was stirred at room temperature for 12h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica to afford crude 3a,4,5,7a-tetrahydro-benzofuran-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (233a) (0.168 g). The oil was purified using column chromatography (SiO₂, EtOAc:P.E 40-60, 6:1) to afford 3a,4,5,7a-tetrahydro-benzofuran-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (233a) (0.121 g, 0.39 mmol, 81% yield) as a viscous yellow oil. Data as above.

Preparation of 5-vinyl-dihydro-furan-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (234) (trans:cis; 1.1:1)⁴⁸

To a stirred solution of ethyl glyoxolate (228) (0.050 g, 0.27 mmol) in anhydrous THF (2 mL) was added zinc bromide (0.112 g, 0.54 mmol). The reaction mixture was left to stir for 10 min before 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester (155) (0.050 g, 0.27 mmol) was added. The reaction mixture was stirred for a further 5 min before a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.031 g, 0.03 mmol) was added. The resulting mixture was stirred at room temperature for 12h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of
silica and the organic extract washed with 1 M HCl (20 mL), sat. NaHCO₃ aq. sol. (20 mL), sat. NaCl aq. sol. (20 mL) and dried (MgSO₄). The solvent was removed under reduced pressure to afford 5-vinyl-dihydro-furan-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (234) (0.046 g, 0.16 mmol, 59% yield) as a viscous yellow oil. ν<sub>max</sub>/cm<sup>-1</sup> (neat) 2954, 1731 (CO<sub>2</sub>R str.), 1462, 1330, 1274, 1215; δ<sub>H</sub> (CDCl₃, 250 MHz) 1.22 (6H, t, J<sub>7.2</sub> Hz, C'H₂Cfu and CH₂Cfu), 2.27 (1H, dd, J<sub>6.8</sub> and 13.1 Hz, 4-C(H)H), 2.53 (1H, dd, J 9.8 and 13.0 Hz, 4-C'(H)H), 2.65 (1H, dd, J 6.2 and 13.0 Hz, 4-C'(H)H), 2.91 (1H, dd, J 7.6 and 13.1 Hz, 4-C(H)H), 3.66 (3H, s, C'O₂C'H₃), 3.70 (3H, s, C'O₂C'H₃), 3.73 (3H, s, CO₂CH₃), 3.77 (3H, s, CO₂CH₃), 4.05-4.20 (4H, m, C'H₂CH₃ and CH₂CH₃), 4.40 (1H, m, 5-C'H), 4.82 (1H, m, 5-CH), 4.96 (1H, m, 2-C'H), 5.08 (1H, m, C'(H)H=CH), 5.11 (1H, s, 2-CH), 5.13 (1H, m, C(H)H=CH), 5.23 (1H, m, C'(H)H=CH), 5.24 (1H, m, C(H)H=CH), 5.74 (1H, m, CH₂=C'H), 5.93 (1H, m, CH₂=CH); δ<sub>c</sub> (CDCl₃, 100 MHz) 13.96 (CH₃C'H₃), 13.98 (CH₃CH₃), 39.12 (4-C'H₂), 39.55 (4-CH₂), 52.97 (CO₂C'H₃), 53.04 (CO₂C'H₃), 53.25 (CO₂CH₃), 53.41 (CO₂CH₃), 61.34 (C'H₂CH₃), 61.37 (C'H₂CH₃), 64.09 (3-C'), 64.44 (3-C'), 80.51 (5-C'H), 81.00 (5-CH), 81.28 (2-C'H), 81.28 (2-CH), 116.67 (C'H₂=CH), 117.74 (CH₂=CH), 136.95 (CH₂=C'H), 136.98 (CH₂=C'H), 167.79 (C'=O), 168.27 (C=O), 169.39 (C'=O), 169.41 (C'=O), 169.63 (C=O), 169.71 (C=O); ms (FAB): m/z 287 (M⁺, 61%), 285 (11), 227 (22), 214 (12), 213 (100); HRMS calc. for C₁₃H₁₈O₇ 287.1131 found 287.1135.

Preparation of 2-phenyl-5-vinyl-dihydro-furan-3,3-dicarboxylic acid -dimethyl ester (227) (trans: cis; 3:1)<sup>47</sup>

To a stirred solution of benzaldehyde (162) (0.029 g, 0.27 mmol) in anhydrous THF (2 mL) was added zinc bromide (0.112 g, 0.54 mmol). The reaction mixture was left to stir for 10 min before 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester
(155) (0.050 g, 0.27 mmol) was added. The reaction mixture was stirred for a further 5 min before a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.031 g, 0.10 mmol) was added. The resulting mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica and the organic extract washed with 1 M HCl (20 mL), sat. NaHCO₃ aq. sol. (20 mL), sat. NaCl aq. sol. (20 mL) and dried (MgSO₄). The solvent was removed under reduced pressure to afford 2-phenyl-5-vinyl-dihydro-furan-3,3-dicarboxylic acid dimethyl ester (227) (0.051 g, 0.18 mmol, 64% yield) as a viscous yellow oil. νmax/cm⁻¹ (neat) 2984, 2938, 2906, 1731 (C=O R str.), 1438, 1330, 1267, 1210; δH (CDCl₃, 400 MHz) 2.20 (1H, dd, J 8.0 and 12.0 Hz, 4-C(H)H), 2.49 (1H, dd, J 8.0 and 12.0 Hz, 4-C'(H)H), 2.77 (1H, dd, J 8.0 and 14.0 Hz, 4-C'(H)H), 3.10 (1H, dd, J 8.0 and 12.0 Hz, 4-C(H)H), 3.11 (3H, s, C'O₂C'H₂), 3.17 (3H, s, CO₂CH₃), 3.77 (3H, s, CO₂CH₃), 3.80 (3H, s, C'O₂C'H₃), 4.41 (1H, m, 5-C'H), 5.05 (1H, m, 5-C'H), 5.25-5.43 (4H, m, C'H₂=C'H and CH₂=CH), 5.68 (1H, s, 2-C'H), 5.79 (1H, s, 2-CH), 5.90 (1H, m, CH₂=CH), 6.10 (1H, m, C'H₂=C'H), 7.24-7.41 (10H, m, 5 x CH arom. And 5 x C'H arom.); δC (CDCl₃, 100 MHz) 40.37 (4-C'H₂), 40.54 (4-CH₂), 52.15 (C'O₂C'H₃), 52.17 (C'O₂C'H₃), 52.82 (CO₂CH₃), 52.98 (CO₂CH₃), 66.22 (3-C'), 79.24 (5-C'H), 79.96 (5-CH), 83.51 (2-CH), 84.24 (2-C'H), 116.10 (CH₂=CH), 117.68 (C'H₂=C'H), 126.97 (CH arom and C'H arom.), 127.81 (CH arom and C'H arom.), 127.87 (CH arom and C'H arom.), 127.99 (CH arom and C'H arom.), 128.13 (CH arom and C'H arom.), 136.48 (C'H₂=C'H), 137.79 (CH₂=CH), 138.15 (2-CHC'), 138.28 (2-CHC'), 168.97 (C'-=O), 169.14 (C'-=O), 170.42 (C=O), 171.22 (C=O), ms (El): m/z 290 (M⁺, 14%), 278 (24), 277 (52), 236 (57), 230 (19), 204 (17), 185 (10), 184 (56), 153 (42), 152 (74), 125 (35), 124 (75), 121 (47), 117 (14), 116 (21), 115 (52), 113 (12), 105 (100); HRMS calc. for C₁₈H₁₈O₅ 290.1154 found 290.1151.
Chapter 6

Preparation of 2-(4-nitro-phenyl)-5-vinyl-dihydro-furan-3,3-dicarboxylic acid dimethyl ester (235) (trans:cis; 1:1.7)\(^{45}\)

![Chemical structure of 2-(4-nitro-phenyl)-5-vinyl-dihydro-furan-3,3-dicarboxylic acid dimethyl ester (235)](image)

To a stirred solution of 4-nitrobenzaldehyde (229) (0.041 g, 0.27 mmol) in anhydrous THF (2 mL) was added zinc bromide (0.112 g, 0.54 mmol). The reaction mixture was left to stir for 10 min before 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester (151) (0.050 g, 0.27 mmol) was added. The reaction mixture was stirred for a further 5 min before a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.031 g, 0.03 mmol) was added. The resulting mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica and the organic extract washed with 1 M HCl (20 mL), sat. NaHCO₃ aq. sol. (20 mL), sat. NaClaq. sol. (20 mL) and dried (MgSO₄). The solvent was removed under reduced pressure to afford crude 2-(4-nitro-phenyl)-5-vinyl-dihydro-furan-3,3-dicarboxylic acid dimethyl ester (235) (0.154 g). The oil was purified using column chromatography (SiO₂, EtOAc:P.E 40-60, 8:1) to afford 2-(4-nitro-phenyl)-5-vinyl-dihydro-furan-3,3-dicarboxylic acid dimethyl ester (235) (0.078 g, 0.23 mmol, 86% yield) as a viscous yellow oil. \(v_{\text{max}}/\text{cm}^{-1}\) (neat) 2954, 1731 (C=O str.), 1523 (NO₂ str.), 1438, 1330, 1274, 1210, 957; \(\delta_{\text{H}}\) (CDCl₃, 400 MHz) 2.16 (1H, dd, \(J_{7.6\text{ Hz and }13.2\text{ Hz}}\), \(4-C\)'CH), 2.50 (1H, dd, \(J_{6.4\text{ Hz and }13.4\text{ Hz}}\), \(4-C\)'),H), 2.68 (1H, dd, \(J_{9.8\text{ Hz and }13.4\text{ Hz}}\), \(4-C\)')H), 2.94 (1H, dd, \(J_{9.6\text{ Hz and }13.2\text{ Hz}}\), \(4-C\)')H), 3.09 (3H, s, \(C'O_2C'\)H₂), 3.14 (3H, s, CO₂CH₃), 3.72 (3H, s, CO₂CH₃), 3.76 (3H, s, \(C'O_2C'\)H₂), 4.39 (1H, m, \(5-C\)'H), 5.03 (1H, m, 5-CH), 5.14 (1H, apparent dt, \(J_{1.2\text{ Hz and }10.4\text{ Hz}}\), \(C(H)H=CH\)), 5.23 (1H, apparent dt, \(J_{1.2\text{ Hz and }10.4\text{ Hz}}\), \(C(H)H=CH\)), 5.29 (1H, apparent dt, \(J_{1.2\text{ Hz and }16.8\text{ Hz}}\), \(C(H)H=CH\)), 5.35 (1H, apparent dt, \(J_{1.2\text{ Hz and }18.4\text{ Hz}}\), \(C(H)H=CH\)), 5.64 (1H, s, 2-C'H), 5.75 (1H, s, 2-CH), 5.84 (1H, m, \(CH_2=CH\)), 6.02 (1H, m, \(C'H_2=C'H\)), 7.54-7.60 (4H, m, 2 x CH arom. and 2 x C'H)
Chapter 6

Preparation of 2-(4-nitro-phenyl)-5-vinyl-dihydro-furan-3,3-dicarboxylic acid dimethyl ester (235) (trans:cis; 1:7)

To a stirred solution of 4-nitrobenzaldehyde (229) (0.041 g, 0.27 mmol) in anhydrous MeOH (2 mL) was added 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester (155) (0.050 g, 0.27 mmol). A catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.031 g, 0.03 mmol) was then added. The resulting mixture was stirred at room temperature for 12h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica and the organic layer washed with 1 M HCl (20 mL), sat. NaHCO₃ aq. sol. (20 mL), sat. NaCl aq. sol. (20 mL) and dried (MgSO₄). The solvent was removed under reduced pressure to afford crude 2-(4-nitro-phenyl)-5-vinyl-dihydro-furan-3,3-dicarboxylic acid dimethyl ester (235) (0.112 g). The oil was purified using column chromatography (SiO₂, EtOAc:P.E 40-60, 8:1) to afford 2-(4-nitro-phenyl)-5-vinyl-dihydro-furan-3,3-dicarboxylic acid dimethyl ester (235) (0.072 g, 0.21 mmol, 80% yield) as a viscous yellow oil as predominantly the cis isomer.

Selected data for the cis isomer (235b):- νmax/cm⁻¹ (neat) 2954, 1731 (CO₂R str.), 1523 (NO₂ str.), 1438, 1330, 1274, 1210, 957; δH (CDCl₃, 400 MHz) 2.50 (1H, dd, J 6.4 and 13.4 Hz, 4-C'(H)H), 2.68 (1H, dd, J 9.8 and 13.4 Hz, 4-C'(H)H), 3.09 (3H, s, C'O₂C'H₃), 3.76 (3H, s, C'O₂C'H₃), 4.39 (1H, m, 5-C'H), 5.23 (1H, apparent dt, J 1.2 and 10.4 Hz, C'(H)H=C'H), 5.35 (1H, apparent dt, J 1.2 and 10.4 Hz, C'(H)H=C'H), 5.64 (1H, s, 2-C'CH₆), 6.02 (1H, m, C'H₂=C'H), 7.56 (2H, d, J 8.8 Hz, 2 x C'H arom.), 8.09 (2H, d, J 8.8 Hz, 2 x C'H arom.); δC (CDCl₃, 100 MHz) 40.44 (4-C'H₂), 52.43 (C'O₂C'H₃), 53.23 (C'O₂C'H₃), 66.15 (3-C'), 79.67 (5-C'H), 83.16 (2-C'H), 118.29 (C'H₂=C'H), 123.03 (2 x C'H arom.), 127.90 (2 x C'H arom.), 135.95 (C'H₂=C'H), 145.03 (2-CHC and 2-CH₂), 147.69 (CNO₂ and C'NO₂), 168.60 (C'=O), 169.61 (C'=O), 170.76 (C'=O).
Preparation of 5-vinyl-4,5-dihydro-[2,2']bifuranyl-3,3-dicarboxylic acid dimethyl ester (236) (trans:cis; 1:1.9)\textsuperscript{18}

To a stirred solution of 2-furan aldehyde (230) (0.026 g, 0.27 mmol) in anhydrous THF (2 mL) was added zinc bromide (0.112 g, 0.54 mmol). The reaction mixture was left to stir for 10 min before 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester (155) (0.050 g, 0.27 mmol) was added. The reaction mixture was stirred for a further 5 min before a catalytic amount of tetrakis(triphenylphosphine)palladium(0) (0.031 g, 0.03 mmol) was added. The resulting mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica and the organic extract washed with 1 M HCl (20 mL), sat. NaHCO\textsubscript{3} aq. sol. (20 mL), sat. NaCl aq. sol. (20 mL) and dried (MgSO\textsubscript{4}). The solvent was removed under reduced pressure to afford 5-vinyl-4,5-dihydro-[2,2']bifuranyl-3,3-dicarboxylic acid dimethyl ester (236) (0.036 g, 0.13 mmol, 48% yield) as a yellow oil without further purification. \( v_{\text{max}}/\text{cm}^{-1} \) (neat) 2952, 1734 (C=O str.), 1501, 1434, 1273, 1160, 1048, 1019, 930, 874, 795; \( \delta_{\text{H}} \) (CDCl\textsubscript{3}, 400 MHz) 2.16 (1H, dd, \( J \) 6.8 and 13.2 Hz, 4-C(H)H), 2.47 (1H, dd, \( J \) 5.6 and 13.2 Hz, 4-C'(H)H), 2.76 (1H, dd, \( J \) 10.8 and 13.2 Hz, 4-C'(H)H), 3.08 (1H, dd, \( J \) 7.6 and 13.2 Hz, 4-C(H)H), 3.39 (3H, s, C'O\textsubscript{2}C'fu), 3.42 (3H, s, C0\textsubscript{2}Cfu), 3.70 (3H, s, C0\textsubscript{2}Cfu), 3.75 (3H, s, C'O\textsubscript{2}C'fu), 4.34 (1H, m, 5-CH), 4.91 (1H, m, 5-C'H), 5.06-5.30 (4H, m, CH\textsubscript{2}=CH and C'H\textsubscript{2}=CH), 5.65 (1H, s, 2-C'H), 5.75 (1H, s, 2-CH), 5.77 (1H, m, CH\textsubscript{2}=CH), 5.94 (1H, m, C'H\textsubscript{2}=C'H), 6.23-6.28 (2H, m, CH arom. and C'H arom.), 7.20-7.61 (4H, m, 2 x CH arom. and 2 x C'H arom.); \( \delta_{\text{C}} \) (CDCl\textsubscript{3}, 100 MHz) 39.16 (4-C'H\textsubscript{2}), 39.30 (4-CH\textsubscript{2}), 52.90 (CO\textsubscript{2}CH\textsubscript{3}), 52.99
Preparation of 2-(4-methoxy-phenyl)-5-vinyl-dihydro-furan-3,3-dicarboxylic acid dimethyl ester (236) (trans:cis; 1:8)

To a stirred solution of 4-methoxy aldehyde (230) (0.037 g, 0.27 mmol) in anhydrous THF (2 mL) was added zinc bromide (0.112 g, 0.54 mmol). The reaction mixture was left to stir for 10 min before 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester (155) (0.050 g, 0.27 mmol) was added. The reaction mixture was stirred for a further 5 min before a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.031 g, 0.03 mmol) was added. The resulting mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica and the organic extract washed with 1 M HCl (20 mL), sat. NaHCO₃ aq. sol. (20 mL), sat. NaCl aq. sol. (20 mL) and dried (MgSO₄). The solvent was removed under reduced pressure to afford 2-(4-methoxy-phenyl)-5-vinyl-dihydro-furan-3,3-dicarboxylic acid dimethyl ester (236) (0.034 g, 0.11 mmol, 39% yield) as a yellow oil without further purification as predominantly the cis isomer.

Selected data for the cis isomer (236b): \( \nu_{\text{max}} / \text{cm}^{-1} \) (neat) 2949, 1730 (C=O str.), 1437, 2333, 1253, 1199, 1107, 1023, 919; \( \delta_H \) (CDCl₃, 400 MHz) 2.42 (1H, dd, \( J = 6.0 \) Hz)
and 13.2 Hz, 4-C'(H)H), 2.68 (1H, dd, J 10.2 and 13.2 Hz, 4-C'(H)H), 3.10 (3H, s, C'O₂C'H₃), 3.70 (3H, s, C'O₂C'H₃), 3.73 (3H, s, OC'H₃), 4.31 (1H, m, 5-C'H), 5.19 (1H, m, C'(H)H=C'H), 5.33 (1H, m, C'(H)H=C'H), 5.56 (1H, s, 2-C'H), 6.01 (1H, m, C'H₂=C'H), 6.75 (2H, d, J 6.8 Hz, 2 x C'H arom.), 7.22 (2H, d, J 20.4 Hz, 2 x C'H arom.); δC (CDCl₃, 100 MHz) 40.26 (4-C'H₂), 52.30 (C'O₂C'H₃), 52.97 (C'O₂C'H₃), 55.61 (OC'H₃), 66.00 (3-C'), 79.09 (5-C'H), 83.97 (2-C'H), 113.19 (2 x C'H arom.), 117.66 (C'H₂=C'H), 128.20 (2 x C'H arom.), 135.95 (C'H₂=C'H), 145.03 (2-CHC'), 147.69 (C'NO₂), 169.09 (C'═O), 171.28 (C'═O); ms (FAB): m/z 320 (M⁺, 3%), 280 (21), 279 (100); HRMS calc. for C₁₇H₂₀O₆ 320.1260 found 320.1266.

Preparation of 2-methyl-5-vinyl-dihydro-furan-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (241) (trans:cis; 4:1)⁴⁷

To a stirred solution of ethyl pyruvate (238) (0.031 g, 0.27 mmol) in anhydrous THF (2 mL) was added zinc bromide (0.112 g, 0.54 mmol). The reaction mixture was left to stir for 10 min before 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester (155) (0.050 g, 0.27 mmol) was added. The reaction mixture was stirred for a further 5 min before a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.031 g, 0.03 mmol) was added. The resulting mixture was stirred at room temperature for 12h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica and the organic extract washed with 1 M HCl (20 mL), sat. NaHCO₃ aq. sol. (20 mL), sat. NaCl aq. sol. (20 mL) and dried (MgSO₄). The solvent was removed under reduced pressure to afford 2-methyl-5-vinyl-4,5-dihydro-[2,2']bifuranyl-3,3-dicarboxylic acid dimethyl ester (241) (0.033 g, 0.11 mmol, 41% yield) as a yellow oil without further purification as predominantly the trans isomer.
Selected data for the trans isomer (241a): $v_{\text{max}}/\text{cm}^{-1}$ (neat) 2987, 2952, 1734 (CO$_2$R str.); 1437, 1331, 1273, 1211, 1130, 1095, 1020, 996, 722; $\delta$H (CDCl$_3$, 400 MHz) 1.20-1.23 (3H, t, J 4.8 Hz, CH$_2$CH$_3$), 1.49 (3H, s, 2-CCH$_3$), 2.42 (1H, m, 4-C(H)H), 2.91 (1H, dd, J 8.8 and 13.6 Hz, 4-C(H)H), 3.66 (3H, s, CO$_2$CH$_3$), 3.70 (3H, s, CO$_2$CH$_3$), 4.07-4.17 (2H, m, CH$_2$CH$_3$), 4.58 (1H, m, 5-CH), 5.16-5.22 (2H, m, CH$_2$=CH), 5.98 (1H, m, CH$_2$=CH); $\delta$c (CDCl$_3$, 100 MHz) 13.97 (CH$_2$CH$_3$), 20.50 (2-CCH$_3$), 40.03 (4-CCH$_3$), 52.86 (CO$_2$CH$_3$), 52.88 (CO$_2$CH$_3$), 61.50 (CH$_2$CH$_3$), 66.90 (3-C), 80.00 (5-C'H), 87.11 (2-C), 117.38 (CH$_2$=CH), 137.80 (CH$_2$=CH), 167.75 (C=O), 170.16 (C=O), 171.42 (C=O).

Preparation of 2-(4-nitro-phenyl)-5-vinyl-dihydro-furan-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (242b) (trans:cis; 0:1)$^{37}$

![Chemical Structure]

To a stirred solution of ethyl 4-nitrophenyl glyoxolate (239) (0.060 g, 0.27 mmol) in anhydrous THF (2 mL) was added zinc bromide (0.112 g, 0.54 mmol). The reaction mixture was left to stir for 10 min before 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester (155) (0.050 g, 0.27 mmol) was added. The reaction mixture was stirred for a further 5 min before a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.031 g, 0.03 mmol) was added. The resulting mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica and the organic extract washed with 1 M HCl (20 mL), sat. NaHCO$_3$ aq. sol. (20 mL), sat. NaCl aq. sol. (20 mL) and dried (MgSO$_4$). The solvent was removed under reduced pressure to afford crude 2-(4-nitro-phenyl)-5-vinyl-dihydro-furan-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (242b) (0.158 g). The oil was purified using column chromatography (SiO$_2$, EtOAc:P.E 40-60, 8:1)

- 197 -
to afford 2-(4-nitro-phenyl)-5-vinyl-dihydro-furan-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (242b) (0.079 g, 0.19 mmol, 72% yield) as a viscous yellow oil. $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2954, 1731 (CO$_2$R str.), 1532 (NO$_2$ str.), 1438, 1330, 1274, 1210; 6 (CDCl$_3$, 400 MHz) 1.25 (3H, t, $J=7.1$ Hz, C'H$_2$C'H$_3$), 2.65 (1H, dd, $J=5.6$ and 13.3 Hz, 4-C'(H)H), 3.18 (3H, s, C'O$_2$C'H$_3$), 3.21 (1H, dd, $J=4.0$ and 8.2 Hz, 4-C'(H)H), 3.83 (3H, s, C'O$_2$C'H$_3$), 4.21 (2H, m, C'H$_2$C'H$_3$), 4.91 (1H, m, 5-C'H), 5.31 (1H, m, C'(H)H=C'H), 5.40 (1H, m, C'(H)H=C'H), 6.26 (1H, m, C'H$_2$=C'H), 7.50 (2H, d, $J=9.2$ Hz, 2 x C'H arom.), 8.18 (2H, d, $J=9.2$ Hz, 2 x C'H arom.); 6 (CDCl$_3$, 100 MHz) 13.88 (C'H$_2$C'H$_3$), 40.53 (4-C'H$_2$), 52.64 (C'O$_2$C'H$_3$), 53.08 (C'O$_2$C'H$_3$), 62.40 (C'H$_2$C'H$_3$), 69.04 (3-C'), 80.97 (5-C'H), 90.40 (2-C'), 118.08 (C'H$_2$=C'H), 122.21 (2 x C'H arom.), 128.89 (2 x C'H arom.), 137.05 (2-C'H$_2$), 137.15 (C'H$_2$=C'H), 143.34 (C'=NO$_2$), 168.57 (C'=O), 169.21 (C'=O), 169.77 (C'=O); ms (FAB): m/z 408 (M$^+$, 13%), 334 (41), 318 (13), 270 (15), 236 (17), 194 (25), 185 (48), 165 (28), 153 (100); HRMS calc. for C$_{19}$H$_{21}$N$_2$O$_8$ 408.1216 found 408.1294.

Preparation of dimethyl-5'-nitro-2'-oxo-5-vinyl-1',2',4,5-tetrahydro-3H-spiro[furan-2,3'-indole]-3,3-dicarboxylate (243) (trans:cis; 1:5:1)$^{17}$

To a stirred solution of 5-nitroisatin (240) (0.048 g, 0.27 mmol) in anhydrous THF (2 mL) was added zinc bromide (0.112 g, 0.54 mmol). The reaction mixture was left to stir for 10 min before 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester (155) (0.050 g, 0.27 mmol) was added. The reaction mixture was stirred for a further 5 min before a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.031 g, 0.03 mmol) was added. The resulting mixture was stirred at room temperature for 12h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica and the organic extract washed with 1 M HCl (20 mL), sat. NaHCO$_3$ aq. sol. (20 mL), sat. NaCl aq. sol. (20 mL) and dried (MgSO$_4$). The solvent was removed under reduced
pressure to afford crude dimethyl-5'-nitro-2'-oxo-5-vinyl-1',2',4,5-tetrahydro-3H-spiro[furan-2,3'-indole]-3,3-dicarboxylate (243) (0.158 g). The oil was purified using column chromatography (SiO₂, EtOAc:P.E 40-60, 4:1) to afford dimethyl-5'-nitro-2'-oxo-5-vinyl-1',2',4,5-tetrahydro-3H-spiro[furan-2,3'-indole]-3,3-dicarboxylate (243) (0.062 g, 0.16 mmol, 61% yield) as a pale solid (m.p. 174-176°C). v_max/cm⁻¹ (thin film) 2358, 1732 (C=O str.), 1682, 1652, 1557, 1539 (N=O str.), 1506, 1489, 1456; δ_H (CDCl₃, 250 MHz) 2.70 (1H, dd, J 5.1 and 13.1 Hz, 4-C'(IDH)), 2.89 (1H, dd, J 6.4 and 13.0 Hz, 4-C'(H)H), 3.16 (1H, dd, J 9.8 and 13.0 Hz, 4-C'(H)H), 3.26 (1H, dd, J 9.6 and 13.1 Hz, 4-C(H)H), 3.70 (6H, s, CO₂CH₃ and C'O₂C'H₃), 3.82 (3H, s, C'O₂C'H₃), 3.83 (3H, s, CO₂CH₃), 5.16-5.37 (6H, m, CH₂=CH, C'H₂=C'H, 5-CH, 5-C'H), 6.09 (1H, m, CH₂=CH), 6.30 (1H, m, C'H₂=C'H), 6.94-6.99 (2H, m, CH arom. and C'H arom.), 7.98-7.99 (2H, m, CH arom. and C'H arom.), 8.14-8.16 (2H, m, NH and N'H), 8.23-8.29 (2H, m, CH arom. and C'H arom.).

Preparation of 4-methoxybenzene ethylester imine (245)⁴⁸

To a solution of ethyl glyoxalate in toluene (50%) (228) (4.10 mL, 20.0 mmol) in Et₂O (30.0 mL) containing molecular sieves (4 Å, 5.000 g) was added p-anisidane (244) (2.610 g, 20.0 mmol). The brown reaction mixture was stirred at room temperature for 12h. The solution was filtered removing the molecular sieves and the solvent was removed under reduced pressure furnishing 4-methoxybenzene ethylester imine (245) (3.340 g, 12.6 mmol, 94% yield) as a brown oil. v_max/cm⁻¹ (neat) 2980, 2837, 1740 (CO₂R str.), 1715 (C=O str.), 1590, 1578, 1505, 1465, 1442, 1370, 1347, 1295, 1250, 1215, 1161, 1095, 836; δ_H (CDCl₃, 400 MHz) 1.41 (3H, t, J 7.2 Hz, CH₂CH₃), 3.84 (3H, s, OCH₃), 4.42 (2H, q, J 7.2 Hz, CH₂CH₃), 6.93 (2H, d, J 7.0 Hz, 2-CH and 6-CH arom.), 7.37 (2H, d, J 7.0 Hz, 3-CH and 5-CH arom.), 7.95 (1H, s, N=CH); δ_C (CDCl₃, 100 MHz) 14.62 (CH₂CH₃), 56.03 (N=CH), 62.32 (CH₂CH₃), 114.90 (2-CH and 6-CH arom.), 124.04 (3-CH and 5-CH arom.), 141.70 (1-C), 148.38 (OCH₃), 160.90 (4-C), 164.0 (C=O).
Preparation of 1-(4-methoxy-phenyl)-5-vinyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (246a) \((trans:cis; 1:0)^4\)

To a stirred solution of 4-methoxybenzene ethylester imine (245) (0.056 g, 0.27 mmol) in anhydrous THF (2 mL) was added zinc bromide (0.112 g, 0.54 mmol). The reaction mixture was left to stir for 10 min before 2-vinylecyclopropane-1,1-dicarboxylic acid dimethyl ester (155) (0.050 g, 0.27 mmol) was added. The reaction mixture was stirred for a further 5 min before a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.031 g, 0.03 mmol) was added. The resulting mixture was stirred at room temperature for 12h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica and the organic layer washed with 1 M HCl (20 mL), sat. NaHCO₃ aq. sol. (20 mL), sat. NaCl aq. sol. (20 mL) and dried (MgSO₄). The solvent was removed under reduced pressure to afford crude 1-(4-methoxy-phenyl)-5-vinyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (246a) (0.126 g) as a brown oil. The oil was purified using column chromatography (SiO₂, EtOAc:PE 40-60, 8:1) to afford 1-(4-methoxy-phenyl)-5-vinyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (246a) (0.065 g, 0.17 mmol, 61% yield) as a viscous brown oil. \(\nu_{\max}/\text{cm}^{-1}\) (neat) 2954, 1731 (C=O str.), 1438, 1411, 1330, 1274, 1210; \(\delta_H\) (CDCl₃, 250 MHz) 1.07 (3H, t, \(J 7.2\) Hz, CH₂CH₃), 2.45 (1H, dd, \(J 1.2\) and 13.2 Hz, 4-C(H)H), 3.12 (1H, dd, \(J 10.0\) and 13.2 Hz, 4-C(H)H), 3.65 (3H, s, CO₂CH₃), 3.66 (3H, s, OCH₃), 3.67 (3H, s, CO₂CH₃), 3.97 (2H, m, CH₂CH₃), 4.74 (1H, m, 5-CH), 4.98 (1H, d, \(J 8.0\) Hz, C(H)H=CH), 5.02 (1H, d, \(J 15.2\) Hz, C(H)H=CH), 5.23 (1H, s, 2-CH), 5.61 (1H, m, CH₂=CH), 6.52 (2H, d, \(J 6.8\) Hz, 2 x CH arom.), 6.70 (2H, d, \(J 6.8\) Hz, 2 x CH arom.); \(\delta_C\) (CDCl₃, 100 MHz) 14.60 (CH₂CH₃), 37.58 (4-CH₂), 53.58 (CO₂CH₃), 53.63 (CO₂CH₃), 55.98
(OCH₃), 60.27 (5-CH), 61.68 (CH₂CH₃), 62.04 (3-C), 67.27 (2-CH), 114.89 (2 x CH arom.), 115.41 (2 x CH arom.), 115.76 (CH₂=CH), 139.15 (CH₂=CH), 139.84 (NC), 152.47 (COMe), 168.47 (C=O), 169.91 (C=O), 171.19 (C=O); ms (FAB): m/z 391 (M⁺, 45%), 390 (10), 319 (19), 318 (100); HRMS calc. for C₂₀H₂₅N₂O₇ 391.1631 found 391.1635.

Preparation of 1-(4-methoxy-phenyl)-5-vinyl-pyrrolidine-2,3,3-tricarboxylic acid trimethyl ester (247a) (trans:cis; 1:0)

To a stirred mixture of 4-methoxybenzene ethylester imine (245) (0.056 g, 0.27 mmol) and 2-vinylcyclopropane-1,1-dicarboxylic acid (155) (0.050 g, 0.27 mmol) in MeOH (5 ml) was added a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.031 g, 0.03 mmol). The resulting mixture was stirred at room temperature for 12h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica and the organic layer washed with 1 M HCl (20 mL), sat. NaHCO₃ aq. sol. (20 mL), sat. NaCl aq. sol. (20 mL) and dried (MgSO₄). The solvent was removed under reduced pressure to afford crude 1-(4-methoxy-phenyl)-5-vinyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (247a) (0.158 g) as a brown oil. The oil was purified using column chromatography (SiO₂, EtOAc:P.E. 40-60 °C, 1:8) to afford crude 1-(4-methoxy-phenyl)-5-vinyl-pyrrolidine-2,3,3-tricarboxylic acid 2-ethyl ester 3,3-dimethyl ester (247a) (0.031 g, 0.08 mmol, 30% yield) as a viscous brown oil. v_max/cm⁻¹ (neat) 2954, 1731 (CO₂R str.), 1438, 1411, 1330, 1274, 1210; δ_H (CDCl₃, 250 MHz) 2.45 (1H, dd, J 1.2 and 13.2 Hz, 4-C(H)H), 3.12 (1H, dd, J 10.0 and 13.2 Hz, 4-C(H)H), 3.63 (3H, s, CO₂CH₃), 3.65 (3H, s, OCH₃), 3.66 (3H, s, OCH₃), 3.67 (3H, s, CO₂CH₃), 4.74 (1H, m, 5-CH), 4.99 (1H, d, J 5.0 Hz,
C(H)H=CH), 5.02 (1H, d, J 12.0 Hz, C(H)H=CH), 5.28 (1H, s, 2-CH), 5.61 (1H, m, CH2=CH), 6.51 (2H, d, J 9.0 Hz, 2 x CH arom.), 6.70 (2H, d, J 9.0 Hz, 2 x CH arom.); δC (CDCl3, 100 MHz) 37.27 (4-CH2), 53.33 (CO2CH3), 53.51 (CO2CH3), 55.60 (OCH3), 55.69 (OCH3), 59.92 (5-CH), 61.78 (3-CH), 66.90 (2-CH), 115.00 (2 x CH arom.), 115.46 (2 x CH arom.), 116.69 (CH2=CH), 138.77 (CH2=CH), 139.35 (N=CH), 152.16 (COMe), 168.21 (C=O), 169.44 (C=O), 171.38 (C=O); ms (ES): m/z 378 (M+, 100%); HRMS calc. for C19H23ON 378.1547 found 378.1545.

Preparation of benzyl-benzylidene-amine (249)

To a solution of benzaldehyde (162) (0.991 g, 9.35 mmol) and molecular sieves (4 Å, 5.000 g) in Et2O (30.0 mL) was added benzylamine (248) (1.000 g, 9.35 mmol). The yellow reaction mixture was stirred at room temperature for 12h. The solution was filtered, removing the molecular sieves and the solvent removed under reduced pressure furnishing benzyl-benzylidene-amine (249) (1.385 g, 7.10 mmol, 76% yield) as a pale yellow oil. v_max/cm^-1 (neat) 3026, 2838, 1643, 1579, 1495, 1451, 1378, 1311, 1291, 1219, 1026, 753; δH (CDCl3, 400 MHz) 4.62 (2H, s, NCH2), 7.38 (1H, m, CH arom.), 7.16-7.20 (4H, m, 4 x CH arom.), 7.48-7.53 (3H, m, 3 x CH arom.), 7.88-7.92 (2H, m, 2 x CH arom.), 8.13 (1H, s, N=CH); δC (CDCl3, 100 MHz) 65.15 (NCH2), 127.11 (CH arom.), 128.10 (2 x CH arom.), 128.41 (2 x CH arom.), 128.62 (2 x CH arom.), 128.72 (2 x CH arom.), 130.88 (CH arom.), 136.28 (NCH2C), 139.44 (N=CHC), 162.07 (N=CH).
Preparation of benzyl-(4-nitro-benzylidene)-amine (250)

The imine was prepared following the general procedure for compound (249) to afford benzyl-(4-nitro-benzylidene)-amine (250) (1.930 g, 8.04 mmol, 86% yield) as a pale yellow powder. $v_{\text{max}}$/cm$^{-1}$ (thin film) 2849, 1645, 1601, 1520 (NO$_2$ str.), 1494, 1452, 1344, 1292, 1107, 854, 839; $\delta_H$ (CDCl$_3$, 400 MHz) 4.79 (2H, s, NCH$_2$), 7.19 (1H, m, CH arom.), 7.25-7.33 (4H, m, 4 x CH arom.), 7.85 (2H, d, J 8.8 Hz, 2 x CH arom.), 8.17 (2H, d, J 8.8 Hz, 2 x CH arom.), 8.37 (1H, s, N=CH); $\delta_C$ (CDCl$_3$, 100 MHz) 65.23 (NCH$_2$), 123.89 (2 x CH arom.), 127.35 (CH arom.), 128.10 (2 x CH arom.), 128.69 (2 x CH arom.), 128.97 (2 x CH arom.), 138.48 (NCH$_2$C), 141.63 (N=CHC), 149.09 (CNO$_2$), 159.51 (N=CH).

Preparation of benzyl-furan-2-ylmethylene-amine (251)

The imine was prepared following the general procedure for compound (249) to afford benzyl-furan-2-ylmethylene-amine (251) (1.383 g, 7.48 mmol, 80% yield) as an orange/brown oil. $v_{\text{max}}$/cm$^{-1}$ (neat) 3027, 2876, 1645, 1587, 1483, 1452, 1358, 1273, 1153, 1080, 1015, 928, 883; $\delta_H$ (CDCl$_3$, 400 MHz) 4.68 (2H, s, NCH$_2$), 6.36 (1H, dd, J 1.6 and 3.6 Hz, CHCHCH), 6.67 (1H, d, J 3.2 Hz C=CH), 7.17 (1H, m, CH arom.), 7.21-7.26 (4H, m, 4 x CH arom.), 7.40 (1H, d, J 1.6 Hz, OCHCH), 8.06 (1H, s, N=CH); $\delta_C$ (CDCl$_3$, 100 MHz) 65.17 (NCH$_2$), 111.70 (CHCHCH), 114.26 (C=CH), 159.51 (N=CH).
127.16 (CH arom.), 128.28 (2 x CH arom.), 128.57 (2 x CH arom.), 138.82 (NCH$_2$C), 144.86 (OCHCH), 150.44 (N=CH), 151.59 (N=CH$_2$).

Preparation of benzyl-(4-methoxy-benzylidene)-amine (252)

The imine was prepared following the general procedure for compound (249) to afford benzyl-(4-methoxy-benzylidene)-amine (252) (1.430 g, 6.36 mmol, 68% yield) as a yellow oil. $v_{\text{max}}$/cm$^{-1}$ (neat) 2842, 1948, 1911, 1605, 1511, 1447, 1374, 1246, 1165, 1107, 1033, 992, 971; $\delta_{\text{H}}$ (CDCl$_3$, 400 MHz) 3.61 (3H, s, OCH$_3$), 4.62 (2H, s, NCH$_2$), 6.67 (2H, d, J 8.8 Hz, 2 x CH arom.), 7.10 (1H, m, CH arom.), 7.16-7.20 (4H, m, 4 x CH arom.), 7.58 (2H, d, J 8.8 Hz, 2 x CH arom.), 8.13 (1H, s, N=CH); $\delta_{\text{C}}$ (CDCl$_3$, 100 MHz) 55.61 (OCH$_3$), 65.12 (NCH$_2$), 114.10 (2 x CH arom.), 127.03 (CH arom.), 128.07 (2 x CH arom.), 128.58 (2 x CH arom.), 129.23 (NCH$_2$C), 129.97 (2 x CH arom.), 139.73 (N=CH$_2$), 161.41 (N=CH), 161.82 (COCH$_3$).
Preparation of 1-benzyl-2-phenyl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (253b) \((trans:cis; 0:1)^{48}\)

To a stirred solution of benzyl-benzylidene-amine (249) \((0.053 \text{ g}, 0.27 \text{ mmol})\) in anhydrous THF \((2 \text{ mL})\) was added zinc bromide \((0.112 \text{ g}, 0.54 \text{ mmol})\). The reaction mixture was left to stir for 10 min before 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester (155) \((0.050 \text{ g}, 0.27 \text{ mmol})\) was added. The reaction mixture was stirred for a further 5 min before a catalytic amount of tetrakis(triphenylphosphine)palladium(0) \((0.031 \text{ g}, 0.03 \text{ mmol})\) was added. The resulting mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc \((20 \text{ mL})\). The palladium catalyst was filtered through a plug of silica and the organic layer washed with 1 M HCl \((20 \text{ mL})\), sat. NaHCO\textsubscript{3} aq. sol. \((20 \text{ mL})\), sat. NaCl aq. sol. \((20 \text{ mL})\) and dried \((\text{MgSO}_4)\). The solvent was removed under reduced pressure to afford 1-benzyl-2-phenyl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (253b) \((0.084 \text{ g}, 0.23 \text{ mmol}, 84\% \text{ yield})\) as a yellow oil without further purification. \(\nu_{\text{max}}/\text{cm}^{-1}\) (neat) 3058, 3027, 2949, 2843, 1732 \((\text{C}O_2\text{R str.})\), 1701, 1601, 1493, 1454, 1436, 1266, 1229, 1198, 1119, 1071, 1028, 918; \(\delta_H\) (CDCl\textsubscript{3}, 400 MHz) 2.13 \((1 \text{ H}, \text{ dd}, J 6.2 \text{ and } 13.4 \text{ Hz}, 4-\text{C'}(\text{H})\text{H})\), 2.65 \((1 \text{ H}, \text{ dd}, J 10.6 \text{ and } 13.4 \text{ Hz}, 4-\text{C'}(\text{H})\text{H})\), 2.97 \((3 \text{ H}, \text{ s}, \text{ C'O}_2\text{C'}\text{H}_2)\), 3.16 \((1 \text{ H}, \text{ m}, 5-\text{C'}\text{H})\), 3.57 \((1 \text{ H}, \text{ d}, J 14.0 \text{ Hz}, \text{ NC'}(\text{H})\text{H})\), 3.61 \((3 \text{ H}, \text{ s}, \text{ C'O}_2\text{C'}\text{H}_3)\), 3.70 \((1 \text{ H}, \text{ d}, J 13.7 \text{ Hz}, \text{ NC'}(\text{H})\text{H})\), 4.56 \((1 \text{ H}, \text{ s}, 2-\text{C'}\text{H})\), 5.06 \((1 \text{ H}, \text{ dd}, J 1.6 \text{ and } 10.0 \text{ Hz}, \text{ C'(H)H=C'(H)})\), 5.19 \((1 \text{ H}, \text{ m}, \text{ C'(H)H=C'(H)})\), 5.76 \((1 \text{ H}, \text{ m}, \text{ CH}_2=\text{C'}\text{H})\), 6.97 \((10 \text{ H}, \text{ m}, 10 \times \text{C'}\text{H arom.})\); \(\delta_C\) (CDCl\textsubscript{3}, 100 MHz) 39.01 \((4-\text{C'}\text{H}_2)\), 51.98 \((\text{C'O}_2\text{C'}\text{H}_3)\), 52.80 \((\text{C'O}_2\text{C'}\text{H}_3)\), 53.77 \((\text{NC'}\text{H}_2)\), 64.01 \((3-\text{C'})\), 64.23 \((5-\text{C'}\text{H})\), 70.32 \((2-\text{C'}\text{H})\), 117.21 \((\text{C'H}_2=\text{CH})\), 126.76 \((\text{C'H arom.})\), 127.50 \((\text{C'H arom.})\), 127.68 \((\text{C'H arom.})\), 127.73 \((\text{C'H arom.})\), 128.47 \((\text{C'H arom.})\), 128.59 \((\text{C'H arom.})\), 129.02 \((\text{C'H arom.})\), 129.91 \((\text{C'H arom.})\), 132.07 \((\text{C'H arom.})\), 132.07 \((\text{C'H arom.})\).
Preparation of 1-benzyl-2-(4-nitro-phenyl)-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (254) (trans:cis; 1.7:1)

To a stirred solution of benzyl-(4-nitro-benzylidene)-amine (250) (0.065 g, 0.27 mmol) in anhydrous THF (2 mL) was added zinc bromide (0.112 g, 0.54 mmol). The reaction mixture was left to stir for 10 min before 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester (155) (0.050 g, 0.27 mmol) was added. The reaction mixture was stirred for a further 5 min before a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.031 g, 0.03 mmol) was added. The resulting mixture was stirred at room temperature for 12h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica and the organic layer washed with 1 M HCl (20 mL), sat. NaHCO₃ aq. sol. (20 mL), sat. NaCl aq. sol. (20 mL) and dried (MgSO₄). The solvent was removed under reduced pressure to afford 1-benzyl-2-(4-nitro-phenyl)-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (250) (0.087 g, 0.21 mmol, 78% yield) as a yellow oil without further purification. $v_{\text{max}}$/cm⁻¹ (neat) 3372, 2358, 1752, 1730 (CO₂R str.), 1519 (NO₂ str.), 1437, 1345, 1240, 1051, 973; $\delta_H$ (CDCl₃, 400 MHz) 2.23 (1H, d, J 6.0 and 13.4 Hz, 4-C(H)H), 2.50 (1H, d, J 6.6 and 13.3 Hz, 4-C'(H)H), 2.63 (1H, d, J 10.8 and 13.4 Hz, 4-C(H)H), 2.69 (1H, d, J 10.0 and 13.3 Hz, 4-C'(H)H), 3.02 (3H, s, CO₂CH₂), 3.09 (3H, s, CO₂CH₂), 3.20
To a stirred solution of benzyl-furan-2-ylmethylene-amine (251) (0.071 g, 0.27 mmol) in anhydrous THF (2 mL) was added zinc bromide (0.112 g, 0.54 mmol). The reaction mixture was left to stir for 10 min before 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester (155) (0.050 g, 0.27 mmol) was added. The reaction mixture was stirred for a further 5 min before a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.031 g, 0.03 mmol) was added. The resulting mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure and the
yellow oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica and the organic layer washed with 1 M HCl (20 mL), sat. NaHCO₃ aq. sol. (20 mL), sat. NaCl aq. sol. (20 mL) and dried (MgSO₄). The solvent was removed under reduced pressure to afford 1-benzyl-2-furan-2-yl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (255) (0.041 g, 0.11 mmol, 41% yield) as a yellow oil without further purification. $\nu_{\text{max}}$/cm$^{-1}$ (neat) 2951, 2842, 1753, 1737, 1731 (CO$_2$R str.), 1554, 1431, 1266, 1199, 1119, 1012, 924; $\delta_H$ (CDCl$_3$, 400 MHz) 2.14 (1H, dd, $J$ 6.4 and 13.2 Hz, 4-C'($H$)H), 2.34 (1H, dd, $J$ 4.8 and 14.0 Hz, 4-C($H$)H), 2.65 (1H, dd, $J$ 10.8 and 13.2 Hz, 4-C'($H$)H), 2.95 (1H, d, $J$ 14.0 Hz, NC'($H$)H), 3.03-3.18 (3H, m, NC($H$)H, 5-CH and 5-C'($H$)), 3.20 (1H, dd, $J$ 9.6 and 14.0 Hz, 4-C($H$)H), 3.31(3H, s, C'O$_2$C'H$_3$), 3.33 (3H, s, CO$_2$CH$_3$), 3.54-3.72 (2H, m, NC($H$)H and NC'($H$)H), 3.63 (3H, s, C'O$_2$C'H$_3$), 3.70 (3H, s, CO$_2$CH$_3$), 4.62 (1H, s, 2-C'($H$)), 4.79 (1H, s, 2-CH), 5.02 (1H, m, C($H$)H=CH), 5.06 (1H, m, C(H)H=CH), 5.11 (1H, m, C'($H$)H=C'H), 5.17 (1H, m, C'($H$)H=C'H), 5.67 (1H, m, CH$_2$=CH), 5.70 (1H, m, C'H$_2$=C'H), 5.94 (1H, m, 2-CHCOCHCH), 6.09 (1H, m, 2-C'H=C'OHC'HC'H), 6.15 (1H, m, 2-C'H=HC'C'H), 6.21 (1H, m, 2-CHCCH), 7.04-7.62 (12H, m, 6 x CH arom. and 6 x C'H arom.); $\delta_C$ (CDCl$_3$, 100 MHz) 36.20 (4-CH$_2$), 37.53 (4-C'H$_2$), 50.32 (NC'H$_2$), 51.56 (C'O$_2$C'H$_3$), 51.63 (CO$_2$CH$_3$), 51.91 (C'O$_2$C'H$_3$), 51.95 (CO$_2$CH$_3$), 53.41 (NCH$_2$), 61.43 (5-CH and 5-C'H), 61.79 (3-C and 3-C'), 63.19 (2-C'H), 63.38 (2-CH), 107.95 (2-C'H=HC'HC'H), 108.84 (2-C'H=HC'C'H), 109.19 (2-CHCCH), 109.49 (2-CHCCH), 112.71 (CH$_2$=CH), 116.41 (C'H$_2$=C'H), 125.67, 125.77, 126.75, 126.99, 127.21, 127.43, 157.55, 128.6, 131.02, 132.0 (5 x CH arom. and 5 x C'H arom.), 138.31 (NCH$_2$C arom and NCH$_2$C' arom.), 138.67 (2-CHCOCH), 139.47 (2-C'H=OC'H), 140.92 (C'H$_2$=C'H), 141.46 (CH$_2$=CH), 150.58 (N=CHC' arom.), 152.03 (N=CHC arom.), 167.63 (C'=O), 168.18 (C=O), 170.10 (C=O), 170.40 (C'=O); ms (FAB): m/z 370 (M$^+$, 53%), 369 (36), 368 (52), 342 (12), 338 (17), 302 (19), 281 (11), 280 (15), 279 (75), 278 (77), 225 (19), 207 (15), 184 (12), 159 (11), 147 (25), 136 (23), 134 (30), 91 (100); HRMS calc. for C$_{21}$H$_{23}$NO$_5$ 370.1654 found 370.1658.
Preparation of 1-benzyl-2-(4-methoxy-phenyl)-5-vinyl-pyrroldine-3,3-dicarboxylic acid dimethyl ester (256b) \((\text{trans:cis; 0:1})\)^48

\[
\begin{align*}
\text{OMe} & \\
\text{N} & \\
\text{OMe} & \\
\end{align*}
\]

To a stirred solution of benzyl-(4-methoxy-benzylidene)-amine (252) (0.061 g, 0.27 mmol) in anhydrous THF (2 mL) was added zinc bromide (0.112 g, 0.54 mmol). The reaction mixture was left to stir for 10 min before 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester (155) (0.050 g, 0.27 mmol) was added. The reaction mixture was stirred for a further 5 min before a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.031 g, 0.03 mmol) was added. The resulting mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica and the organic layer washed with 1 M HCl (20 mL), sat. NaHCO₃ aq. sol. (20 mL), sat. NaCl aq. sol. (20 mL) and dried (MgSO₄). The solvent was removed under reduced pressure to afford 1-benzyl-2-(4-methoxy-phenyl)-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (256b) (0.043 g, 0.11 mmol, 40% yield) as a yellow oil without further purification.

\[\nu_{\text{max}}/\text{cm}^{-1} \ (\text{neat}) \ 2950, \ 1732 \ (\text{CO}_2 \text{R str.}), \ 1600, \ 1510, \ 1435, \ 1248, \ 1197, \ 1119, \ 1028, \ 721, \ 695; \ \delta_H \ (\text{CDCl}_3, \ 400 \text{ MHz}) \ 2.11 \ (1H, dd, J 6.6 and 13.2 Hz, 4-C'(H)H), \ 2.61 \ (1H, dd, J 10.4 and 13.2 Hz, 4-C'(H)H), \ 3.05 \ (3H, s, C'O₂C'H₃), \ 3.13 \ (1H, m, 5-C'H), \ 3.54 \ (1H, d, J 14.2 Hz, NC'(H)H), \ 3.61 \ (3H, s, C'O₂C'H₃), \ 3.70 \ (3H, s, OC'H₃), \ 3.72 \ (1H, d, J 14.2 Hz, NC'(H)H), \ 4.48 \ (1H, s, 2-C'H), \ 5.06 \ (1H, dd, J 1.2 and 10.2 Hz, C'(H)H=C'H), \ 5.17 \ (1H, dd, J 1.2 and 16.0 Hz, C'(H)H=C'H), \ 5.76 \ (1H, m, C'H₂=C'H), \ 6.73 \ (2H, d, J 11.2 Hz, 2 x C'H arom.), \ 7.24 \ (2H, d, J 11.2 Hz, 2 x C'H arom.), \ 7.40-7.63 \ (5H, m, 5 x C'H arom.); \ \delta_C \ (\text{CDCl}_3, \ 100 \text{ MHz}) \ 38.91 \ (4-C'H₂), \ 52.09 \ (C'O₂C'H₃), \ 52.75 \ (C'O₂C'H₃), \ 53.49 \ (NC'H₂), \ 55.22 \ (OC'H₃), \ 63.81 \ (3-C'H), \ 64.10 \ (5-C'H), \ 69.77 \ (2-C'H), \ 113.13 \ (2 x C'H arom.), \ 117.12 \ (C'H₂=C'H), \]
127.68 (C' H arom.), 129.91 (2 x C' H arom.), 131.25 (NC'H₃C' arom.), 132.06 (2 x C' H arom.), 132.16 (2 x C' H arom.), 133.04 (2-C'HC' arom.), 139.99 (C'H₂=C' H), 158.96 (C'O C'H₃ arom.), 169.73 (C'=O), 172.06 (C'=O); ms (FAB): m/z 409 (M⁺, 28%), 408 (40), 378 (19), 350 (11), 318 (41), 302 (19), 280 (19), 279 (90), 265 (17), 224 (16), 201 (14), 174 (39), 159 (23), 154 (15), 147 (11), 136 (16), 135 (11), 121 (20), 109 (12), 107 (12), 105 (33), 97 (12), 95 (19), 93 (12), 91 (100); HRMS calc. for C₂₄H₂₇NO₅ 409.1889 found 409.1884.

Preparation of benzylidene-(2-bromo-benzyl)-amine (258)

![Diagram of benzylidene-(2-bromo-benzyl)-amine (258)]

To a solution of benzaldehyde (162) (0.477 g, 4.50 mmol) and molecular sieves (4 Å, 5.000 g) in Et₂O (30.0 mL) was added 2-bromobenzylamine hydrochloride (257) (1.000 g, 4.50 mmol). The yellow reaction mixture was stirred at room temperature for 12h. The solution was filtered, removing the molecular sieves and the solvent removed under reduced pressure furnishing benzylidene-(2-bromo-benzyl)-amine (258) (0.826 g, 3.01 mmol, 67% yield) as a pale yellow oil. vₘₐₓ/cm⁻¹ (neat) 3060, 3026, 2848, 1645, 1566, 1465, 1450, 1438, 1309, 1042, 1025, 750; δₜ (CDCl₃, 400 MHz) 7.06 (1H, m, CH arom.), 7.23 (1H, m, CH arom.), 7.35-7.39 (4H, m, 4 x CH arom.), 7.51 (1H, m, CH arom.), 7.71-7.76 (2H, m, 2 x CH arom.), 8.36 (1H, apparent t, J 1.4 Hz, N=CH); δₜ (CDCl₃, 100 MHz) 64.30 (NCH₂), 123.36 (CBr), 127.53 (CH arom.), 128.32 (2 x CH arom.), 128.49 (CH arom.), 128.67 (2 x CH arom.), 129.77 (CH arom.), 130.94 (CH arom.), 132.54 (CH arom.), 138.71 (NCH₂C), 150.99 (N=CHC), 162.99 (N=CH).
Preparation of (2-bromo-benzyl)-(4-nitro-benzylidine)-amine (259)

![Image of molecule](image.png)

The imine was prepared following the general procedure for compound (258) to afford (2-bromo-benzyl)-(4-nitro-benzylidine)-amine (259) (1.061 g, 3.33 mmol, 74% yield) as a pale yellow solid. $v_{\text{max}}$/cm$^{-1}$ (thin film) 2879, 1650, 1566 (NO$_2$ str.), 1483, 1467, 1438, 1357, 1327, 1275, 1154, 1080, 1024, 926; $\delta_H$ (CDCl$_3$, 400 MHz) 4.96 (2H, s, NCH$_2$), 7.16-7.20 (1H, m, CH arom.), 7.31-7.34 (1H, m, CH arom.), 7.41-7.44 (1H, m, CH arom.), 7.58-7.61 (1H, m, CH arom.), 7.97 (2H, d, $J$ 9.8 Hz, 2 x CH arom.), 8.29 (2H, d, $J$ 9.8 Hz, 2 x CH arom.), 8.50 (1H, m, N=CH); $\delta_C$ (CDCl$_3$, 100 MHz) 64.43 (NCH$_2$), 123.78 (CBr), 123.92 (2 x CH arom.), 127.68 (CH arom.), 128.88 (CH arom.), 128.99 (2 x CH arom.), 130.00 (CH arom.), 132.78 (CH arom.), 137.82 (NCH$_2$C), 141.51 (N=CHC), 149.23 (CNO$_2$), 160.38 (N=CH). ms (EI): $m/z$ 320 (M$^+$, 24%, Br$^{21}$), 318 (M$^+$, 24%, Br$^{79}$), 171 (98), 169 (100); HRMS calc. For C$_{14}$H$_{11}$N$_2$O$_2$Br$^{79}$ 318.0004 found 318.0006.

Preparation of (2-bromo-benzyl)-furan-2-ylmethylene-amine (260)

![Image of molecule](image.png)

To a solution of 2-furyl aldehyde (230) (0.432 g, 4.50 mmol), MgSO$_4$ (0.594 g, 4.95 mmol), Et$_3$N (0.909 g, 9.00 mmol) in CH$_2$Cl$_2$ (30 mL) was added 2-bromobenzylamine hydrochloride (257) (1.000 g, 4.50 mmol). The brown reaction mixture was stirred at room temperature for 12h. The solution was filtered and the solvent removed under reduced pressure to afford (2-bromo-benzyl)-furan-2-
ylmethylene-amine (260) (0.807 g, 3.06 mmol, 68% yield) as a brown oil. $v_{\text{max}}/\text{cm}^{-1}$ (neat) 2852, 1650, 1645, 1567, 1484, 1439, 1154, 1024, 926, 884, 741; $\delta_H$ (CDCl$_3$, 400 MHz) 4.89 (2H, s, NCH$_2$), 6.43 (1H, dd, $J$ 1.6 Hz and 3.2 Hz, CHCHCHO), 6.74 (1H, d, $J$ 3.2 Hz, CHCHCHO), 7.07 (1H, ddd, $J$ 1.6, 8.0 and 15.0 Hz, CH arom.), 7.23 (1H, ddd, $J$ 1.2, 7.6 and 15.0 Hz, CH arom.), 7.35 (1H, dd, $J$ 1.6 and 7.6 Hz, CH arom.), 7.47 (1H, d, $J$ 1.6 Hz, CHCHCHO), 7.49 (1H, dd, $J$ 1.2 and 8.0 Hz, CH arom.), 8.13 (1H, s, N=CH); $\delta_C$ (CDCl$_3$, 100 MHz) 64.36 (CH$_2$N), 111.71 (CHCHCHO), 114.58 (CHCHCHO), 123.01 (CBr), 127.61 (CH arom.), 128.68 (CH arom.), 130.26 (CH arom.), 132.60 (CH arom.), 138.11 (NCH$_2$), 144.99 (CHCHCHO), 151.29 (N=CH), 151.51 (N=CH$_2$); ms (FAB): $m/z$ 266 (M$^+$, 87%, Br$_{81}$), 264 (M$^+$, 100%, Br$_{79}$); HRMS calc. For Cl$_2$H$_{10}$NOBr$_{79}$ 264.0024 found 264.0021.

Preparation of (2-bromo-benzyl)-(4-methoxy-benzylidine)-amine (261)

The imine was prepared following the general procedure for compound (260) to afford (2-bromo-benzyl)-(4-methoxy-benzylidine)-amine (261) (0.970 g, 3.19 mmol, 71% yield) as a brown oil. $v_{\text{max}}/\text{cm}^{-1}$ (neat) 2879, 1650, 1566, 1483, 1467, 1438, 1357, 1327, 1275, 1154, 1024, 926, 884; $\delta_H$ (CDCl$_3$, 400 MHz) 3.85 (3H, s, OCH$_3$), 4.71 (2H, s, NCH$_2$), 6.87 (2H, d, $J$ 9.2 Hz, 2 x CH arom.), 7.04-7.08 (1H, m, CH arom.), 7.22-7.25 (1H, m, CH arom.), 7.34-7.36 (1H, m, CH arom.), 7.48-7.50 (1H, m, CH arom.), 7.68 (2H, d, $J$ 8.8 Hz, 2 x CH arom.), 8.28 (1H, s, N=CH). $\delta_C$ (CDCl$_3$, 100 MHz) 55.39 (OCH$_3$), 64.17 (NCH$_2$), 114.02 (N=CH$_2$), 123.50 (CBr), 127.48 (CH arom.), 128.38 (CH arom.), 129.73 (CH arom.), 129.87 (2 x CH arom.), 138.96 (NCH$_2$), 161.82 (COCH$_3$), 162.27 (N=CH$_2$).
Preparation of 1-(2-bromo-benzyl)-2-phenyl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (262b) \((\text{trans:} \text{cis}; 0:1)\)

To a stirred solution of benzylidene-(2-bromo-benzyl)-amine \((2S8)\) \(0.148 \text{ g}, 0.54 \text{ mmol}\) in anhydrous THF \((5 \text{ mL})\) was added zinc bromide \(0.224 \text{ g}, 1.08 \text{ mmol}\). The reaction mixture was left to stir for 10 min before 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester \((1SS)\) \(0.100 \text{ g}, 0.54 \text{ mmol}\) was added. The reaction mixture was stirred for a further 5 min before a catalytic amount of tetrakis(triphenylphosphine) palladium(0) \(0.062 \text{ g}, 0.05 \text{ mmol}\) was added. The resulting mixture was stirred at room temperature for 12h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc \(20 \text{ mL}\). The palladium catalyst was filtered through a plug of silica and the organic extract washed with 1 M HCl \(20 \text{ mL}\), sat. NaHCO$_3$ aq. sol. \(20 \text{ mL}\), sat. NaCl aq. sol. \(20 \text{ mL}\) and dried \((\text{MgSO}_4)\). The solvent was removed under reduced pressure to afford crude 1-(2-bromo-benzyl)-2-phenyl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester \((262b)\) \(0.212 \text{ g}\). The oil was purified using column chromatography \((\text{SiO}_2, \text{EtOAc}:\text{P.E.} 40-60, 8:1)\) to afford 1-(2-bromo-benzyl)-2-phenyl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester \((262b)\) \(0.151 \text{ g}, 0.33 \text{ mmol}, 61\% \text{ yield}\) as a yellow oil. $v_{\text{max}}/\text{cm}^{-1}$ (neat) 2949, 1733 (CO$_2$R str.), 1452, 1433, 1268, 1227, 1197, 1165, 1135, 1025, 917; $\delta$ \(\text{H} (\text{CDCl}_3, 400 \text{ MHz})\) 2.20 \((1H, \text{dd,} J 5.6 \text{ and } 13.3 \text{ Hz, 4-} \text{C'(IDH)}\), 2.71 \((1H, \text{dd,} J 11.3 \text{ and } 13.3 \text{ Hz, 4-C'(H)H})\), 2.99 \((3H, \text{s,} \text{C'O}_2\text{C'H}_3)\), 3.17 \((1H, \text{m,} 5-\text{C'H})\), 3.70 \((1H, \text{d,} J 13.7 \text{ Hz,} \text{NC'(H)H})\), 3.72 \((3H, \text{s,} \text{C'O}_2\text{C'H}_3)\), 3.84 \((1H, \text{d,} J 13.7 \text{ Hz,} \text{NC'(H)H})\), 4.70 \((1H, \text{s,} 2-\text{C'H})\), 4.89 \((1H, \text{dd,} J 1.2 \text{ and } 14.4 \text{ Hz,} \text{C'(H)H=C'H})\), 4.92 \((1H, \text{dd,} J 1.0 \text{ and } 16.8 \text{ Hz,} \text{C'(H)H=C'H})\), 5.72 \((1H, \text{m,} \text{C'H}_2=\text{C'H})\), 6.80 \((1H, \text{m,} \text{C'H arom.)}, 6.96 \((1H, \text{m,} \text{C'H arom.)}, 6.98-7.06 \((3H, \text{m,} 3 \text{ x C'H arom.)}, 7.16-7.22 \((3H, \text{m,} 3 \text{ x C'H arom.)}, 7.25 \((1H, \text{m,} \text{C'H arom.)}; \delta_c$
Preparation of 1-(2-bromo-benzyl)-2-phenyl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (262b) (trans:cis; 0:1)

To a stirred solution of benzylidene-(2-bromo-benzyl)-amine (258) (0.148 g, 0.54 mmol) in anhydrous CH2Cl2 (5 mL) was added zinc bromide (0.224 g, 1.02 mmol). The reaction mixture was left to stir for 10 min before bicyclo[3.1.0]hex-2-ene-6,6-dicarboxylic acid dimethyl ester (155) (0.100 g, 0.54 mmol) was added. The reaction mixture was stirred for a further 5 min before a catalytic amount of bis(dibenzylideneacetone) palladium(0) (0.050 g, 0.05 mmol) was added. The resulting mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica to afford crude 1-(2-bromo-benzyl)-2-phenyl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (262b) (0.154 g). The oil was purified using column chromatography (SiO2, EtOAc:P.E 40:60, 8:1) to afford 1-(2-bromo-benzyl)-2-phenyl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (262b) (0.012 g, 0.03 mmol, 5% yield) as a yellow oil. Data as above.

Preparation of 1-(2-bromo-benzyl)-2-phenyl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (262b) (trans:cis; 0:1)

To a stirred solution of benzylidene-(2-bromo-benzyl)-amine (258) (0.148 g, 0.54 mmol) in anhydrous MeOH (2 mL) was added 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester (155) (0.100 g, 0.54 mmol). A catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.031 g, 0.03 mmol) was then added. The resulting mixture was stirred at room temperature for 12 h. The solvent was removed
under reduced pressure and the oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica and the organic layer washed with 1 M HCl (20 mL), sat. NaHCO₃ aq. sol. (20 mL), sat. NaCl aq. sol. (20 mL) and dried (MgSO₄). The solvent was removed under reduced pressure to afford crude 1-(2-bromo-benzyl)-2-phenyl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (262b) (0.129 g). The oil was purified using column chromatography (SiO₂, EtOAc:P.E 40-60, 8:1) to afford 1-(2-bromo-benzyl)-2-phenyl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (262b) (0.084 g, 0.18 mmol, 34% yield) as a viscous yellow oil. Data as above.

Preparation of 1-(2-bromo-benzyl)-2-(4-nitrophenyl)-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (263) (trans:cis; 1.1:1)

To a stirred solution of (2-bromo-benzyl)-(4-nitro-benzylidene)-amine (259) (0.174 g, 0.54 mmol) in anhydrous THF (5 mL) was added zinc bromide (0.224 g, 1.08 mmol). The reaction mixture was left to stir for 10 min before 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester (155) (0.100 g, 0.54 mmol) was added. The reaction mixture was stirred for a further 5 min before a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.062 g, 0.05 mmol) was added. The resulting mixture was stirred at room temperature for 12h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica and the organic extract washed with 1 M HCl (20 mL), sat. NaHCO₃ aq. sol. (20 mL), sat. NaCl aq. sol. (20 mL) and dried (MgSO₄). The solvent was removed under reduced pressure to afford crude 1-(2-bromo-benzyl)-2-(4-nitrophenyl)-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (263) (0.212 g). The oil was purified using column chromatography.
(SiO₂, EtOAc:P.E. 40-60, 8:1) to afford 1-(2-bromo-benzyl)-2-(4-nitrophenyl)-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (263) (0.193 g, 0.38 mmol, 71% yield) as a yellow oil. νₘₚₑₓ/cm⁻¹ (neat) 2949, 1734 (C=O str.), 1605, 1523 (NO₂ str.), 1466, 1434, 1346, 1273, 1228, 1196, 1136, 1026, 926; δₜ (CDCl₃, 400 MHz) 2.17 (1H, dd, J 5.0 and 13.2 Hz, 4-C(H)H), 2.27 (1H, dd, J 5.4 and 13.4 Hz, 4-C'(H)H), 2.66 (1H, dd, J 11.6 and 13.4 Hz, 4-C'(H)H), 2.73 (1H, dd, J 12.0 and 13.2 Hz, 4-C'(H)H), 3.02 (3H, s, CO₂CH₃), 3.03 (3H, s, C'O₂C'H₃), 3.18-3.28 (2H, m, 5-CH and 5-C'H), 3.24-3.34 (2H, m, 5-CH and 5-C'H), 3.57-3.64 (2H, m, NC'(H) and NC(H)H), 3.75 (3H, s, CO₂C'H₃), 3.76 (3H, s, C'O₂C'H₃), 3.97 (1H, d, J 13.2 Hz, NC'(H)H), 4.02 (1H, d, J 12.8 Hz, NC(H)H), 4.83 (1H, s, 2-C'H), 5.09-5.15 (1H, m, C(H)H=CH) and C'(H)H=C'H), 5.21 (1H, s, 2-CH), 5.22-5.28 (2H, m, C(H)H=CH and C'(H)H=C'H), 5.25 (1H, s, 2-CH), 5.83-5.91 (2H, m, CH₂=CH and C'H₂=C'H), 6.71-7.82 (16H, m, 8 x CH arom. and 8 x C'H arom.); δₜ (CDCl₃, 100 MHz) 38.80 (4-C'H2), 39.61 (4-CH₂), 51.76 (C=O₂H₃), 52.19 (C'O₂C'H₃), 53.22 (CO₂CH₃), 53.39 (C'O₂C'H₃), 56.61 (N'CH₂), 57.25 (NCH₂), 63.11 (3-C), 64.25 (3-C'), 66.86 (5-CH), 67.10 (5-C'H), 69.69 (2-C'H), 70.94 (2-CH), 118.21 (C'H₂=C'H), 117.73 (CH₂=CH), 124.13 (C'Br), 124.39 (CBr), 122.17 (2 x C'H arom.), 126.41 (CH arom. and C'H arom.), 126.61 (CH arom.), 126.92 (CH' arom.), 128.27 (2 x CH arom.), 128.60 (C'H arom.), 129.29 (2 x C'H arom.), 131.28 (CH arom.), 131.38 (CH arom.), 131.97 (CH arom.), 132.14 (CH arom.), 132.28 (CH' arom.), 132.41 (C'H arom.), 133.75 (NCH₂C and NC'H₂C'), 138.10 (C'H₂=C'H), 139.21 (CH₂=CH), 142.11 (2-CHC and 2-C'H'C'), 147.45 (CNO₂ and C'NO₂), 166.67 (C=O and C'=O), 171.74 (C=O and C'=O); ms (FAB): m/z 505 (M⁺, 4%, Br⁺₁), 503 (M⁺, 5%, Br⁻₁), 393 (13), 368 (11), 322 (28), 169 (30), 131 (13), 95 (56), 81 (61), 55 (100); HRMS calc. for C₂₃H₂₄N₂O₆Br⁻⁷⁻ found 503.0820.

Trans isomer (263a) isolated; νₘₚₑₓ/cm⁻¹ (neat) 2998, 2950, 2836, 1734 (C=O str.), 1610, 1510, 1434, 1249, 1070, 1026, 911, 845, 753; δₜ (CDCl₃, 400 MHz) 2.17 (1H, dd, J 5.0 and 13.2 Hz, 4-C(H)H), 2.27 (1H, dd, J 12.0 and 13.2 Hz, 4-C(H)H), 3.00 (3H, s, CO₂CH₃), 3.24 (1H, m, 5-CH), 3.90 (1H, d, J 12.8 Hz, NC(H)H), 3.76 (3H, s, CO₂CH₃), 4.02 (1H, d, J 12.8 Hz, NC(H)H), 5.09 (1H, m, C(H)H=CH), 5.22 (1H, m, C(H)H=CH), 5.25 (1H, s, 2-CH), 5.86 (1H, m, CH₂=CH), 6.70-6.77 (2H, m, CH arom.), 6.89 (1H, apparent td, J 1.2, 7.6, and 14.8 Hz, CH arom.), 7.00 (2H, m, CH arom.), 7.22 (1H, apparent dd, J 1.8 and 8.0 Hz, CH arom.), 7.50 (1H, apparent dd, J 216 -
1.8 and 9.6 Hz, CH arom.); $\delta_c$ (CDCl$_3$, 100 MHz) 39.61 (4-CH$_2$), 51.77 (CO$_2$CH$_3$), 53.25 (CO$_2$CH$_3$), 57.24 (NCH$_2$), 64.25 (3-C), 66.86 (5-CH), 69.69 (2-CH), 117.73 (CH$_2$=CH), 124.39 (CBr), 126.41 (CH arom.), 126.62 (CH arom.), 128.27 (2 x CH arom.), 131.22 (CH arom.), 131.38 (CH arom.), 131.97 (CH arom.), 132.14 (CH arom.), 137.35 (NCH$_2$C), 139.21 (CH$_2$=CH), 139.83 (NCH$_2$C), 142.11 (2-CHC), 147.45 (CNO$_2$), 166.67 (C=O), 171.74 (C=O).

Preparation of 1-(2-bromo-benzyl)-2-(4-nitrophenyl)-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (263) (trans:cis; 1:1:1)

To a stirred solution of (2-bromo-benzyl)-(4-nitro-benzylidene)-amine (259) (0.174 g, 0.54 mmol) in anhydrous CH$_2$Cl$_2$ (5 mL) was added zinc bromide (0.224 g, 1.02 mmol). The reaction mixture was left to stir for 10 min before bicyclo[3.1.0]hex-2-ene-6,6-dicarboxylic acid dimethyl ester (155) (0.100 g, 0.54 mmol) was added. The reaction mixture was stirred for a further 5 min before a catalytic amount of bis(dibenzylideneacetone) palladium(0) (0.050 g, 0.05 mmol) was added. The resulting mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica to afford crude 1-(2-bromo-benzyl)-2-(4-nitrophenyl)-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (263) (0.154 g). The oil was purified using column chromatography (SiO$_2$, EtOAc:P.E 40-60, 8:1) to afford 1-(2-bromo-benzyl)-2-(4-nitrophenyl)-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (263) (0.016 g, 0.03 mmol, 6% yield) as a yellow oil. Data as above.
Preparation of 1-(2-bromo-benzyl)-2-furan-2-yl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (264) (trans:cis; 1:1.1)

To a stirred solution of (2-bromo-benzyl)-furan-2-ylmethylene-amine (260) (0.142 g, 0.54 mmol) in anhydrous THF (5 mL) was added zinc bromide (0.224 g, 1.08 mmol). The reaction mixture was left to stir for 10 min before 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester (155) (0.100 g, 0.54 mmol) was added. The reaction mixture was stirred for a further 5 min before a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.062 g, 0.05 mmol) was added. The resulting mixture was stirred at room temperature for 12h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica and the organic extract washed with 1 M HCl (20 mL), sat. NaHCO3 aq. sol. (20 mL), sat. NaCl aq. sol. (20 mL) and dried (MgSO4). The solvent was removed under reduced pressure to afford crude 1-(2-bromo-benzyl)-2-furan-2-yl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (264) (0.189 g). The oil was purified using column chromatography (SiO2, EtOAc:P.E. 40-60, 8:1) to afford 1-(2-bromo-benzyl)-2-furan-2-yl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (264) (0.092 g, 0.21 mmol, 38% yield) as a brown oil. 

\[ \text{v}_{\text{max/cm}^{-1}} \text{(neat)} = 2950, 1735 \text{ (CO}_2 \text{R str)}, 1675, 1433, 1268, 1204, 1149, 1068, 1025, 925; \delta_H \text{ (CDCl}_3, 400 \text{ MHz)} = 2.24 \text{ (1H, dd, J 5.6 and 13.2 Hz, 4-C'(H)H)}, 2.33 \text{ (1H, dd, J 4.8 and 14.0 Hz, 4-C(H)H) }, 2.71 \text{ (1H, dd, J 11.2 and 13.2 Hz, 4-C'(H)H)}, 3.23 \text{ (1H, dd, J 9.6 and 14.0 Hz, 4-C(H)H)}, 3.31 \text{ (1H, d, J 15.6 Hz, NC(H)H)}, 3.32 \text{ (3H, s, CO}_2 \text{ClH)}, 3.36 \text{ (3H, s, C'O}_2 \text{C'H)}; 3.57 \text{ (1H, d, J 15.6 Hz, NC(H)H)}, 3.70 \text{ (1H, m, 5-C'H)}, 3.72 \text{ (3H, s, CO}_2 \text{CH}_3); 3.74 \text{ (3H, s, C'O}_2 \text{C'H)}; 3.78 \text{ (1H, d, J 14.4 Hz, NC'(H)H)}, 3.82 \text{ (1H, d, J 14.4 Hz, NC'(H)H)}, 4.73 \text{ (1H, s, 2-C'H)}, 4.87 \text{ (1H, s, 2-CH)}, 4.95 \text{ (1H, m, C'(H)H=C'H)}, 5.00 \text{ (1H, m,}
C(H)=CH), 5.11 (1H, m, C(H)H=CH), 5.13 (1H, m, C'(H)H=C'H), 5.61-5.76 (2H, m, CH2–CH and C'H2=C'H), 5.97-5.99 (2H, m, 2-CHCOCHCH and 2-C'HCH'O-CH'CH'), 6.02 (1H, dd, J 1.6 and 3.2 Hz, 2-C'HCH'C'H'), 6.22 (1H, dd, J 1.6 and 3.2 Hz, 2-CHCCCH), 6.87 (1H, m, CH arom), 6.99-7.03 (2H, m, 2-CHCOCHCH and 2-C'HCHOC'H'), 7.11 (1H, d, J 0.8 and 1.6 Hz, 2-C'HCHOC'H'), 7.23-7.28 (3H, m, CH arom. and 2 x C'H arom.), 7.32 (1H, m, 2-CHCOCH), 7.39 (1H, m, C'tri', 7.53 (1H, m, C'BrC'H); δc (CDCl3, 100 MHz) 37.13 (4-CH2), 38.76 (4-C'H2), 50.92 (NCH2), 52.59 (CO2CH3), 52.69 (C'O2C'H3), 53.09 (CO2CH3), 53.17 (C'O2C'H3), 56.19 (NC'H2), 62.25 (2-CH), 62.89 (3-C), 63.03 (3-C'), 64.48 (5-CH), 65.83 (2-C'H), 66.71 (5-C'H), 108.47 (2-C'HCH'C'HCH'), 110.03 (2-C'HCH'C'H), 110.07 (2-CHCCCHCH), 110.70 (2-CHCCCH), 116.90 (CH2=CH), 117.17 (C'H2=C'H), 123.44 (C'Br), 123.89 (CBr), 126.62, 127.24, 128.01, 128.03, 130.24, 131.30, 132.14, 132.36 (4 x C'H arom. and 4 x C'H arom.), 138.28 (NCH2C'), 138.44 (NCH2C'), 139.41 (C'H2=C'H), 140.23 (CH2=CH), 151.16 (2-CHC), 153.46 (2-C'HCH'), 166.62 (C'=O), 168.84 (C=O), 171.05 (C'=O), 171.55 (C=O); ms (EI): m/z 450 (M+, 100%, Br81), 448 (M+, 99%, Br79); HRMS calc. for C21H22NO7Br 448.0754 found 448.0750.

Preparation of 1-(2-bromo-benzyl)-2-furan-2-yl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (264) (trans:cis; 1:3.8)

To a stirred solution of (2-bromo-benzyl)-furan-2-ylmethylene-amine (260) (0.142 g, 0.54 mmol) in anhydrous CH2Cl2 (5 mL) was added zinc bromide (0.224 g, 1.02 mmol). The reaction mixture was left to stir for 10 min before bicyclo[3.1.0]hex-2-ene-6,6-dicarboxylic acid dimethyl ester (155) (0.100 g, 0.54 mmol) was added. The reaction mixture was stirred for a further 5 min before a catalytic amount of bis(dibenzylideneacetone) palladium(0) (0.050 g, 0.05 mmol) was added. The resulting mixture was stirred at room temperature for 12h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica to afford crude 1-(2-bromo-benzyl)-2-furan-2-yl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (264) (0.165 g). The oil was purified using column chromatography (SiO2, EtOAc:P.E 40:60, 8:1) to afford 1-(2-bromo-benzyl)-2-furan-2-yl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (264) (0.097 g, 0.22 mmol, 40% yield) as a brown oil.
Selected data for cis isomer (264b): \( \nu_{\text{max}}/\text{cm}^{-1} \) (neat) 2950, 1735 (CO\(_2\) R str), 1675, 1433, 1268, 1204, 1149, 1068, 1025, 925; \( \delta_{\text{H}} \) (CDCl\(_3\), 400 MHz) 2.24 (1H, dd, \( J = 5.6 \) and 13.2 Hz, 4-C'(H)H), 2.71 (1H, dd, \( J = 11.2 \) and 13.2 Hz, 4-C'(H)H), 3.18 (1H, m, 5-C'H), 3.36 (3H, s, CO\(_2\)C'H\(_3\)), 3.74 (3H, s, CO\(_2\)C'H\(_3\)), 3.78 (1H, d, \( J = 14.4 \) Hz, NC'(H)H), 3.82 (1H, d, \( J = 14.4 \) Hz, NC'(H)H), 4.73 (1H, s, 2-C'H), 4.95 (1H, m, C'(H)H=C'H), 5.13 (1H, m, C'(H)H=C'H), 5.71 (1H, m, C'H\(_2\)=C'H), 5.84 (1H, m, 2-C'HC'O'C'H\(_3\)), 6.02 (1H, dd, \( J = 1.6 \) and 3.2 Hz, 2-C'HC'C'H), 7.00 (1H, m, C'H arom.), 7.11 (1H, d, \( J = 0.8 \) and 1.6 Hz, 2-C'HC'O'C'H), 7.26-34 (2H, m, 2 x C'H arom.), 7.54 (1H, m, C'H arom.); \( \delta_{\text{C}} \) (CDCl\(_3\), 100 MHz) 38.76 (4-C'H\(_2\)), 52.69 (C'O\(_2\)C'H\(_3\)), 53.17 (C'O\(_2\)C'H\(_3\)), 56.19 (NC'H\(_2\)), 63.03 (3-C'), 65.83 (2-C'H), 66.71 (5-C'H), 108.47 (2-C'HC'C'H\(_3\)), 110.04 (2-C'HC'C'H), 117.17 (C'H\(_2\)=C'H), 123.44 (C'Br), 138.44 (NC'H\(_2\)C'), 139.41 (C'H\(_2\)=C'H), 143.37 (2-C'HC'O'C'H), 153.46 (2-C'HC'), 168.62 (C'=O), 171.05 (C'=O).

**Preparation of 1-(2-bromo-benzyl)-2-furan-2-yl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (264) (trans:cis; 1:1.1)**

To a stirred solution of (2-bromo-benzyl)-furan-2-ylmethylene-amine (260) (0.142 g, 0.54 mmol) in anhydrous MeOH (2 mL) was added 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester (155) (0.100 g, 0.54 mmol). A catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.031 g, 0.03 mmol) was then added. The resulting mixture was stirred at room temperature for 12h. The solvent was removed under reduced pressure and the oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica and the organic layer washed with 1 M HCl (20 mL), sat. NaHCO\(_3\)aq. sol. (20 mL), sat. NaCl aq. sol. (20 mL) and dried (MgSO\(_4\)). The solvent was removed under reduced pressure to afford crude 1-(2-bromo-benzyl)-2-furan-2-yl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (264) (0.182 g). The oil was purified using column chromatography (SiO\(_2\), EtOAc:P.E 40-60, 8:1) to afford 1-(2-bromo-benzyl)-2-furan-2-yl-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (264) (0.063 g, 0.14 mmol, 26% yield) as a brown oil. Data as above.
Preparation of 1-(2-bromo-benzyl)-2-(4-methoxy-phenyl)-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (265b) (trans:cis; 0:1)

To a stirred solution of (2-bromo-benzyl)-(4-methoxy-benzylidine)-amine (261) (0.164 g, 0.54 mmol) in anhydrous THF (5 mL) was added zinc bromide (0.224 g, 1.08 mmol). The reaction mixture was left to stir for 10 min before 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester (155) (0.100 g, 0.54 mmol) was added. The reaction mixture was stirred for a further 5 min before a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.062 g, 0.05 mmol) was added. The resulting mixture was stirred at room temperature for 12h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica and the organic extract washed with 1 M HCl (20 mL), sat. NaHCO₃ aq. sol. (20 mL), sat. NaCl aq. sol. (20 mL) and dried (MgSO₄). The solvent was removed under reduced pressure to afford crude 1-(2-bromo-benzyl)-2-(4-methoxy-phenyl)-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (265b) (0.234 g). The oil was purified using column chromatography (SiO₂, EtOAc:P.E. 40-60, 8:1) to afford 1-(2-bromo-benzyl)-2-(4-methoxy-phenyl)-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (265b) (0.108 g, 0.22 mmol, 41% yield) as a brown oil. v_max/cm⁻¹ (neat) 1731 (CO₂R str), 1657, 1641, 1610, 1511, 1461, 1433, 1247, 1200, 1171, 1026, 752; δ_H (CDCl₃, 400 MHz) 2.18 (1H, dd, J = 5.6 and 13.2 Hz, 4-C'(H)H), 2.68 (1H, dd, J = 11.2 and 13.2 Hz, 4-C'(H)H), 3.09 (3H, s, C'02C'H₃), 3.10-3.20 (2H, m, 5-C'(H)H), 3.44 (1H, d, J = 16.0 Hz, NC'(H)H), 3.62-3.66 (1H, m, NC'(H)H), 3.69 (3H, s, C'O₂C'H₃), 3.72 (3H, s, OC'H₃), 4.64 (1H, s, 2-C'(H)H), 4.85 (1H, m, C'(H)H=C'H), 5.03 (1H, m, C'(H)H=C'H), 5.65 (1H, m, C'H₂=C'H), 6.59-6.61 (2H, m, 2 x C'H arom.), 6.82 (1H, m, C'H arom.), 6.98 (1H, m, C'H arom.), 7.13-7.15 (2H, m, 2 x C'H arom.), 7.20-
Preparation of 1-(2-bromo-benzyl)-2-(4-methoxy-phenyl)-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (265b) (trans: cis; 0:1)

To a stirred solution of (2-bromo-benzyl)-(4-methoxy-benzylidine)-amine (261) (0.164 g, 0.54 mmol) in anhydrous CH₂Cl₂ (5 mL) was added zinc bromide (0.224 g, 1.02 mmol). The reaction mixture was left to stir for 10 min before bicyclo[3.1.0]hex-2-ene-6,6-dicarboxylic acid dimethyl ester (155) (0.100 g, 0.54 mmol) was added. The reaction mixture was stirred for a further 5 min before a catalytic amount of bis(dibenzylideneacetone) palladium(0) (0.050 g, 0.05 mmol) was added. The resulting mixture was stirred at room temperature for 12h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica to afford crude 1-(2-bromo-benzyl)-2-(4-methoxy-phenyl)-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (265b) (0.285 g). The oil was purified using column chromatography (SiO₂, EtOAc:P.E 40-60, 8:1) to afford 1-(2-bromo-benzyl)-2-(4-methoxy-phenyl)-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (265b) (0.129 g, 0.26 mmol, 49% yield) as a brown oil. Data as above.

Preparation of 1-(2-bromo-benzyl)-2-(4-methoxy-phenyl)-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (265) (trans: cis; 1.2:1)

To a stirred solution of (2-bromo-benzyl)-(4-methoxy-benzylidine)-amine (261) (0.164 g, 0.54 mmol) in anhydrous MeOH (2 mL) was added 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester (155) (0.100 g, 0.54 mmol). A catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.031 g, 0.03 mmol) was then added.
The resulting mixture was stirred at room temperature for 12h. The solvent was removed under reduced pressure and the oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica and the organic layer washed with 1 M HCl (20 mL), sat. NaHCO₃ aq. sol. (20 mL), sat. NaCl aq. sol. (20 mL) and dried (MgSO₄). The solvent was removed under reduced pressure to afford crude 1-(2-bromo-benzyl)-2-(4-methoxy-phenyl)-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (265) (0.218 g). The oil was purified using column chromatography (SiO₂, EtOAc:P.E 40-60, 8:1) to afford 1-(2-bromo-benzyl)-2-(4-methoxy-phenyl)-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (265) (0.161 g, 0.33 mmol, 61% yield) as a brown oil. v_max/cm⁻¹ (neat) 1731 (C₀₂R str), 1657, 1641, 1610, 1511, 1461, 1433, 1247, 1200, 1171, 1026, 752; δ_H (CDCl₃, 400 MHz) 2.13 (1H, dd, J 5.6 and 14.2 Hz, 4-C(H)H), 2.18 (1H, dd, J 5.6 and 13.2 Hz, 4-C'(H)H), 2.68 (1H, dd, J 11.2 and 13.2 Hz, 4-C'(H)H), 3.06 (3H, s, CO₂CH₃), 3.09 (3H, s, C'O₂C'H₃), 3.10-3.20 (2H, m, 5-CH and 5-C'H), 3.23 (1H, dd, J 8.0 and 14.2 Hz, 4-C(H)H), 3.44 (1H, d, J 16.0 Hz, NC'(H)H), 3.65-3.66 (2H, m, NC'(H)H and NC'(H)H), 3.72 (3H, s, OCfu), 3.75 (3H, s, OC'fu), 3.78 (3H, s, OCfu), 3.81 (1H, d, J 14.4 Hz, NC(H)H), 4.64 (1H, s, 2-C'H), 4.85 (1H, m, C'(H)=C'H), 4.86 (1H, m, C(H)H=CH), 4.89 (1H, s, 2-CH), 5.03 (1H, m, C'(H)H=C'H), 5.10 (1H, m, C(H)H=CH), 5.65 (2H, m, CH₂=CH and C'H₂=C'H), 5.99-6.61 (2H, m, 2 x C'H arom.), 6.71-6.73 (2H, m, 2 x CH arom.), 6.82 (1H, m, C'H arom.), 6.96-7.00 (2H, m, CH arom. and C'H arom.), 7.13-7.15 (2H, m, 2 x C'H arom.), 7.16-7.19 (2H, m, 2 x CH arom.), 7.20-7.29 (3H, m, C'H arom. and 2 x CH arom.), 7.36 (1H, m, C'H arom.), 7.62 (1H, m, CH arom.); δ_c (CDCl₃, 100 MHz) 38.03 (4-CH₂), 39.07 (4-C'H₂), 50.51 (NC'H₂), 52.07 (C'O₂C'H₃), 52.31 (CO₂CH₃), 52.90 (C'O₂C'H₃), 52.97 (CO₂CH₃), 55.17 (OCH₃), 55.20 (OC'H₃), 56.33 (NCH₂), 62.70 (5-CH), 64.28 (3-C'), 64.45 (3-C), 67.36 (5-C'H), 69.17 (2-CH), 71.99 (2-C'H), 112.79 (2 x C'H arom.), 113.42 (2 x CH arom) 116.64 (CH₂=CH), 117.99 (C'H₂=C'H), 123.17 (CBr), 124.19 (C'Br), 126.47 (CH arom.), 127.25 (C'H arom.), 127.80 (C'H arom.), 127.96 (CH arom.), 129.67 (2 x CH arom. and 2 x C'H arom.), 129.88 (NCH₂C), 130.01 (C'H arom.), 131.79 (CH arom.), 131.88 (NC'H₂C'), 132.09 (CH arom.), 132.20 (C'H arom.), 137.42 (C'H₂=C'H), 138.24 (2-CHC), 138.38 (2-C'H₂C'), 139.44 (CH₂=CH), 158.78 (COCH₃), 159.16 (C'O'C'H₃), 169.31 (C=O), 169.76 (C'=O), 172.19 (C'=O), 172.32 (C'=O).
Preparation of 4,5,6,8aR-tetrahydro-3aHR-cyclohepta[b]furan-2,3,3-tricarboxylic acid 2S-ethyl ester 3,3-dimethyl ester (266a)

To a stirred solution of ethyl glyoxolate (228) (0.045 g, 0.44 mmol) in anhydrous THF (5 mL) was added zinc bromide (0.200 g, 0.89 mmol). The reaction mixture was left to stir for 10 min before bicyclo[5.1.0]oct-2-ene-8,8-dicarboxylic acid dimethyl ester (197) (0.100 g, 0.51 mmol) was added. The reaction mixture was stirred for a further 5 min before a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.051 g, 0.10 mmol) was added. The resulting mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica to afford crude 4,5,6,8aR-tetrahydro-3aHR-cyclohepta[b]furan-2,3,3-tricarboxylic acid 2S-ethyl ester 3,3-dimethyl ester (266a) (0.171 g). The oil was purified using column chromatography (SiO2, EtOAc:P.E. 40-60, 6:1) to afford 4,5,6,8aR-tetrahydro-3aHR-cyclohepta[b]furan-2,3,3-tricarboxylic acid 2S-ethyl ester 3,3-dimethyl ester (266a) (0.070 g, 0.21 mmol, 48% yield) as a viscous yellow oil.

\[
\text{v}_{\text{max}}/\text{cm}^{-1} \quad (\text{neat}) \quad 2950, 1739, 1734 \quad (\text{CO}_2\text{R str.}), \quad 1436, 1268, 1230, 1210, 1105, 1024.
\]

\[
\delta_\text{H} \quad (\text{CDCl}_3, \quad 400 \quad \text{MHz}) \quad 1.30 \quad (3\text{H}, \text{t, } J \quad 7.2 \quad \text{Hz, } \text{CH}_2\text{CH}_3), \quad 1.37 \quad (1\text{H}, \text{m, } 4\text{-C(H)H}), \quad 1.55 \quad (1\text{H}, \text{m, } 5\text{-C(H)H}), \quad 1.64 \quad (1\text{H}, \text{m, } 5\text{-C(H)H}), \quad 1.73 \quad (1\text{H}, \text{m, } 4\text{-C(H)H}), \quad 2.05-2.14 \quad (2\text{H}, \text{m, } 6\text{-CH}_2), \quad 3.30 \quad (1\text{H}, \text{m, } 3\text{-a-CH}), \quad 3.71 \quad (3\text{H}, \text{s, } \text{CO}_2\text{CH}_3), \quad 3.76 \quad (3\text{H}, \text{s, } \text{CO}_2\text{CH}_3), \quad 4.12-4.23 \quad (2\text{H}, \text{m, } \text{CH}_2\text{CH}_3), \quad 5.05 \quad (1\text{H}, \text{s, } 2\text{-CH}), \quad 5.28 \quad (1\text{H}, \text{s, } 2\text{-CH}), \quad 5.54-5.58 \quad (2\text{H}, \text{m, } 7\text{-CH and } 8\text{-CH}); \quad \delta_\text{C} \quad (\text{CDCl}_3, \quad 100 \quad \text{MHz}) \quad 14.09 \quad (\text{CH}_2\text{CH}_3), \quad 22.01 \quad (5\text{-CH}_2) \quad 24.11 \quad (4\text{-CH}_2), \quad 26.53 \quad (6\text{-CH}_2), \quad 46.47 \quad (3\text{-a-CH}), \quad 52.64 \quad (\text{CO}_2\text{CH}_3), \quad 52.86 \quad (\text{CO}_2\text{CH}_3), \quad 61.44 \quad (\text{CH}_2\text{CH}_3), \quad 67.46 \quad (3\text{-C}), \quad 80.42 \quad (2\text{-CH}), \quad 86.78 \quad (8\text{-a-CH}), \quad 126.27 \quad (7\text{-CH}), \quad 129.86 \quad (8\text{-CH}), \quad 168.64 \quad (2 \times \text{C=O}), \quad 170.03 \quad (\text{C=O}).
Preparation of 4,6aR-dihydro-3aHR-cyclopenta[b]furan-2,3,3-tricarboxylic acid 2S-ethyl ester 3,3-dimethyl ester (274a)

To a stirred solution of ethyl glyoxolate (228) (0.052 g, 0.51 mmol) in anhydrous THF (5 mL) was added zinc bromide (0.228 g, 1.02 mmol). The reaction mixture was left to stir for 10 min before bicyclo[3.1.0]hex-2-ene-6,6-dicarboxylic acid dimethyl ester (202) (0.100 g, 0.51 mmol) was added. The reaction mixture was stirred for a further 5 min before a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.059 g, 0.05 mmol) was added. The resulting mixture was stirred at room temperature for 12h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica to afford crude 4,6aR-dihydro-3aHR-cyclopenta[b]furan-2,3,3-tricarboxylic acid 2S-ethyl ester 3,3-dimethyl ester (274a) (0.167 g). The oil was purified using column chromatography (SiO₂, EtOAc:P.E. 40-60, 6:1) to afford 4,6aR-dihydro-3aHR-cyclopenta[b]furan-2,3,3-tricarboxylic acid 2S-ethyl ester 3,3-dimethyl ester (274a) (0.123 g, 0.41 mmol, 81% yield) as a viscous yellow oil.

vₘᵋₙ/cm⁻¹ (neat) 2983, 2953, 1731 (CO₂R str.), 1621, 1434, 1378, 1353, 1264, 1097, 1068, 1300, 974; δₜ (CDCl₃, 400 MHz) 1.22 (3H, t, J₇.₂ Hz, CH₂C₆H₅), 2.19 (1H, m, 4-C(H)H), 2.49 (1H, apparent ddt, J 2.4, 9.2, 18.0 Hz, 4-C(H)H), 3.64 (1H, s, 3a-CH), 3.67 (3H, s, CO₂C₆H₅), 3.71 (3H, s, CO₂C₆H₅), 4.12-4.18 (2H, m, CH₂C₆H₅), 4.60 (1H, s, 2-CH), 5.34 (1H, apparent dt, J 2.4 and 6.8 Hz, 6a-CH), 5.66 (1H, m, 5-CH), 5.91 (1H, m, 6-CH); δₛ (CDCl₃, 100 MHz) 14.04 (CH₂C₆H₅), 34.54 (4a-CH), 45.96 (3a-CH), 52.66 (CO₂C₆H₅), 53.04 (CO₂C₆H₅), 61.40 (CH₂C₆H₅), 67.49 (3-C), 78.56 (2-CH), 88.66 (6a-CH), 128.83 (5-CH), 135.63 (6-CH), 168.05 (C=O), 168.60 (C=O), 168.62 (C=O); ms (FAB): m/z 299 (M⁺, 46%), 239 (18), 225 (25), 181 (11), 165 (50), 154 (32), 138 (13), 137 (29), 136 (32), 133 (21), 107 (24), 105 (19), 95 (14), 91 (100); HRMS calc. for C₁₄H₁₈O₇ 299.1131 found 299.1128.
Preparation of 4,6aR-dihydro-3aHR-cyclopenta[b]furan-2,3,3-tricarboxylic acid 2S-ethyl ester 3,3-dimethyl ester (274a)

To a stirred solution of ethyl glyoxolate (228) (0.052 g, 0.51 mmol) in anhydrous CH$_2$Cl$_2$ (5 mL) was added zinc bromide (0.228 g, 1.02 mmol). The reaction mixture was left to stir for 10 min before bicyclo[3.1.0]hex-2-ene-6,6-dicarboxylic acid dimethyl ester (202) (0.100 g, 0.51 mmol) was added. The reaction mixture was stirred for a further 5 min before a catalytic amount of bis(dibenzylideneacetone) palladium(0) (0.059 g, 0.05 mmol) was added. The resulting mixture was stirred at room temperature for 12h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica to afford crude 4,6aR-dihydro-3aHR-cyclopenta[b]furan-2,3,3-tricarboxylic acid 2S-ethyl ester 3,3-dimethyl ester (274a) (0.184 g). The oil was purified using column chromatography (SiO$_2$, EtOAc:P.E 40-60, 6:1) to afford 4,6aR-dihydro-3aHR-cyclopenta[b]furan-2,3,3-tricarboxylic acid 2S-ethyl ester 3,3-dimethyl ester (274a) (0.128 g, 0.43 mmol, 84% yield) as a viscous yellow oil. Data as shown above.

Preparation of 2R-(4-nitro-phenyl)-4,6aR-dihydro-3aHR-cyclopenta[b]furan-3,3-dicarboxylic acid dimethyl ester (275a)

To a stirred solution of 4-nitrobenzaldehyde (229) (0.077 g, 0.51 mmol) in anhydrous THF (5 mL) was added zinc bromide (0.228 g, 1.02 mmol). The reaction mixture was left to stir for 10 min before bicyclo[3.1.0]hex-2-ene-6,6-dicarboxylic acid dimethyl ester (202) (0.100 g, 0.51 mmol) was added. The reaction mixture was stirred for a further 5 min before a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.059 g, 0.05 mmol) was added. The resulting mixture was stirred at room temperature for 12h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through
a plug of silica to afford crude 2R-(4-nitro-phenyl)-4,6aR-dihydro-3aHR-cyclopenta[b]furan-3,3-dicarboxylic acid dimethyl ester (275a) (0.098 g). The oil was purified using column chromatography (SiO₂, EtOAc:PE 40-60, 6:1) to afford 2R-(4-nitro-phenyl)-4,6aR-dihydro-3aHR-cyclopenta[b]furan-3,3-dicarboxylic acid dimethyl ester (275a) (0.032 g, 0.09 mmol, 18% yield) as a viscous orange/yellow oil. ν<sub>max</sub>/cm<sup>-1</sup> (neat) 2953, 1732 (CO<sub>2</sub>R str.), 1699, 1652, 1601, 1527 (NO<sub>2</sub> str.), 1456, 1435, 1348, 1321, 1197, 1011, 984, 857; δ<sub>H</sub> (CDCl<sub>3</sub>, 250 MHz) 2.16 (1H, m, 4-C(H)H), 2.66 (1H, apparent ddt, J = 2.0, 7.2, 16.0 Hz, 4-C(H)H), 3.27 (3H, s, CO₂Cfu), 3.63 (1H, s, 3a-CH), 3.75 (3H, s, CO₂Cfu), 5.31 (1H, s, 2-CH), 5.54 (1H, apparent dt, J = 2.0 and 7.2 Hz, 6a-CH), 5.81 (1H, m, 5-CH), 6.06 (1H, m, 6-CH), 7.70 (2H, d, J = 8.9 Hz, 2 x CH arom.), 8.15 (2H, d, J = 8.9 Hz, 2 x CH arom.); δ<sub>C</sub> (CDCl<sub>3</sub>, 100 MHz) 35.67 (4-CH₂), 46.42 (3a-CH), 52.18 (CO₂Cfu), 52.53 (CO₂Cfu), 70.14 (3-C), 79.59 (2-CH), 87.99 (6a-CH), 122.91 (2 x CH arom.), 127.96 (2 x CH arom.), 129.52 (5-CH), 135.57 (6-CH), 144.64 (2-CH₂), 147.74 (ONO₂), 168.54 (C=O), 169.27 (C=O); ms (FAB): m/z 348 (M⁺, 8%), 197 (33), 166 (28), 165 (100); HRMS calc. for C₁₇H₁₇NΟ₇: 347.1083 found 347.1089.

Preparation of 2R-(4-nitro-phenyl)-4,6aR-dihydro-3aHR-cyclopenta[b]furan-3,3-dicarboxylic acid dimethyl ester (275a)

To a stirred solution of 4-nitrobenzaldehyde (229) (0.077 g, 0.51 mmol) in anhydrous CH₂Cl₂ (5 mL) was added zinc bromide (0.228 g, 1.02 mmol). The reaction mixture was left to stir for 10 min before bicyclo[3.1.0]hex-2-ene-6,6-dicarboxylic acid dimethyl ester (202) (0.100 g, 0.51 mmol) was added. The reaction mixture was stirred for a further 5 min before a catalytic amount of bis(dibenzylideneacetone)palladium(0) (0.059 g, 0.05 mmol) was added. The resulting mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica to afford crude 2R-(4-nitro-phenyl)-4,6aR-dihydro-3aHR-cyclopenta[b]furan-3,3-dicarboxylic acid dimethyl ester (275a) (0.168 g). The oil was purified using column chromatography (SiO₂, EtOAc:PE 40-60, 6:1) to afford 2R-(4-nitro-phenyl)-4,6aR-dihydro-3aHR-cyclopenta[b]furan-3,3-dicarboxylic acid dimethyl ester (275a) (0.087 g, 0.25 mmol, 49% yield) as a viscous orange/yellow oil. Data as shown above.
Preparation of 2-oxo-3S,3aR,4,6aR-tetrahydro-2H-cyclopenta[b]furan-3-carboxylic acid dimethyl ester (276)

To a stirred solution of propionaldehyde (232) (0.030 g, 0.51 mmol) in anhydrous THF (5 mL) was added zinc bromide (0.228 g, 1.02 mmol). The reaction mixture was left to stir for 10 min before bicyclo[3.1.0]hex-2-ene-6,6-dicarboxylic acid dimethyl ester (202) (0.100 g, 0.51 mmol) was added. The reaction mixture was stirred for a further 5 min before a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.059 g, 0.05 mmol) was added. The resulting mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica to afford crude 2-oxo-3S,3aR,4,6aR-tetrahydro-2H-cyclopenta[b]furan-3-carboxylic acid dimethyl ester (276) (0.109 g). The oil was purified using column chromatography (SiO₂, EtOAc:PE 40-60, 6:1) to afford 2-oxo-3S,3aR,4,6aR-tetrahydro-2H-cyclopenta[b]furan-3-carboxylic acid dimethyl ester (276) (0.011 g, 0.06 mmol, 12% yield) as a viscous colourless oil. νmax/cm⁻¹ (neat) 2928, 1724 (C=O str.), 1442, 1426, 1365, 1294, 1179; δH (CDCl₃, 400 MHz) 2.25 (1H, m, 4-C(H)H), 2.67 (1H, m, 4-C(H)H), 3.22 (1H, d, J 6.5 Hz, 3-CH), 3.36 (1H, m, 3a-CH), 3.67 (3H, s, CO₂CH₃), 5.45 (1H, m, 6a-CH), 5.76 (1H, m, 5-CH), 5.96 (1H, m, 6-CH); δC (CDCl₃, 100 MHz) 38.45 (4-CH₂), 40.14 (3a-CH), 53.21 (O=CH₂), 53.90 (3-CH), 88.69 (6a-CH), 128.87 (5-CH), 136.86 (6-CH), 168.37 (C=O), 171.75 (2-C=O); ms (EI): m/z 182 (M⁺, 2%), 138 (29), 106 (17), 95 (11), 79 (100); HRMS calc. for C₉H₁₀O₄ 182.0579 found 182.0574.
Preparation of 5-vinyl-dihydro-furan-2,2,3,3-tetracarboxylic acid diethyl ester dimethyl ester (281b) \((\text{trans: cis; 0:1})^{47}\)

To a stirred solution of diketomalonate (278) (0.032 g, 0.27 mmol) in anhydrous THF (2 mL) was added zinc bromide (0.112 g, 0.54 mmol). The reaction mixture was left to stir for 10 min before 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester (155) (0.050 g, 0.27 mmol) was added. The reaction mixture was stirred for a further 5 min before a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.031 g, 0.03 mmol) was added. The resulting mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica and the organic extract washed with 1 M HCl (20 mL), sat. NaHCO₃ aq. sol. (20 mL), sat. NaCl aq. sol. (20 mL) and dried (MgSO₄). The solvent was removed under reduced pressure to afford crude 5-vinyl-dihydro-furan-2,2,3,3-tetracarboxylic acid diethyl ester dimethyl ester (281b) (0.178 g). The oil was purified using column chromatography (SiO₂, EtOAc:PE 40-60, 8:1) to afford 5-vinyl-dihydro-furan-2,2,3,3-tetracarboxylic acid diethyl ester dimethyl ester (281b) (0.070 g, 0.19 mmol, 72% yield) as a viscous yellow oil. ν\text{max/cm}^{-1} (neat) 2983, 2954, 1753, 1736, 1731 (CO₂R str.), 1438, 1277, 1240, 1120, 1095, 1039, 997, 722; δ\text{H (CDCl₃, 400 MHz)} 1.26-1.82 (6H, m, 2 x C'H₂C'H₃), 2.63-2.73 (2H, m, 4-C'(H₂), 3.67 (3H, s, C'O₂C'H₃), 3.69 (3H, s, C'O₂C'H₃), 4.15-4.30 (4H, m, 2 x C'H₂C'H₃), 4.87 (1H, m, 5-C'H), 5.13 (1H, m, C'(H)H=C'H), 5.26 (1H, m, C'(H)H=C'H), 5.85 (1H, m, C'H₂=C'H); δ\text{C (CDCl₃, 100 MHz)} 13.82 (C'H₂C'H₃), 13.93 (C'H₂C'H₃), 41.56 (4-C'H₂), 53.06 (C'O₂C'H₃), 53.28 (C'O₂C'H₃), 62.24 (C'H₂C'H₃), 62.48 (C'H₂C'H₃), 67.03 (3-C'), 82.07 (5-C'H), 89.94 (2-C'), 118.35 (C'H₂=C'H), 136.51 (C'H₂=C'H), 167.32 (C'=O), 167.73 (C'=O), 168.54 (C'=O), 169.54 (C'=O); ms (FAB): m/z 359 (M⁺, 5%), 285 (14), 280 (20), 279 (100); HRMS calc. for C₁₆H₂₉O₉ 359.1342 found 359.1337.
Preparation of dimethyl 2R-phenyl-1-(phenylmethyl)-1,2,3,3aR,4,6aR-hexahydrocyclopenta[b]pyrrole-3,3-dicarboxylic acid dimethyl ester (283a)

To a stirred solution of benzyl-benzlidene-amine (249) (0.099 g, 0.51 mmol) in anhydrous THF (5 mL) was added zinc bromide (0.230 g, 1.02 mmol). The reaction mixture was left to stir for 10 min before bicyclo[3.1.0]hex-2-ene-6,6-dicarboxylic acid dimethyl ester (202) (0.100 g, 0.51 mmol) was added. The reaction mixture was stirred for a further 5 min before a catalytic amount of tetrakis(triphenylphosphine)palladium(0) (0.059 g, 0.05 mmol) was added. The resulting mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica to afford crude dimethyl 2R-phenyl-1-(phenylmethyl)-1,2,3,3aR,4,6aR-hexahydrocyclopenta[b]pyrrole-3,3-dicarboxylic acid dimethyl ester (283a) (0.121 g) as a viscous orange/yellow oil. The oil was purified using column chromatography (SiO2, EtOAc:PE 40-60, 6:1) to afford dimethyl 2R-phenyl-1-(phenylmethyl)-1,2,3,3aR,4,6aR-hexahydrocyclopenta[b]pyrrole-3,3-dicarboxylic acid dimethyl ester (283a) (0.018 g, 0.05 mmol, 9% yield) as a viscous orange/yellow oil. 

$\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2953, 1733 (C=O str.), 1599, 1520, 1436, 1347, 1274, 1143, 1022, 854; $\delta_{t}$ (CDCl$_3$, 400 MHz) 2.02 (1H, m, 4-CH$_2$), 2.57 (1H, apparent ddt, J 2.4, 9.9 and 17.6 Hz, 4-CH$_2$(H)), 3.25 (1H, d, J 14.6 Hz, NC(H)H), 3.39 (3H, s, CO$_2$CH$_3$), 3.47 (1H, m, 3a-CH), 3.59 (1H, d, J 14.6 Hz, NC(H)H), 3.62 (3H, s, CO$_2$CH$_3$), 4.33 (1H, s, 2-CH), 5.00 (1H, apparent d, J 7.2 Hz, 6a-CH), 5.58 (1H, m, 5-CH), 5.85 (1H, m, 6-CH), 7.22-7.35 (6H, m, 8 x CH arom.), 7.41-4.4 (2H, m, 2 x CH arom.), 7.53-56 (2H, m, 2 x CH arom.); $\delta_{c}$ (CDCl$_3$, 100 MHz) 36.54 (4-CH$_2$), 44.55 (3a-CH), 51.49 (NCH$_2$), 51.84 (CO$_2$CH$_3$), 52.00 (CO$_2$CH$_3$), 67.96 (6a-CH), 68.84 (3-CH), 68.95 (2-CH), 126.58 (4 x CH arom.), 127.86 (4 x CH arom.), 128.31 (2 x CH arom.), 128.88 (5-CH), 138.90 (6-CH), 138.16 (NCH$_2$C arom.), 139.31 (2-CHC arom.), 170.09
(C=O), 170.29 (C=O); ms (EI): m/z 391 (M+, 20%), 300 (48), 268 (20), 234 (35), 194 (37), 165 (13), 132 (14), 121 (67) and 91 (100); HRMS calc. for C_{24}H_{23}NO_4 391.1784 found 391.1786.

**Preparation of dimethyl 2R-phenyl-1-(phenylmethyl)-1,2,3,3aR,4,6aR-hexahydrocyclopenta[b]pyrrole-3,3-dicarboxylic acid dimethyl ester (283a)**

To a stirred solution of benzyl-benzlidene-amine (249) (0.099 g, 0.51 mmol) in anhydrous CH\_2\_Cl\_2 (5 mL) was added zinc bromide (0.230 g, 1.02 mmol). The reaction mixture was left to stir for 10 min before bicyclo[3.1.0]hex-2-ene-6,6-dicarboxylic acid dimethyl ester (202) (0.100 g, 0.51 mmol) was added. The reaction mixture was stirred for a further 5 min before a catalytic amount of bis(dibenzylideneacetone) palladium(0) (0.059 g, 0.05 mmol) was added. The resulting mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica to afford crude dimethyl 2R-phenyl-1-(phenylmethyl)-1,2,3,3aR,4,6aR-hexahydrocyclopenta[b]pyrrole-3,3-dicarboxylic acid dimethyl ester (283a) (0.148 g) as a viscous orange/yellow oil. The oil was purified using column chromatography (SiO\_2, EtOAc:P.E 40-60, 6:1) to afford dimethyl 2R-phenyl-1-(phenylmethyl)-1,2,3,3aR,4,6aR-hexahydrocyclopenta[b]pyrrole-3,3-dicarboxylic acid dimethyl ester (283a) (0.032 g, 0.08 mmol, 16% yield) as a viscous orange/yellow oil. Data as shown above.
Preparation of 1-benzyl-2R-(4-nitro-phenyl)-1,3aR,4,6aR-tetrahydro-2H-cyclopenta[b]pyrrole-3,3-dicarboxylic acid dimethyl ester (284a)

To a stirred solution of benzyl-(4-nitro-benzylidene)-amine (250) (0.122 g, 0.51 mmol) in anhydrous THF (5 mL) was added zinc bromide (0.230 g, 1.02 mmol). The reaction mixture was left to stir for 10 min before bicyclo[3.1.0]hex-2-ene-6,6-dicarboxylic acid dimethyl ester (202) (0.100 g, 0.51 mmol) was added. The reaction mixture was stirred for a further 5 min before a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.059 g, 0.05 mmol) was added. The resulting mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica to afford crude 1-benzyl-2R-(4-nitro-phenyl)-1,3aR,4,6aR-tetrahydro-2H-cyclopenta[b]pyrrole-3,3-dicarboxylic acid dimethyl ester (284a) (0.134 g) as a viscous yellow oil. The oil was purified using column chromatography (SiO₂, EtOAc:P.E 40-60, 6:1) to afford 1-benzyl-2R-(4-nitro-phenyl)-1,3aR,4,6aR-tetrahydro-2H-cyclopenta[b]pyrrole-3,3-dicarboxylic acid dimethyl ester (284a) (0.033 g, 0.08 mmol, 15% yield) as a viscous yellow oil.

υmax/cm⁻¹ (neat) 2922, 2360, 1733 (C=O str.), 1716, 1683, 1652, 1646, 1558, 1539 (NO₂ str.), 1520, 1506, 1456, 1339; δH (CDCl₃, 400 MHz) 2.11 (1H, m, 4-C(!!)H), 2.60 (1H, m, 4-C(H)H), 3.34 (1H, d, J 14.4 Hz, NC(!!)H), 3.37 (3H, s, CO₂Cfu), 3.54 (1H, d, J 14.4 Hz, NC(H)H), 3.71 (3H, s, CO₂Cfu), 4.50 (1H, s, 2-CH), 4.61 (1H, m, 6a-CH), 5.63 (1H, m, 5-CH), 5.95 (1H, m, 6-CH), 7.24-7.42 (5H, m, 5 x CH arom.), 7.74 (2H, d, J 16.0 Hz, 2 x CH arom.), 8.15 (2H, d, J 9.0 Hz, 2 x CH arom.); δC (CDCl₃, 100 MHz) 36.54 (4-CH₂), 44.71 (3a-CH), 51.58 (NCH₂), 52.65 (CO₂CH₃), 52.66 (CO₂CH₃), 68.22 (6a-CH), 68.49 (2-CH), 68.99 (3-CH), 123.03 (2 x CH₂ arom.), 126.93 (2 x CH₃ arom.), 127.68 (CH arom.), 128.49 (2 x CH₃ arom.)
arom.), 128.65 (2 x CH arom.), 129.47 (5-CH arom.), 134.36 (6-CH), 138.46 (NCH₂C), 146.34 (2-CHC), 147.62 (CNO₂), 169.43 (C=O), 169.10 (C=O); ms (El): m/z 436 (M⁺, 3%), 345 (39), 279 (11), 234 (25), 233 (21), 166 (30), 165 (16), 164 (26), 139 (16), 131 (33), 127 (12), 125 (26), 111 (47), 105 (40), 99 (21), 97 (68), 91 (100); HRMS calc. for C₂₄H₂₄N₂O₄ 436.1634 found 436.1628.

**Preparation of 1-benzyl-2R-(4-nitro-phenyl)-1,3aR,4,6aR-tetrahydro-2H-cyclopenta[b]pyrrole-3,3-dicarboxylic acid dimethyl ester (284a)**

To a stirred solution of benzyl-(4-nitro-benzylidene)-amine (250) (0.122 g, 0.51 mmol) in anhydrous CH₂Cl₂ (5 mL) was added zinc bromide (0.230 g, 1.02 mmol). The reaction mixture was left to stir for 10 min before bicyclo[3.1.0]hex-2-ene-6,6-dicarboxylic acid dimethyl ester (202) (0.100 g, 0.51 mmol) was added. The reaction mixture was stirred for a further 5 min before a catalytic amount of bis(dibenzylideneacetone) palladium(0) (0.059 g, 0.05 mmol) was added. The resulting mixture was stirred at room temperature for 12h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica to afford crude 1-benzyl-2R-(4-nitro-phenyl)-1,3aR,4,6aR-tetrahydro-2H-cyclopenta[b]pyrrole-3,3-dicarboxylic acid dimethyl ester (284a) (0.168 g) as a viscous yellow oil. The oil was purified using column chromatography (SiO₂, EtOAc:P.E 40-60, 6:1) to afford 1-benzyl-2R-(4-nitro-phenyl)-1,3aR,4,6aR-tetrahydro-2H-cyclopenta[b]pyrrole-3,3-dicarboxylic acid dimethyl ester (284a) (0.140 g, 0.32 mmol, 63% yield) as a viscous orange/yellow oil. Data as shown above.
Preparation of \textit{N}-benzylidene-benzenesulfonamide (285)\textsuperscript{73}

\begin{center}
\begin{tikzpicture}
\node[inner sep=0] (image) at (0,0) {
\includegraphics[width=0.5\textwidth]{example-image-a}
};
\end{tikzpicture}
\end{center}

To a stirred solution of benzaldehyde (162) (1.06 g, 10 mmol), arenesulfonamide (1.71 g, 10 mmol) in formic acid (15 mL) and water (15 mL) was added sodium p-toluenesulfinate (1.82 g, 11 mmol). The reaction mixture was stirred for 12h at RT. The resulting white precipitate was filtered off and washed with water (2 x 10 mL), pentane (10 mL) and dissolved in CH\textsubscript{2}Cl\textsubscript{2} (100 mL). To the solution was added sat. aq. NaHCO\textsubscript{3} and the solution was stirred vigorously for 2h at RT. The organic phase was decanted and the aqueous phase extracted with CH\textsubscript{2}Cl\textsubscript{2} (70 mL). The organic extracts were combined and dried (NaHCO\textsubscript{3}). The solvent was removed under reduced pressure to afford \textit{N}-benzylidene-benzenesulfonamide (285) (0.784, 3.2 mmol, 32\% yield) as a white powder. \(v_{\text{max}}/\text{cm}^{-1}\) (neat) 3351, 3260, 1699, 1573, 1450, 1320, 782, 675; \(\delta\)\textsubscript{1H} (CDCl\textsubscript{3}, 250 MHz) 2.44 (3H, s, CH\textsubscript{3}), 7.36-7.38 (2H, m, 2 x CH arom.), 7.46-7.52 (2H, m, 2 x CH arom.), 7.62 (1H, m, CH arom.), 7.58-7.95 (4H, m, 3 x CH arom.), 9.03 (1H, s, N=CH); \(\delta\)\textsubscript{C} (CDCl\textsubscript{3}, 100 MHz) 21.69 (CH\textsubscript{3}), 128.12 (2 x CH arom.), 129.17 (2 x CH arom.), 129.84 (2 x CH arom.), 131.34 (2 x CH arom.), 132.37 (C arom.), 134.97 (CH arom.), 135.10 (C arom.), 144.65 (C arom.), 170.18 (N=CH).
Preparation of 1-(2-bromo-benzyl)-2R-(4-nitro-phenyl)-1,3aR,4,6aR-tetrahydro-2H-cyclopenta[b]pyrrole-3,3-dicarboxylic acid dimethyl ester (286a)

To a stirred solution of (2-bromo-benzyl)-(4-nitro-benzylidine)-amine (259) (0.162 g, 0.51 mmol) in anhydrous CH₂Cl₂ (5 mL) was added zinc bromide (0.230 g, 1.02 mmol). The reaction mixture was left to stir for 10 min before bicyclo[3.1.0]hex-2-ene-6,6-dicarboxylic acid dimethyl ester (202) (0.100 g, 0.51 mmol) was added. The reaction mixture was stirred for a further 5 min before a catalytic amount of bis(dibenzylideneacetone) palladium(0) (0.059 g, 0.05 mmol) was added. The resulting mixture was stirred at room temperature for 12h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica to afford crude 1-(2-bromo-benzyl)-2R-(4-nitro-phenyl)-1,3aR,4,6aR-tetrahydro-2H-cyclopenta[b]pyrrole-3,3-dicarboxylic acid dimethyl ester (286a) (0.210 g) as a viscous yellow oil. The oil was purified using column chromatography (SiO₂, EtOAc:P.E 40-60, 6:1) to afford 1-(2-bromo-benzyl)-2R-(4-nitro-phenyl)-1,3aR,4,6aR-tetrahydro-2H-cyclopenta[b]pyrrole-3,3-dicarboxylic acid dimethyl ester (286a) (0.129 g, 0.25 mmol, 49% yield) as a viscous yellow oil. v_max/cm⁻¹ (neat) 2949, 1734 (C02R str.), 1522 (NO2 str.), 1434, 1346, 1273, 1228, 1196, 1136, 1026; δ_H (CDCl₃, 400 MHz) 2.07 (1H, m, 4-C(H)H), 2.56 (1H, m, 4-C(H)H), 3.26 (1H, d, J 11.0 Hz, NC(H)H), 3.30 (3H, s, CO₂CH₃), 3.51 (1H, m, 3a-CH), 3.64 (3H, s, CO₂CH₃), 3.73 (1H, d, J 11.0 Hz, NC(H)H), 4.52 (1H, s, 2-CH), 4.61 (1H, m, 5-CH), 5.48 (1H, m, 5-CH), 5.92 (1H, m, 6-CH), 7.05 (1H, m, CH arom.), 7.30 (1H, m, CH arom.), 7.43 (1H, m, CH arom.), 7.66 (1H, m, CH arom.), 7.71 (2H, d, J 7.6 Hz, 2 x CH arom.), 8.06 (2H, d, J 9.2 Hz, 2 x CH arom.); δ_C (CDCl₃, 100 MHz) 36.55 (4-CH₂), 44.91 (3a-CH), 50.99 (NCH₂), 52.35 (CO₂CH₃), 52.50 (CO₂CH₃), 67.98 (6a-CH), 68.48 (2-CH), 68.70 (3-CH), 122.79 (CBr), 127.76 (2
x CH arom.), 128.27 (5-CH arom.), 128.43 (CH arom.), 129.59 (2 x CH arom.), 132.42 (2 x CH arom.), 132.57 (CH arom.), 134.87 (6-CH), 146.06 (NCH=O), 147.66 (CNO), 152.50 (2-CH), 169.50 (C=O), 169.79 (C=O).

**Preparation of 2-(2-bromo-phenyl)-5-vinyl-dihydrofuran-3,3-dicarboxylic acid dimethyl ester (278) (cis:trans; 1.8:1)**

![Diagram](image.png)

To a stirred mixture of 2-bromobenzaldehyde (278) (0.110 g, 0.54 mmol) and 2-vinylcyclopropane-1,1-dicarboxylic acid (155) (0.100 g, 0.54 mmol) in MeOH (5 ml) was added a catalytic amount of tetrakis (triphenylphosphine) palladium(0) (0.062 g, 0.05 mmol). The resulting mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica and the organic layer washed with 1 M HCl (20 mL), sat. NaHCO₃ aq. sol. (20 mL), sat. NaCl aq. sol. (20 mL) and dried (MgSO₄). The solvent was removed under reduced pressure to afford crude 2-(2-bromo-phenyl)-5-vinyl-dihydrofuran-3,3-dicarboxylic acid dimethyl ester (278) as a yellow oil. The oil was purified using column chromatography (SiO₂, EtOAc:PE. 40-60 °C, 1:8) to afford 2-(2-bromo-phenyl)-5-vinyl-dihydrofuran-3,3-dicarboxylic acid dimethyl ester (278) (0.194 g, 0.53 mmol, 96% yield) as a yellow oil. νmax/cm⁻¹ (neat) 2951, 2135, 1735 (CO₂R str.), 1469, 1434, 1267, 1227, 1203, 1024, 935, 756; δH (CDCl₃, 100 MHz) 2.29 (1H, dd, J 5.4 and 12.8 Hz, 4-C(H)H), 2.35 (1H, dd, J 4.6 and 13.2 Hz, 4-C'(H)H), 2.72 (1H, dd, J 11.6 and 13.2 Hz, 4-C(H)H), 3.03 (1H, dd, J 10.0 and 17.2 Hz, 4-C'(H)H), 3.07 (3H, s, C'O₂C'H₃), 3.16 (3H, s, CO₂CH₃), 3.68 (3 H, s, CO₂CH₃), 3.77 (3H, s, C'O₂C'H₃), 4.37 (1H, m, 5-C'(H)), 4.98 (1H, m, 5-CH), 5.11 (1H, m, C(H)H=CH), 5.22 (1H, m, C'(H)H=C'H), 5.24 (1H, m, C(H)H=CH), 5.36 (1H, m, C'(H)H=C'H), 5.81 (1H, m, CH₂=CH), 5.97 (1H, m, C'H₂=C'H), 6.23 (1H, s, 2-C'H), 6.30 (1H, s, 2-CH), 7.02-
7.06 (2H, m, C’H arom. and CH arom.), 7.19-7.23 (2H, m, C’H arom. and CH arom.),
7.30 (1H, m, C’H arom.), 7.34 (1H, m, CH arom.), 7.42-7.45 (2H, m, C’H arom. and
CH arom.); δC (400 MHz) 40.64 (4-CH2), 40.72 (4-C’H2), 52.11 (C’O2C’H3), 52.30
(CO2CH3), 52.30 (CO2CH3), 53.27 (C’O2C’H3), 65.86 (3-C), 65.95 (3-C’), 79.27 (5-
C’H), 80.58 (5-C’H), 82.79 (2-C’H), 83.30 (2-CH), 116.40 (CH2=CH), 118.11
(C’H2=C’H), 123.09 (C arom.), 123.51 (C’ arom.), 127.18 (C’H arom.), 128.74 (CH
arom.), 129.54 (CH arom. and C’H arom.), 132.36 (C’H2=C’H), 132.67 (CH2=CH),
135.74 (CH arom. and C’H arom.), 137.62 (CH arom. and C’H arom.), 138.10 (C’Br),
138.74 (CBr), 168.55 (C’=O), 168.76 (C=O), 170.21 (C=O), 170.93 (C’=O); ms (ES):
m/z 388 (M+, 100%, Br81), 386 (M+, 96%, Br79); HRMS calc. for C16H17O579Br
386.0598 found 386.0601.

Preparation of 1,1,4-trimethoxy-but-2-ene (289)

![Structure of 1,1,4-trimethoxy-but-2-ene (289)](attachment)

To a stirred solution of 2-vinylcyclopropane-1,1-dicarboxylic acid (155) (0.100 g, 0.54
mmol) in MeOH (10 ml) was added tetrakis (triphenylphosphine) palladium(0) (0.062
g, 0.05 mmol). The reaction mixture was stirred at RT for 12h. The reaction mixture
was then dissolved into EtOAc (25 ml) and flushed through a plug of silica with a
further two portions of EtOAc (2 x 25 ml). The solvent was evaporated in vacuo to
afford 1,1,4-trimethoxy-but-2-ene (289) as colourless oil. ν<sub>max</sub>/cm<sup>-1</sup> (neat) 2995, 2950,
2135, 1735, 1730, 1434, 1267, 1227, 1202, 1024, 935, 756; δH (CDCl<sub>3</sub>, 250 MHz)
2.59-2.66 (4H, m, 2 x CH2), 3.27 (3H, s OCH3), 3.41-3.43 (1H, m, CH), 3.73 (6H, s, 2
x CO2CH3), 5.62-5.63 (2H, s, CH=CH).
Preparation of 2-bromo-3,4,5-trimethoxy-benaldehyde (170)^47

A stirred solution of 3,4,5-trimethoxybenzaldehyde (171) (3.500 g, 17.9 mmol) in anhydrous CH$_2$Cl$_2$ (75 mL) and acetic acid (0.1 mL) was cooled to 0°C in an ice bath. Bromine (0.92 mL, 19.9 mmol) dissolved in anhydrous CH$_2$Cl$_2$ (5 mL) was added drop wise by syringe over 10 min. The orange reaction mixture was left to stir at 0°C for 1 h before addition of sat. Na$_2$S$_2$O$_3$ aq. sol. (100 mL) and the mixture extracted with CH$_2$Cl$_2$ (3 x 100 mL). The organic extracts were then washed with sat. NaHCO$_3$ sol. (100 mL), sat. NaCl aq. sol. (100 mL) and dried (Na$_2$SO$_4$). The solvent was removed under reduced pressure to afford crude 2-bromo-3,4,5-trimethoxy-benaldehyde (170) (4.183 g) as a pale yellow solid. The solid was purified using column chromatography (SiO$_2$, Et$_2$O:P.E 40-60, 1:1) to afford 2-bromo-3,4,5-trimethoxy-benaldehyde (170) (3.498 g, 12.8 mmol, 72% yield) as colourless needles.

$\nu_{\text{max}}$/cm$^{-1}$ (thin film) 2941, 2866, 1692 (CO$_2$R str.), 1577, 1564, 1470, 1451, 1404, 1384, 1326, 1198, 1167, 1608, 1006, 981, 921; $\delta_{\text{H}}$ (CDCl$_3$, 400 MHz) 3.92 (3H, s, OCH$_3$), 3.93 (3H, s, OCH$_3$), 4.00 (3H, s, OCH$_3$), 7.32 (1H, s, CH arom.), 10.31 (1H, s, HCO); $\delta_{\text{C}}$ (CDCl$_3$, 100 MHz) 56.26 (OCH$_3$), 61.22 (OCH$_3$), 61.29 (OCH$_3$), 107.458 (CH arom.), 115.66 (C arom.), 128.80 (C arom.), 148.72 (C arom.), 150.78 (C arom.), 153.03 (C arom.), 191.11 (HCO).
Preparation of 2-(2-bromo-3,4,5-trimethoxy-phenyl)-5-vinyl-dihydrofuran-3,3-dicarboxylic acid dimethyl ester (290) (trans:cis; 1:3.8)\textsuperscript{47}

To a stirred solution of 2-bromo-3,4,5-trimethoxy-benaldehyde (170) (0.148 g, 0.54 mmol) in anhydrous THF (5 mL) was added zinc bromide (0.243 g, 0.54 mmol). The reaction mixture was left to stir for 10 min before 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester (155) (0.100 g, 0.51 mmol) was added. The reaction mixture was stirred for a further 5 min before a catalytic amount of tetrakis(triphenylphosphine) palladium(O) (0.062 g, 0.05 mmol) was added. The resulting mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure and the white solid dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica and the organic layer washed with 1 M HCl (20 mL), sat. NaHCO\textsubscript{3} aq. sol. (20 mL), sat. NaCl aq. sol. (20 mL) and dried (MgSO\textsubscript{4}). The solvent was removed under reduced pressure to afford crude 2-(2-bromo-3,4,5-trimethoxy-phenyl)-5-vinyl-dihydrofuran-3,3-dicarboxylic acid dimethyl ester (290) (0.164 g). The white solid was purified using column chromatography (SiO\textsubscript{2}, EtOAc:PE 40-60, 8:1) to afford 2-(2-bromo-3,4,5-trimethoxy-phenyl)-5-vinyl-dihydrofuran-3,3-dicarboxylic acid dimethyl ester (290) (0.149 g, 0.31 mmol, 58% yield) as white needles. $v_{\text{max}}$ cm\textsuperscript{-1} (neat) 2952, 1734 (C=O str.), 1436, 1164, 1106; $\delta_{\text{H}}$ (CDCl\textsubscript{3}, 400 MHz) 2.37 (1H, dd, $J_{4.8}$ and 13.2 Hz, 4-C(H)H), 2.45 (1H, dd, $J_{4.8}$ and 13.2 Hz, 4-C'(H)H), 2.79 (1H, dd, $J_{11.6}$ and 13.2 Hz, 4-C(H)=CH), 3.14 (1H, dd, $J_{7.6}$ and 13.2 Hz, 4-C'(H)H), 3.23 (3H, s, C'02C'H\textsubscript{3}), 3.30 (3H, s, CO\textsubscript{2}CH\textsubscript{3}), 3.74 (3 H, s, CO\textsubscript{2}CH\textsubscript{3}), 3.79 (3H, s, C'O\textsubscript{2}C'H\textsubscript{3}), 3.84 (3H, s, OCH\textsubscript{3}), 3.85 (3H, s, OCH\textsubscript{3}), 3.86 (3H, s, OCH\textsubscript{3}), 4.47 (1H, m, 5-C'(H)), 5.05 (1H, m, 5-C(H)), 5.19 (1H, apparent dt, $J_{1.2}$, 2.8 and 10.4 Hz, C(H)H=CH), 5.29 (1H, apparent dt, $J_{0.8}$, 2.4,
10.4 Hz, C'(H)=C'HC'H), 5.35 (1H, apparent dt, J 1.2, 2.8 and 17.8 Hz, C(H)H=CH), 5.45 (1H, apparent d, J 1.2, 2.8 and 17.8 Hz, C'(H)=C'H), 5.90 (1H, m, CH=2=CH), 6.05 (1H, m, C'H=2=C'H), 6.30 (1H, s, 2-C'H), 6.35 (1H, s, 2-CH), 6.75 (1H, s, CH arom.), 6.79 (1H, s, CH arom.); δc (400 MHz) 40.71 (4-CH2), 41.08 (4=C'H2), 51.49 (C'O2=C'H3), 52.20 (CO2=CH3), 52.35 (CO2=CH3), 52.66 (C'O2=C'H3), 56.04 (2 x OCH3), 56.10 (2 x OCH3), 61.00 (OCH3), 61.11 (OCH3), 65.72 (3-C), 67.81 (3=C'), 78.98 (5-C'H), 80.26 (5-CH), 82.81 (2-C'H), 83.17 (2-CH), 107.45 (CH arom.), 108.07 (C'H arom.), 110.07 (CBr), 110.20 (C'Bri, 116.29 (CH=2=CH), 117.67 (C'H=2=C'H), 133.59 (2-CH2C'), 133.99 (2=C'H2C'), 135.86 (CH=2=CH), 137.60 (C'H=2=C'H), 142.94 (C'O=CH and COCH3), 150.33 (C'O=CH3), 150.42 (COCH3), 152.38 (C'O=CH3), 152.44 (COCH3), 168.52 (C+=O), 168.58 (C=O), 170.14 (C'=O), 170.83 (C=O); ms (El): m/z 478 (M+, 60%, Br81), 476 (M+, 51%, Br79), 418 (11), 279 (10), 234 (18), 214 (13), 204 (100); HRMS calc. for C19H23O679Br 476.0915 found 476.0919.

Preparation of 2-(2-bromo-3,4,5-trimethoxy-phenyl)-5-vinyl-dihydrofuran-3,3-dicarboxylic acid dimethyl ester (290) (trans: cis; 1:5)47

To a stirred solution of 2-bromo-3,4,5-trimethoxy-benaldehyde (170) (0.148 g, 0.54 mmol) in anhydrous CH2Cl2 (5 mL) was added zinc bromide (0.243 g, 1.08 mmol). The reaction mixture was left to stir for 10 min before 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester (155) (0.100 g, 0.54 mmol) was added. The reaction mixture was stirred for a further 5 min before a catalytic amount of bis(dibenzylideneacetone) palladium(0) (0.049 g, 0.05 mmol) was added. The resulting mixture was stirred at room temperature for 12h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica to afford crude 2-(2-bromo-3,4,5-trimethoxy-phenyl)-5-vinyl-dihydrofuran-3,3-dicarboxylic acid dimethyl ester (290) (0.231 g). The oil was purified using column chromatography (SiO2, EtOAc:PE 40-60, 8:1) to afford 2-(2-bromo-3,4,5-trimethoxy-phenyl)-5-vinyl-dihydrofuran-3,3-dicarboxylic acid dimethyl ester (290) (0.093 g, 0.19 mmol, 36% yield) as white needles. Data as above.
Preparation of 2-(2-bromo-3,4,5-trimethoxy-phenyl)-5-vinyl-dihydrofuran-3,3-dicarboxylic acid dimethyl ester (290) (trans:cis; 1:3.8)\textsuperscript{47}  

To a stirred solution of 2-bromo-3,4,5-trimethoxy-benaldehyde (170) (0.148 g, 0.54 mmol) in anhydrous MeOH (5 mL) was added 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester (155) (0.100 g, 0.54 mmol). A catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.062 g, 0.05 mmol) was then added. The resulting mixture was stirred at room temperature for 12h. The solvent was removed under reduced pressure and the oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica and the organic layer washed with 1 M HCl (20 mL), sat. NaHCO\textsubscript{3} aq. sol. (20 mL), sat. NaCl aq. sol. (20 mL) and dried (MgSO\textsubscript{4}). The solvent was removed under reduced pressure to afford crude 2-(2-bromo-3,4,5-trimethoxy-phenyl)-5-vinyl-dihydrofuran-3,3-dicarboxylic acid dimethyl ester (290) (0.189 g). The oil was purified using column chromatography (SiO\textsubscript{2}, EtOAc:P.E 40-60, 8:1) to afford 2-(2-bromo-3,4,5-trimethoxy-phenyl)-5-vinyl-dihydrofuran-3,3-dicarboxylic acid dimethyl ester (290) (0.097 g, 0.21 mmol, 38% yield) as white needles. Data as above.

Preparation of 2-(1-bromo-2-phenyl-vinyl)-5-vinyl-dihydro-furan-3,3-dicarboxylic acid dimethyl ester (292) (trans:cis; 1:1.7)

To a stirred solution of \(\alpha\)-bromocinnamaldehyde (291) (0.113 g, 0.54 mmol) in anhydrous THF (5 mL) was added zinc bromide (0.243 g, 0.54 mmol). The reaction mixture was left to stir for 10 min before 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester (155) (0.100 g, 0.54 mmol) was added. The reaction mixture was stirred for a further 5 min before a catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.062 g, 0.05 mmol) was added. The resulting mixture was stirred at
room temperature for 12h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica and the organic extract washed with 1 M HCl (20 mL), sat. NaHCO₃ aq. sol. (20 mL), sat. NaCl aq. sol. (20 mL) and dried (MgSO₄). The solvent was removed under reduced pressure to afford crude 2-(1-bromo-2-phenyl-vinyl)-5-vinyl-dihydro-furan-3,3-dicarboxylic acid dimethyl ester (292) (0.139 g). The oil was purified using column chromatography (SiO₂, EtOAc:PE 40-60, 8:1) and afforded the desired 2-(1-bromo-2-phenyl-vinyl)-5-vinyl-dihydro-furan-3,3-dicarboxylic acid dimethyl ester (292) (0.178 g, 0.45 mmol, 86% yield) as a viscous yellow oil. A small amount of the cis and trans isomer were isolated from the mixture of the two diastereoisomers (cis isomer 0.022 g, 0.06 mmol, 10% yield and trans isomer 0.014 g, 0.04 mmol, 7% yield).

Mixture trans:cis isomers (292a:292b):- $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2951, 1731 (C=O str.), 1681, 1489, 1434, 1269, 1156, 1090, 932; $\delta_{\text{H}}$ (CDCl₃, 400 MHz) 2.15 (1H, dd, $J = 6.8$ Hz and 13.2 Hz, 4-C(H)H), 2.42 (1H, dd, $J = 5.6$ Hz and 13.2 Hz, 4-C'(H)H), 2.78 (1H, dd, $J = 11.0$ Hz and 13.2 Hz, 4-C'(H)H), 3.05 (1H, dd, $J = 6.8$ Hz and 13.2 Hz, 4-C(H)H), 3.61 (3H, s, C'O₂C'H₃), 3.63 (3H, s, CO₂CH₃), 3.71 (3H, s, CO₂CH₃), 3.77 (3H, s, C'O₂C'H₃), 4.32 (1H, m, 5-C'H), 4.93 (1H, m, 5-CH), 5.10 (1H, m, C(H)H=CH), 5.19 (1H, m, C'(H)H=C'H), 5.26 (1H, m, C(H)H=CH), 5.32 (1H, m, C'(H)H=C'H), 5.41 (1H, s, 2-C'H), 5.53 (1H, s, 2-CH), 5.76 (1H, m, CH₂=CH), 5.98 (1H, m, C'H₂=CH'), 7.11 (1H, s, C'Br=C'H'), 7.14 (1H, s, CBr=CH), 7.19-7.30 (6H, m, 3 x CH arom. and 3 x C'H arom.), 7.48-7.51 (4H, m, 2 x CH arom. and 2 x C'H arom.); $\delta_{\text{C}}$ (CDCl₃, 100 MHz) 40.03 (4-C'H₂), 40.18 (4-CH₃), 53.03 (C'O₂C'H₃), 53.12 (CO₂CH₃), 53.17 (CO₂CH₃), 53.41 (C'O₂C'H₃), 64.94 (3-C, 65.50 (3-C'), 79.84 (5-C'H), 80.77 (5-CH), 86.68 (2-CH and 2-C'H), 116.57 (CH₂=CH), 118.34 (C'H₂=CH'), 122.99 (C' arom.), 123.03 (C arom.), 128.52 (3 x CH arom. and 3 x C'H), 129.13 (2 x CH arom. and 2 x C'H), 130.59 (CBr=CH), 131.77 (C'Br=C'H), 135.14 (CBr=CH), 135.09 (C'Br=C'H), 136.06 (C'H₂=CH'), 137.53 (CH₂=CH), 168.06 (C'=O), 168.38 (C=O), 170.06 (C'=O), 170.70 (C'=O); ms (EI): m/z 396 (M⁺, 1%, Br81), 394 (M⁺, 1%, Br79), 316 (26), 315 (71), 277 (11), 211 (12), 209 (11), 184 (17), 161 (13), 153 (46), 152 (38), 145 (14), 141 (14), 139 (13), 132 (20), 131 (77), 129 (10), 128 (10), 125 (24), 124 (31), 121 (53), 115 (34), 113 (22), 111 (22), 109
Trans isomer (292a):- $v_{\text{max}}/\text{cm}^{-1}$ (neat) 2951, 1731 (CO$_2$R str.), 1681, 1489, 1434, 1269, 1156, 1090, 932; $\delta$H (CDCl$_3$, 400 MHz) 2.15 (1H, dd, J 6.8 Hz and 13.2 Hz, 4-C(H)H), 3.05 (1H, dd, J 6.8 Hz and 13.2 Hz, 4-C(H)H), 3.63 (3H, s, CO$_2$CH$_3$), 3.71 (3H, s, CO$_2$CH$_3$), 4.93 (1H, apparent q, J 6.8 Hz, 5-CH), 5.10 (1H, apparent d, J 10.4 Hz, C(H)=CH), 5.26 (1H, apparent d, J 17.2 Hz, C(H)=CH), 5.53 (1H, s, 2-CH), 5.76 (1H, m, CH$_2$=CH), 7.14 (1H, s, CBr=CH), 7.24 (3H, m, 3 x CH arom.), 7.50 (2H, m, 2 x CH arom.); $\delta$C (CDCl$_3$, 100 MHz) 40.18 (4-CH$_2$), 53.12 (CO$_2$CH$_3$), 53.17 (CO$_2$CH$_3$), 64.94 (3-C), 80.77 (5-CH), 86.68 (2-CH), 116.57 (CH$_2$=CH), 123.03 (C arom.), 128.52 (3 x CH arom.), 129.13 (2 x CH arom.), 130.59 (CBr=CH), 135.14 (CBr=CH), 137.53 (CH$_2$=CH), 168.38 (C=O), 170.06 (C=O).

Cis isomer (292b):- $v_{\text{max}}/\text{cm}^{-1}$ (neat) 2951, 1731 (CO$_2$R str.), 1681, 1489, 1434, 1269, 1156, 1090, 932; $\delta$H (CDCl$_3$, 400 MHz) 2.42 (1H, dd, J 5.6 Hz and 13.2 Hz, 4-C'(H)H), 2.78 (1H, dd, J 11.0 Hz and 13.2 Hz, 4-C'(H)H), 3.61 (3H, s, C'O$_2$C'H$_3$), 3.77 (3H, s, C'O$_2$C'H$_3$), 4.32 (1H, m, 5-C'H), 5.19 (1H, apparent dt, J 1.0 and 9.6 Hz, C'(H)H=C'H), 5.32 (1H, apparent dt, J 1.0 and 16.8 Hz, C'(H)H=C'H), 5.41 (1H, s, 2-C'H), 5.98 (1H, m, C'H$_2$=C'H), 7.11 (1H, s, C'Br=C'H), 7.26 (3H, m, 3 x C'H arom.), 7.48 (2H, m, 2 x C'H arom.); $\delta$C (CDCl$_3$, 100 MHz) 40.03 (4-C'H$_2$), 53.03 (C'O$_2$C'H$_3$), 53.41 (C'O$_2$C'H$_3$), 65.50 (3-C'), 79.84 (5-C'H), 86.68 (2-C'H), 118.34 (C'H$_2$=C'H), 122.99 (C' arom.), 128.28 (3 x C'H arom.), 129.12 (2 x C'H arom.), 131.77 (C'Br=C'H), 135.09 (C'Br=C'H), 136.06 (C'H$_2$=C'H), 168.06 (C'=O), 170.70 (C'=O).

**Preparation of 2-(1-bromo-2-phenyl-vinyl)-5-vinyl-dihydro-furan-3,3-dicarboxylic acid dimethyl ester (292) (trans: cis; 1:7)**

To a stirred solution of a-bromocinnamaldehyde (291) (0.113 g, 0.54 mmol) in anhydrous CH$_2$Cl$_2$ (5 mL) was added zinc bromide (0.243 g, 1.08 mmol). The reaction mixture was left to stir for 10 min before 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester (155) (0.100 g, 0.54 mmol) was added. The reaction mixture was stirred for a further 5 min before a catalytic amount of
bis(dibenzylideneacetone) palladium(0) (0.049 g, 0.05 mmol) was added. The resulting mixture was stirred at room temperature for 12h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica to afford crude 2-(1-bromo-2-phenyl-vinyl)-5-vinyl-dihydro-furan-3,3-dicarboxylic acid dimethyl ester (292) (0.168 g). The oil was purified using column chromatography (SiO₂, EtOAc:P.E 40-60, 8:1) to afford 2-(1-bromo-2-phenyl-vinyl)-5-vinyl-dihydro-furan-3,3-dicarboxylic acid dimethyl ester (292) (0.013 g, 0.3 mmol, 6% yield) as a viscous yellow oil. Data as above.

**Preparation of 2-(1-bromo-2-phenyl-vinyl)-5-vinyl-dihydro-furan-3,3-dicarboxylic acid dimethyl ester (292) (trans:cis; 1:2.1)**

To a stirred solution of α-bromocinnamaldehyde (291) (0.113 g, 0.54 mmol) (0.148 g, 0.54 mmol) in anhydrous MeOH (5 mL) was added 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester (155) (0.100 g, 0.54 mmol). A catalytic amount of tetrakis(triphenylphosphine) palladium(0) (0.062 g, 0.05 mmol) was then added. The resulting mixture was stirred at room temperature for 12h. The solvent was removed under reduced pressure and the oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica and the organic layer washed with 1 M HCl (20 mL), sat. NaHCO₃ aq. sol. (20 mL), sat. NaCl aq. sol. (20 mL) and dried (MgSO₄). The solvent was removed under reduced pressure to afford crude 2-(1-bromo-2-phenyl-vinyl)-5-vinyl-dihydro-furan-3,3-dicarboxylic acid dimethyl ester (292) (0.189 g). The oil was purified using column chromatography (SiO₂, EtOAc:P.E 40-60, 8:1) to afford 2-(1-bromo-2-phenyl-vinyl)-5-vinyl-dihydro-furan-3,3-dicarboxylic acid dimethyl ester (292) (0.183 g, 0.46 mmol, 86% yield) as viscous yellow oil. Data as above.

**Preparation of 2-(1-bromo-2-phenyl-vinyl)-5-vinyl-dihydro-furan-3,3-dicarboxylic acid dimethyl ester (292) (trans:cis; 1:2.1)**

To a stirred solution of α-bromocinnamaldehyde (291) (0.113 g, 0.54 mmol) (0.148 g, 0.54 mmol) in anhydrous MeOH (5 mL) was added 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester (155) (0.100 g, 0.54 mmol). A catalytic amount of
Tetrakis(triphenylphosphine) palladium(0) (0.062 g, 0.05 mmol) was then added. The resulting mixture was stirred at reflux for 2 h. The solvent was removed under reduced pressure and the oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica and the organic layer washed with 1 M HCl (20 mL), sat. NaHCO₃ aq. sol. (20 mL), sat. NaCl aq. sol. (20 mL) and dried (MgSO₄). The solvent was removed under reduced pressure to afford crude 2-(1-bromo-2-phenyl-vinyl)-5-vinyl-dihydro-furan-3,3-dicarboxylic acid dimethyl ester (292) (0.178 g). The oil was purified using column chromatography (SiO₂, EtOAc:P.E 40-60, 8:1) to afford 2-(1-bromo-2-phenyl-vinyl)-5-vinyl-dihydro-furan-3,3-dicarboxylic acid dimethyl ester (292) (0.164 g, 0.42 mmol, 77% yield) as a viscous yellow oil. Data as above.

**Preparation of 6-benzylidene-5-methylene-7-oxa-bicyclo[2.2.1]heptane-2,2-dicarboxylic acid dimethyl ester (293b)**

[Chemical structure image]

**Stepwise procedure using PPh₃ ligand**

To a stirred mixture of 2-(1-bromo-2-phenyl-vinyl)-5-vinyl-dihydro-furan-3,3-dicarboxylic acid dimethyl ester (291b) (0.200 g, 0.51 mmol) in Et₃N (5 mL) was added Pd(OAc)₂ (0.011 g, 0.05 mmol), PPh₃ (0.525 g, 0.20 mmol). The resulting mixture was stirred at reflux for 72 h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica and the organic extract washed with 1 M HCl (20 mL), sat. NaHCO₃ aq. sol. (20 mL), sat. NaCl aq. sol. (20 mL) and dried (MgSO₄). The solvent was removed under reduced pressure to afford crude 6-benzylidene-5R-methylene-7-oxa-bicyclo[2.2.1]heptane-2R,2-dicarboxylic acid dimethyl ester (293b) (0.321 g). The orange oil was purified using column chromatography (SiO₂, EtOAc:P.E. 40-60, 8:1) to afford 6-benzylidene-5R-methylene-7-oxa-bicyclo[2.2.1]heptane-2R,2-dicarboxylic acid dimethyl ester (293b)
(0.017 g, 0.04 mmol, 8% yield) as a yellow oil. \( \nu_{\text{max}}/\text{cm}^{-1} \) (neat) 2952, 1731 (CO$_2$R str.), 1682, 1434, 1270, 1156, 932, 752; \( \delta_H \) (CDCl$_3$, 400 MHz) 2.12 (1H, dd, J 5.2 and 12.8 Hz, 4-C(H)H), 2.52 (1H, d, J 12.8 Hz, 4-C(H)H), 3.50 (3H, s, CO$_2$CH$_3$), 3.58 (3H, s, CO$_2$CH$_3$), 4.62 (1H, d, J 4.8 Hz, 5-CH), 4.74 (1H, s, 6-C=C(H)H) 4.95 (1H, s, 6-C=C(H)H), 5.18 (1H, s, 5a-CH), 6.34 (1H, s, 7-C=C(H)), 7.03-7.16 (5H, m, 5 x CH arom.); \( \delta_C \) (CDCl$_3$, 100 MHz) 38.84 (4-CH$_3$), 53.04 (CO$_2$CH$_3$), 53.10 (CO$_2$CH$_3$), 63.86 (3-C), 83.33 (2-CH), 86.17 (5-CH), 106.70 (6-C=C(H)$_2$), 127.74 (7-C=C(H)), 128.15 (2 x CH arom.), 128.48 (2 x CH arom.), 130.59 (CH arom.), 135.96 (7-C), 136.02 (7-C=C(H)$_2$) 144.73 (6-C), 168.38 (C=O), 170.46 (C=O).

Preparation of 10-methylene-3-phenyl-1,5,10a-tetrahydro-pyrrolo[1,2-b]isoquinoline-2,2-dicarboxylic acid dimethyl ester (294b)

Stepwise procedure using PPh$_3$ ligand

To a stirred mixture of 1-(2-bromo-benzyl)-2-(4-methoxy-phenyl)-5-vinylpyrrolidine-3,3-dicarboxylic acid dimethyl ester (258b) (0.100 g, 0.23 mmol) in Et$_3$N (5 mL) was added Pd(OAc)$_2$ (0.005 g, 0.02 mmol) and PPh$_3$ (0.021 g, 0.08 mmol). The resulting mixture was stirred at refluxed for 72h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica and the organic extract washed with 1 M HCl (20 mL), sat. NaHCO$_3$ aq. sol. (20 mL), sat. NaCl aq. sol. (20 mL) and dried (MgSO$_4$). The solvent was removed under reduced pressure to afford crude 10-methylene-3-phenyl-1,5,10a-tetrahydro-pyrrolo[1,2-b]isoquinoline-2,2-dicarboxylic acid dimethyl ester (294b) (0.215 g). The orange oil was purified using column chromatography (SiO$_2$, EtOAc:P.E. 40-60, 8:1) to afford 10-methylene-3-phenyl-1,5,10a-tetrahydro-pyrrolo[1,2-b]isoquinoline-2,2-dicarboxylic acid
dimethyl ester (294b) (0.023 g, 0.06 mmol, 28% yield) as a yellow oil. \( v_{\text{max}}/\text{cm}^{-1} \) (neat) 2951, 2921, 1736 (CO\(_2\)R str.), 1682, 1454, 1435, 1360, 1328, 1267, 1228, 1210, 1197, 1176, 1091, 1061, 1028, 916; \( \delta_1 \) (CDCl\(_3\), 400 MHz) 2.58 (1H, dd, \( J 5.6 \) and 12.4 Hz, 4-C(H)H), 2.97 (3H, s, CO\(_2\)CH\(_3\)), 3.01 (1H, dd, \( J 10.8 \) and 12.4 Hz, 4-C(H)H), 3.13 (1H, m, 4a-CH), 3.35 (1H, d, \( J 14.8 \) Hz, 10-C(H)H), 3.74 (3H, s, CO\(_2\)CH\(_3\)), 3.78 (1H, d, \( J 14.8 \) Hz, 10-C(H)H), 4.46 (1H, s, 2-CH), 5.02 (1H, d, \( J 1.6 \) Hz, 5-C=C(H)H), 5.69 (1H, d, \( J 2.0 \) Hz, 5-C=C(H)H), 6.90 (1H, m, CH arom.), 7.08-7.25 (5H, m, 5 x CH arom.), 7.36-7.40 (2H, m, 2 x CH arom.), 7.66-7.68 (1H, m, CH arom.); \( \delta_c \) (CDCl\(_3\), 100 MHz) 37.25 (4-CH\(_2\)), 52.15 (CO\(_2\)CH\(_3\)), 53.00 (CO\(_2\)CH\(_3\)), 54.50 (10-CH\(_2\)) 62.43 (4a-CH), 64.05 (3-C), 74.59 (2-CH), 106.49 (5-C=CCH\(_2\)), 123.79 (CH arom.), 126.63 (2 x CH arom.), 127.03 (2 x CH arom.), 127.93 (2 x CH arom.), 128.02 (2 x CH arom.), 132.00 (5a-C), 134.74 (9a-C), 137.75 (2-CHC), 142.99 (5-C), 169.57 (C=O), 172.31 (C=O); ms (EI): \( m/z \) 378 (M\(^+\), 100%); HRMS calc. for C\(_{23}\)H\(_{23}\)N\(_3\)O\(_4\) 378.1700 found 378.1699.

**Stepwise procedure using P(o-Tol)\(_3\) ligand**

To a stirred mixture of 1-(2-bromo-benzyl)-2-(4-methoxy-phenyl)-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (258b) (0.100 g, 0.23 mmol) in Et\(_3\)N (5 mL) was added Pd(OAc)\(_2\) (0.005 g, 0.02 mmol), P(o-Tol)\(_3\) (0.024 g, 0.08 mmol). The resulting mixture was stirred at reflux for 72h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica and the organic extract was washed with 1 M HCl (20 mL), sat. NaHCO\(_3\) aq. sol. (20 mL), sat. NaCl aq. sol. (20 mL) and dried (MgSO\(_4\)). The solvent was removed under reduced pressure to afford crude 10-methylene-3-phenyl-1,5,10,10a-tetrahydro-pyrrolo[1,2-b]isoquinoline-2,2-dicarboxylic acid dimethyl ester (294b) (0.211 g). The orange oil was purified using column chromatography (SiO\(_2\), EtOAc:P.E. 40-60, 8:1) to afford 10-methylene-3-phenyl-1,5,10,10a-tetrahydro-pyrrolo[1,2-b]isoquinoline-2,2-dicarboxylic acid dimethyl ester (294b) (0.014 g, 0.03 mmol, 15% yield) as a yellow oil. Data as above.
Stepwise procedure using P(o-Tol)₃ ligand

To a stirred mixture of 1-(2-bromo-benzyl)-2-(4-methoxy-phenyl)-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (258b) (0.050 g, 0.11 mmol) in CH₃CN (5 mL) was added Pd(OAc)₂ (0.002 g, 0.01 mmol), P(o-Tol)₃ (0.013 g, 0.04 mmol) and K₂CO₃ (0.045 g, 0.33 mmol). The resulting mixture was stirred at reflux for 72h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica and the organic extract washed with 1 M HCl (20 mL), sat. NaHCO₃aq. sol. (20 mL), sat. NaCl aq. sol. (20 mL) and dried (MgSO₄). The solvent was removed under reduced pressure to afford crude 10-methylene-3-phenyl-1,5,10,10a-tetrahydro-pyrrolo[1,2-b]isoquinoline-2,2-dicarboxylic acid dimethyl ester (294b) (0.211 g). The orange oil was purified using column chromatography (SiO₂, EtOAc:P.E. 40-60, 8:1) to afford 10-methylene-3-phenyl-1,5,10,10a-tetrahydro-pyrrolo[1,2-b]isoquinoline-2,2-dicarboxylic acid dimethyl ester (294b) (0.012 g, 0.03 mmol, 12% yield) as a yellow oil. Data as above.

One pot procedure

To a stirred solution of benzylidene-(2-bromo-benzyl)-amine (258) (0.428 g, 1.65 mmol) in anhydrous THF (2 mL) was added zinc bromide (0.676 g, 3.03 mmol). The reaction mixture was left to stir for 10 min before 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester (155) (0.300 g, 1.65 mmol) was added. The reaction mixture was stirred for a further 5 min before a catalytic amount of tetrakis(triphenylphosphine)palladium(0) (0.190 g, 0.16 mmol) was added. The resulting mixture was stirred at room temperature for 12h. At which point Et₃N (8 mL) was added and the reaction mixture was stirred at reflux for 72h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica and the organic extract washed with 1 M HCl (20 mL), sat. NaHCO₃aq. sol. (20 mL), sat. NaCl aq. sol. (20 mL) and dried (MgSO₄). The solvent was removed under reduced pressure to afford crude 10-methylene-3-phenyl-1,5,10,10a-tetrahydro-pyrrolo[1,2-b]isoquinoline-2,2-dicarboxylic acid dimethyl ester (294b) (0.312 g). The oil was purified using column chromatography (SiO₂, EtOAc:P.E. 40-60, 8:1) to afford 10-
methylene-3-phenyl-1,5,10,10a-tetrahydro-pyrrolo[1,2-b]isoquinoline-2,2-dicarboxylic acid dimethyl ester (294b) (0.299 g, 0.79 mmol, 48% yield) as a yellow oil. Data as above.

Preparation of 10-methylene-3-(4-nitro-phenyl-1,5,10,10a-tetrahydro-pyrrolo[1,2-b]isoquinoline-2,2-dicarboxylic acid dimethyl ester (295a)

Stepwise procedure using PPh₃ ligand

To a stirred mixture of 1-(2-bromo-benzyl)-2-(4-nitrophenyl)-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (259a) (0.050 g, 0.10 mmol) in Et₃N (5 mL) was added Pd(OAc)₂ (0.002 g, 0.01 mmol), PPh₃ (0.010 g, 0.04 mmol). The resulting mixture was stirred at reflux for 72h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica and the organic extract washed with 1 M HCl (20 mL), sat. NaHCO₃ aq. sol. (20 mL), sat. NaCl aq. sol. (20 mL) and dried (MgSO₄). The solvent was removed under reduced pressure to afford crude 10-methylene-3-(4-nitro-phenyl-1,5,10,10a-tetrahydro-pyrrolo[1,2-b]isoquinoline-2,2-dicarboxylic acid dimethyl ester (295a) (0.081 g). The orange oil was purified using column chromatography (SiO₂, EtOAc:P.E. 40-60, 8:1) to afford 10-methylene-3-(4-nitro-phenyl-1,5,10,10a-tetrahydro-pyrrolo[1,2-b]isoquinoline-2,2-dicarboxylic acid dimethyl ester (295a) (0.012 g, 0.03 mmol, 28% yield) as a yellow oil. v_max/cm⁻¹ (neat) 2919, 2849, 1732 (CO₂ R str.), 1539 (NO₂ str.), 1456, 1435, 1263, 1230, 1172, 1074; Data was tentatively assigned: δ_H (CDCl₃, 400 MHz) 2.58 (1H, dd, J 5.0 and 12.6 Hz, 4-C(H)H), 3.08 (3H, s, CO₂CH₃), 3.08 (1H, m, 4-C(H)H), 3.11 (1H, m, 4a-CH), 3.72-3.83 (2H, m, 10-CH₂), 3.82 (3H, s, CO₂CH₃), 5.08 (1H, d, J 12.0 Hz, 5-
C=C(H)H), 5.27 (1H, s, 2-CH), 5.71 (1H, d, J 2.0 Hz, 5-C=C(H)H), 6.97 (1H, m, CH arom.), 7.09 (1H, m, CH arom.), 7.24 (3H, m, 3 x CH arom.), 7.53 (2H, m, 2 x CH arom.), 7.72 (1H, m, CH arom.); δC (CDCl3, 100 MHz) 38.25 (4-CH2), 53.17 (CO2CH3), 53.16 (CO2CH3), 53.77 (10-CH2), 61.13 (4a-CH), 64.11(3-C), 71.75 (2-CH), 106.21 (5-C=CH2), 123.89 (CH arom.), 126.60 (CH arom.), 126.95 (CH arom.), 127.25 (CH arom.), 127.78 (CH arom.), 129.14 (CH arom.), 130.75 (CH arom.), 132.27 (CH arom.), 134.95 (5a-C), 138.53 (9a-C), 143.22 (2-CH=), 144.91 (5-C), 147.21 (CON2O) 169.54 (C=O), 171.11 (C=O); ms (EI): m/z 422 inconclusive.

Preparation of 3-(4-methoxy-phenyl)-10-methylene-1,5,10a-tetrahydro-pyrrolo[1,2-b]isoquinoline-2,2-dicarboxylic acid dimethyl ester (296b)

Stepwise procedure using PPh3 ligand

To a stirred mixture of 1-(2-bromo-benzyl)-2-(4-nitrophenyl)-5-vinyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (261b) (0.050 g, 0.12 mmol) in Et3N (5 mL) was added Pd(OAc)2 (0.02 g, 0.01 mmol), PPh3 (0.010 g, 0.04 mmol). The resulting mixture was stirred at reflux for 72h. The solvent was removed under reduced pressure and the yellow oily residue dissolved in EtOAc (20 mL). The palladium catalyst was filtered through a plug of silica and the organic extract washed with 1 M HCl (20 mL), sat. NaHCO3 aq. sol. (20 mL), sat. NaCl aq. sol. (20 mL) and dried (MgSO4). The solvent was removed under reduced pressure to afford crude 10-methylene-3-(4-nitro-phenyl-1,5,10a-tetrahydro-pyrrolo[1,2-b]isoquinoline-2,2-dicarboxylic acid dimethyl ester (296b) (0.017 g) as a yellow oil. Data was assigned tentatively using 1H NMR and m/z analysis from the crude material as subsequent purification by column chromatography (SiO2, EtOAc:P.E. 40-60, 8:1) failed to
isolate 10-methylene-3-(4-nitro-phenyl-1,5,10,10a-tetrahydro-pyrrolo[1,2-b]isoquinoline-2,2-dicarboxylic acid dimethyl ester (296b). \( \nu_{\text{max}}/\text{cm}^{-1} \) (thin film) 2952, 1731 (CO\(_2\)R str.), 1682, 1434, 1270, 1156, 1090, 932; Data was tentatively assigned:

\( \delta_{\text{H}} \) (CDCl\(_3\), 400 MHz) 3.99 (1H, m, 4-C(\( \text{H} \))H), 3.15 (3H, s, CO\(_2\)CH\(_3\)), 3.08 (1H, m, 4-C(\( \text{H} \))H), 3.33 (1H, m, 4a-CH), 3.40 (1H, d, \( J = 16.4 \text{ Hz} \)), 10-C(\( \text{H} \))H), 3.72 (3H, s, CO\(_2\)CH\(_3\)), 3.73 (1H, s, OCH\(_3\)), 3.92 (1H, d, \( J = 16.4 \text{ Hz} \)), 10-C(\( \text{H} \))H), 5.08 (1H, m, 5-C=\( \text{C} \)(\( \text{H} \))H), 5.52 (1H, d, \( J = 2.0 \text{ Hz} \)), 2-CH), 5.64 (1H, d, \( J = 1.6 \text{ Hz} \)), 5-C=\( \text{C} \)(\( \text{H} \))H), 6.71 (1H, m, CH arom.), 7.06-7.62 (7H, m, 7 x CH arom.); ms (EI): \( m/z \) 407 (\( M^+ \), 26%), 406 (13), 278 (50), 277 (100); HRMS calc. for C\(_{24}\)H\(_{28}\)N\(_2\)O\(_5\) 407.1733 found 407.1726.

**Preparation of (4-methoxy-phenyl)-(4-nitro-benzylidene)-amine (300)**

![Diagram](image)

The imine was prepared following the general procedure for compound (260) to afford (4-methoxy-phenyl)-(4-nitro-benzylidene)-amine (300) (0.807 g, 3.06 mmol, 78% yield) as a yellow solid. \( \nu_{\text{max}}/\text{cm}^{-1} \) (neat) 2852, 1650, 1645, 1567 (NO\(_2\) str.), 1484, 1439, 1154, 1024, 926, 884, 741; \( \delta_{\text{H}} \) (CDCl\(_3\), 400 MHz) 3.77 (3H, s, OCH\(_3\)), 6.88 (2H, d, \( J = 8.9 \text{ Hz} \)), 2 x CH arom.), 7.23 (2H, d, \( J = 9.0 \text{ Hz} \)), 2 x CH arom.), 7.97 (2H, d, \( J = 8.7 \text{ Hz} \)), 2 x CH arom.), 8.23 (2H, d, \( J = 8.7 \text{ Hz} \)), 2 x CH arom.), 8.50 (1H, s, N=CH); \( \delta_{\text{C}} \) (CDCl\(_3\), 100 MHz) 55.74 (CH\(_2\)N), 114.55 (2 x CH arom.), 122.66 (2 x CH arom.), 124.01 (2 x CH arom.), 129.10 (2 x CH arom.), 141.96 (C arom.), 143.57 (OCH\(_3\)), 148.98 (CNO\(_2\)), 154.81 (N=CH), 159.25 (N=CH\(_2\)).
Chapter 7 - References


