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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

Craig Early

Loughborough University
Loughborough
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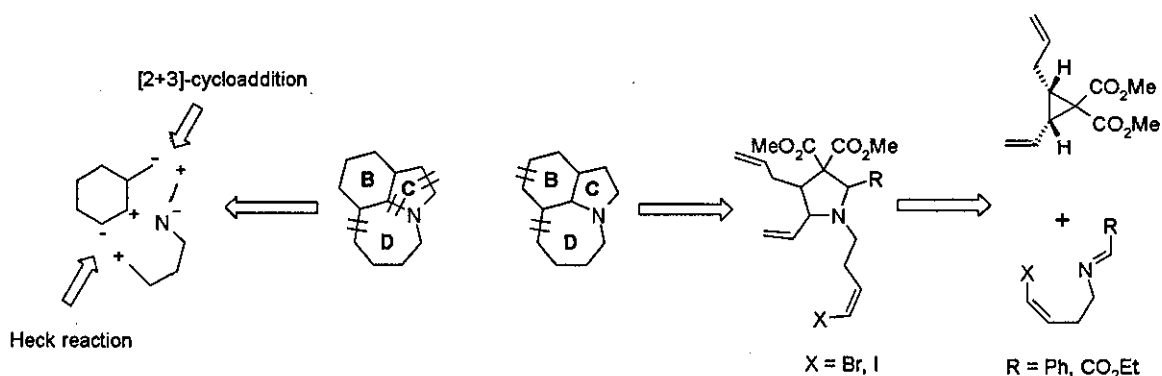
Abstract

Craig Early
Loughborough University

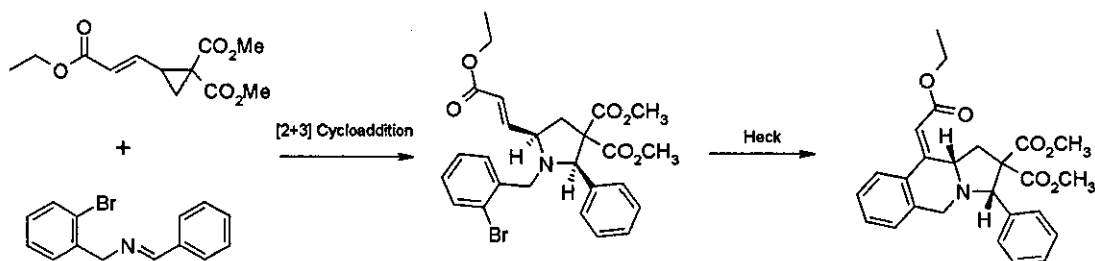
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Palladium Catalysed Routes to the Tricyclic Core of the *Stemona* Alkaloids

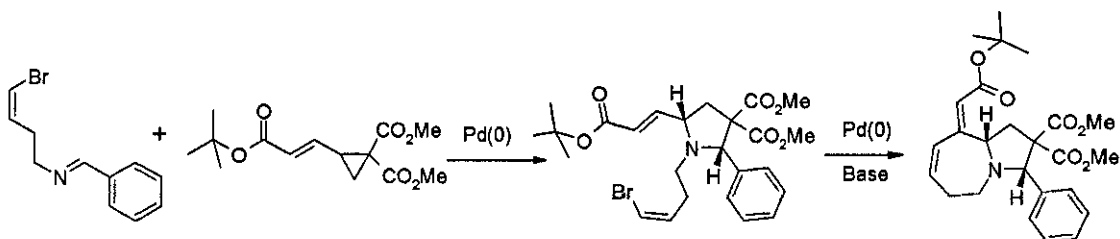
The *Stemona* alkaloids are a structurally interesting class of alkaloids isolated from the roots and rhizomes of the *Stemonaceae* plant family. During this project we have investigated the viability of constructing the tricyclic core of the *Stemona* alkaloids using a cascade Heck/carbopalladation reaction sequence, starting from an allylvinylcyclopropane building block, utilising the group's [2+3] palladium catalysed cycloaddition chemistry.



We have briefly investigated applying our palladium catalysed [2+3] cycloaddition methodology towards doubly activated vinylcyclopropanes, preparing a selection of tetrahydrofuran and pyrrolidine precursors which underwent a Heck mediated cyclisation to yield a variety of functionalised polycycles. As well as further developing this methodology towards a tandem cycloaddition/Heck one pot strategy.



We have also investigated applying this methodology towards the construction of the azepine core of the Stemoamide group of *Stemona* alkaloids. Using the group's [2+3] cycloaddition chemistry to construct suitable pyrrolidines and subjecting them to Heck mediated cyclisations as well as investigating the viability of a tandem cycloaddition/Heck one pot strategy.



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Abbreviations

Ac	acetyl
Aloc	allyloxycarbonyl
aq.	aqueous
Ar	aromatic
9-BBN	9-borabicyclo[3.3.1.]nonyl
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
br	broad
BuLi	butyllithium
^tBu	<i>tert</i> -butyl
cat.	Catalytic
CAN	ceric ammonium nitrate
CSA	camphorsulfonic acid
d	doublet
D	deuterium (NMR spectroscopy)
DBU	1,8-diazabicyclo[2.2.2]undecane
dba	dibenzylideneacetone
DCE	dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	distortionless enhancement by polarisation transfer
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminium hydride
DMAP	4-(dimethylamino)pyridine
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
DMTSF	Dimethylsulfonium tetrafluoroborate
EI	electron ionisation
Equiv.	equivalents
Et	ethyl
EWG	electron withdrawing group
FAB	fast atom bombardment

FDPP	pentafluorophenyl diphenylphosphinate
h	hour
HMPA	hexamethylphosphoramide
Hz	hertz
IR	infra-red
L	ligand
<i>J</i>	coupling constant (NMR spectroscopy)
KHMDS	potassium hexamethyldisilazide
KHMDSA	potassium hexamethyldisylazane
LDA	lithium diisopropyl amide
LHMDS	lithium hexamethyldisilazide
<i>m</i>	meta
<i>m</i>-CPBA	meta-chloroperoxybenzoic acid
min.	minutes
mp	melting point
Ms	mesyl, MeSO ₂
<i>m/z</i>	mass to charge ratio
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
<i>o</i>	ortho
<i>p</i>	para
P.E.	petroleum ether (40-60)
Ph	phenyl
PMB	<i>para</i> -methoxybenzene
PPh₃	triphenylphosphine
PPTS	pyridinium <i>p</i> -toluenesulfonate
q	quartet
Red-Al	sodium bis(2-methoxyethoxy)aluminium hydride
rt	room temperature
s	singlet
S_N2	bimolecular nucleophilic substitution
str.	stretch
t	triplet
TBAF	tetrabutylammonium fluoride

TBAI	tetrabutylammonium iodide
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBS	<i>tert</i> -butyldimethylsilyl
TBSOTf	triisobutylsilyl triflate
TLC	thin layer chromatography
TMSI	trimethylsilyl iodide
Tol	toluene
Ts	<i>para</i> -toluenesulfonyl
TPAP	tetrapropylammonium perruthenate

Chapter 1 – New routes to functionalised heterocycles.

1.1 Synthesis of the *Stemona* Alkaloids:

The *Stemona* alkaloids are a structurally interesting class of alkaloids that are isolated from the roots and rhizomes of the *Stemonaceae* plant family.¹ *Stemonaceae* represent a rather isolated family within the monocotyledons consisting of 3 genera (*Stemona*, *Croomia* and *Stichoneuron*) and about 32 species.¹ Their range of distribution is centred in south-east Asia but also extends to tropical Australia and one species is even located in south-east United States.^{1,2,3} This root extract has been used for many years in traditional Chinese folk medicine to treat a number of respiratory diseases, such as bronchitis and tuberculosis,³ and has also shown exceptional insecticidal activity.⁴

Physiologically active *Stemonaceous* plants possess the structurally novel azepinoindole (B, C, D) ring system (**Figure 1**).



Figure 1: Azepinoindole ring system.¹

Stemona is the largest genus with about 25 species occurring as subshrubs or twinning herbs, which prefer a seasonal climate and occur in dry vegetation.⁴ The *Stemona* alkaloids are structurally characterised by the presence of the pyrrolo[1,2- α]azepine nucleus^{4,5} and subsequently can be characterised into five groups according to their structural features (**Figure 2**).⁴

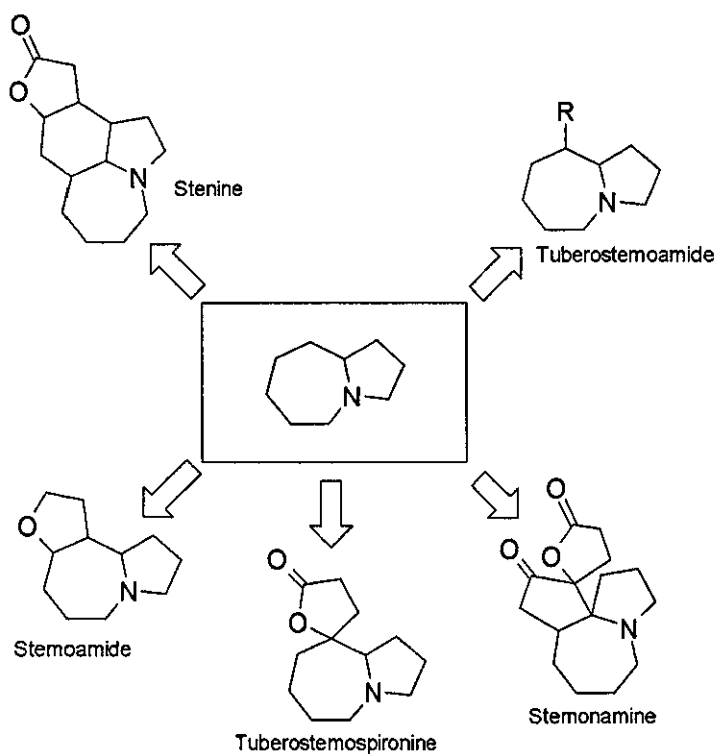
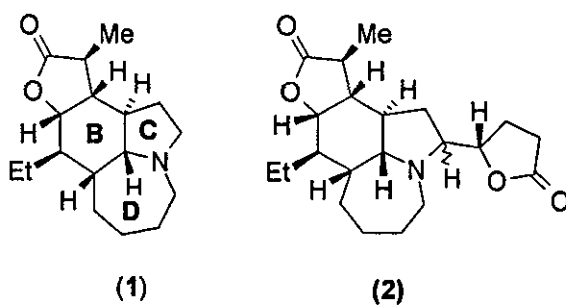


Figure 2: *Stemona* alkaloid groups.⁴

1.1.1 The Stenine Group:

The stenine group comprises seven structural types which include stenine (1), tuberostemonine (2), tuberostemonal (3) and neotuberostemonine (4) (Figure 3).⁴



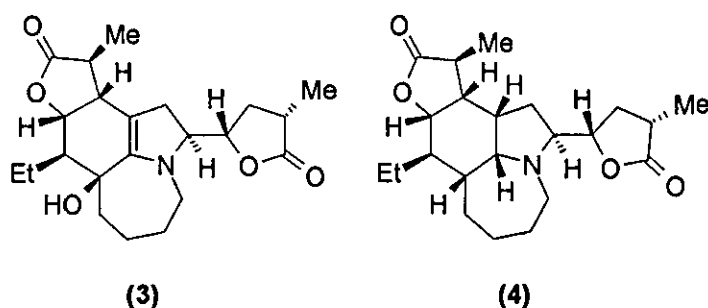
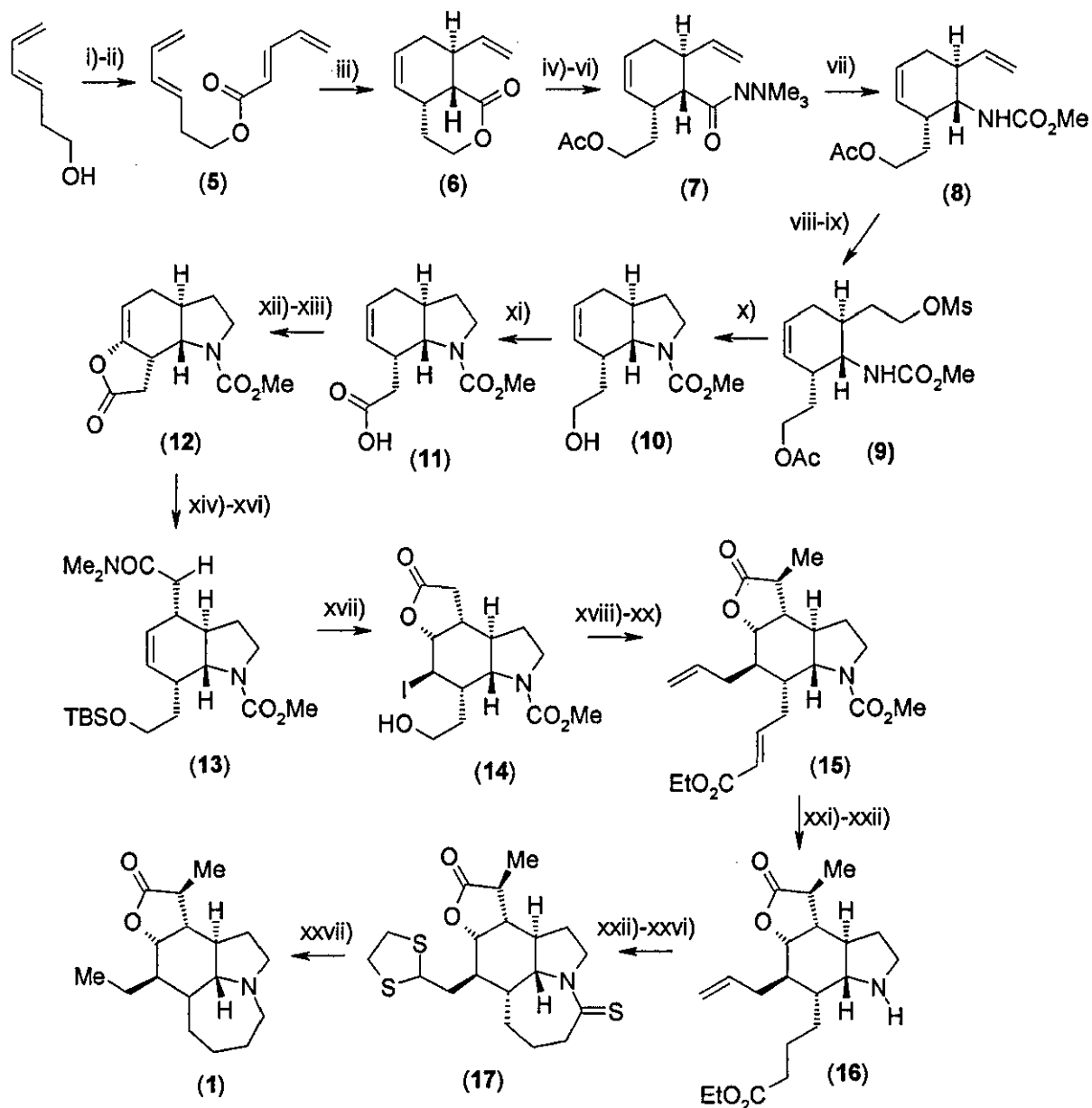


Figure 3: Representatives of the Stenine group of *Stemona* alkaloids.

The stenine group is named after the parent compound stenine (1), which possesses the structurally novel azepinoindole B, C, D ring system (Figure 3). The polycyclic cores of these natural products, which contain a wide variety of physiological properties along with structural complexity, have long provided organic chemists a real challenge in the total synthesis of the compounds. To date there is no general, facile route to these compounds, though a number of long and challenging total syntheses to stenine and related compounds do exist.⁴

Looking into the literature reveals several total syntheses of stenine, one being Hart's synthesis which is built around the use of an intramolecular Diels-Alder strategy to construct the B-ring of the azepinoindole core.⁶ Treatment of (*E*)-3,5-hexadienol with *n*-butyllithium and (*E*)-2,4-pentadienoyl chloride gave ester (5), which underwent a Lewis acid promoted cycloaddition to give cycloadduct (6). Installation of the lone nitrogen of stenine (1) was achieved using an aminimide variant of the Curtius rearrangement. Thus, treatment of (6) with hydrazine in deoxygenated methanol, followed by exhaustive methylation, then acylation of the resulting aminimide, gave (7) with the nitrogen of the azepine ring in place. Thermolysis of (7) in mesitylene gave the intermediate isocyanate, which when treated with methanol gave carbonate (8). Hydroboration, then oxidation with sodium perborate, followed by mesylation, gave product (9), which was treated with 2 eq. methyllithium, to construct the B, C ring system of the stenine core (10). Introduction of the alcohol was accomplished using a halolactonisation-dehydrohalogenation strategy. Thus, carboxylic acid (11), prepared from oxidation of alcohol (10), was treated with iodine and sodium bicarbonate, followed by dehydrohalogenation, to give (12). Reduction of the lactone ring, followed by protection

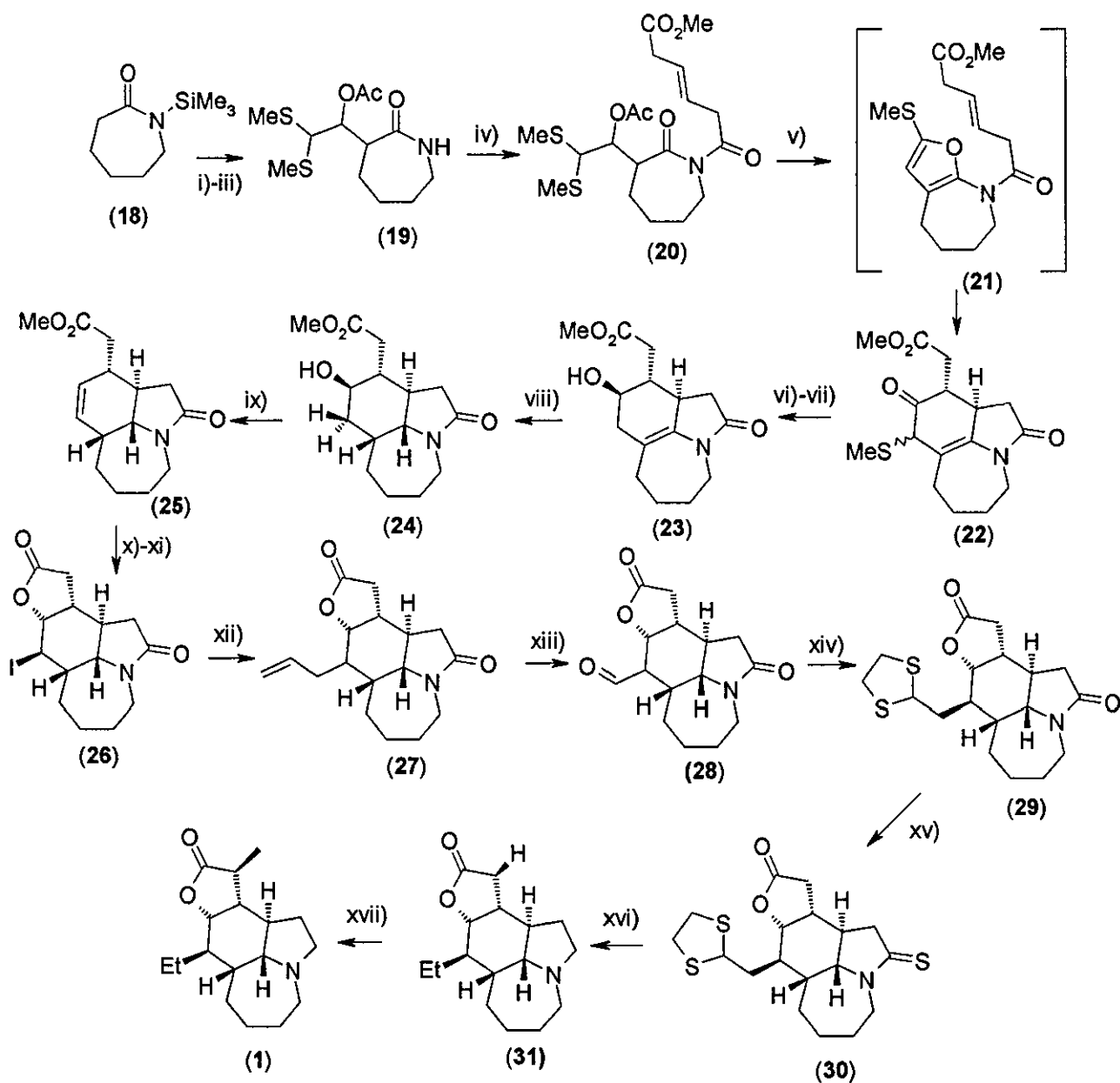
of the primary alcohol, was then treated with an amide acetal to give amide (13) *via* a Claisen rearrangement. Electrophile initiated cyclisation of (13), accompanied by the loss of the TBDMS group, gave iodolactone (14). The iodine was displaced using a Keck allylation, which provided functionality at that position, followed by a Swern oxidation. Wittig olefination of the resulting aldehyde, gave α , β -unsaturated ester (15). Subsequent conjugate reduction and removal of the carbamate protecting group gave (16), which set the stage for construction of the azepine core. Johnson-Lemieux oxidation furnished the aldehyde which was converted to the thioketal. Treatment with Lawesson's reagent gave thiolactam (17) and simultaneous reduction of the thioketal and thiolactam afforded racemic stenine (1). The intramolecular Diels-Alder cycloaddition-aminimide rearrangement sequence to form the perhydroindole structure (7) was the key step in this synthesis. This set the stage for the construction of the B, C ring of the tricyclic core, which set the required *trans* stereochemistry across the ring junction (Scheme 1).



i) $n\text{-BuLi}$, -78°C ; ii) $(E)\text{-CH}_2=\text{CHCH}=\text{CHCOCl}$, (100%); iii) Et_2AlCl , CHCl_3 , 85°C , (67%); iv) NH_2NH_2 , MeOH , (87%); v) MeI , K_2CO_3 , MeOH , reflux, (100%); vi) CH_3COOCl , (100%); vii) mesitylene, reflux, (94%); viii) 9-BBN, $\text{NaBO}_3 \cdot 4\text{H}_2\text{O}$, (95%); ix) MsCl , Et_3N , (100%); x) MeLi (2 equiv) & K_2CO_3 , MeOH , (94%); xi) Jones reagent, acetone, (83%); xii) I_2 , $\text{NaHCO}_3(\text{aq})$, (95%); xiii) DBU, (98%); xiv) NaBH_4 , K_2CO_3 , (100%); xv) TBS-Cl , CH_2Cl_2 , (100%); xvi) $\text{MeC(OMe)}_2\text{NMe}_2$, (93%); xvii) I_2 , (75%); xviii) $n\text{-Bu}_3\text{SnCH}_2\text{CH}=\text{CH}_2$, AIBN, benzene, reflux, (83%); xix) LDA , THF, MeI , (87%); xx) Et_3N , DMSO, $(\text{COCl})_2$ & $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Et}$, (90%); xxi) Red-Al, Cu-Br, (85%); xxii) Me_2Si , CH_2Cl_2 , rt, (94%); xxiii) mesitylene, reflux, (91%); xxiv) OsO_4 (cat), NaIO_4 , (84%); xxv) $\text{HSCH}_2\text{CH}_2\text{SH}$, $\text{SiO}_2\text{-SOCl}_2$, (100%); xxvi) $(p\text{-MeOC}_6\text{H}_4\text{PS}_2)_2$, (100%); xxvii) W-2 Raney-Ni, EtOH , (75%).

Scheme 1: Hart's synthesis of stenine⁽⁶⁾.

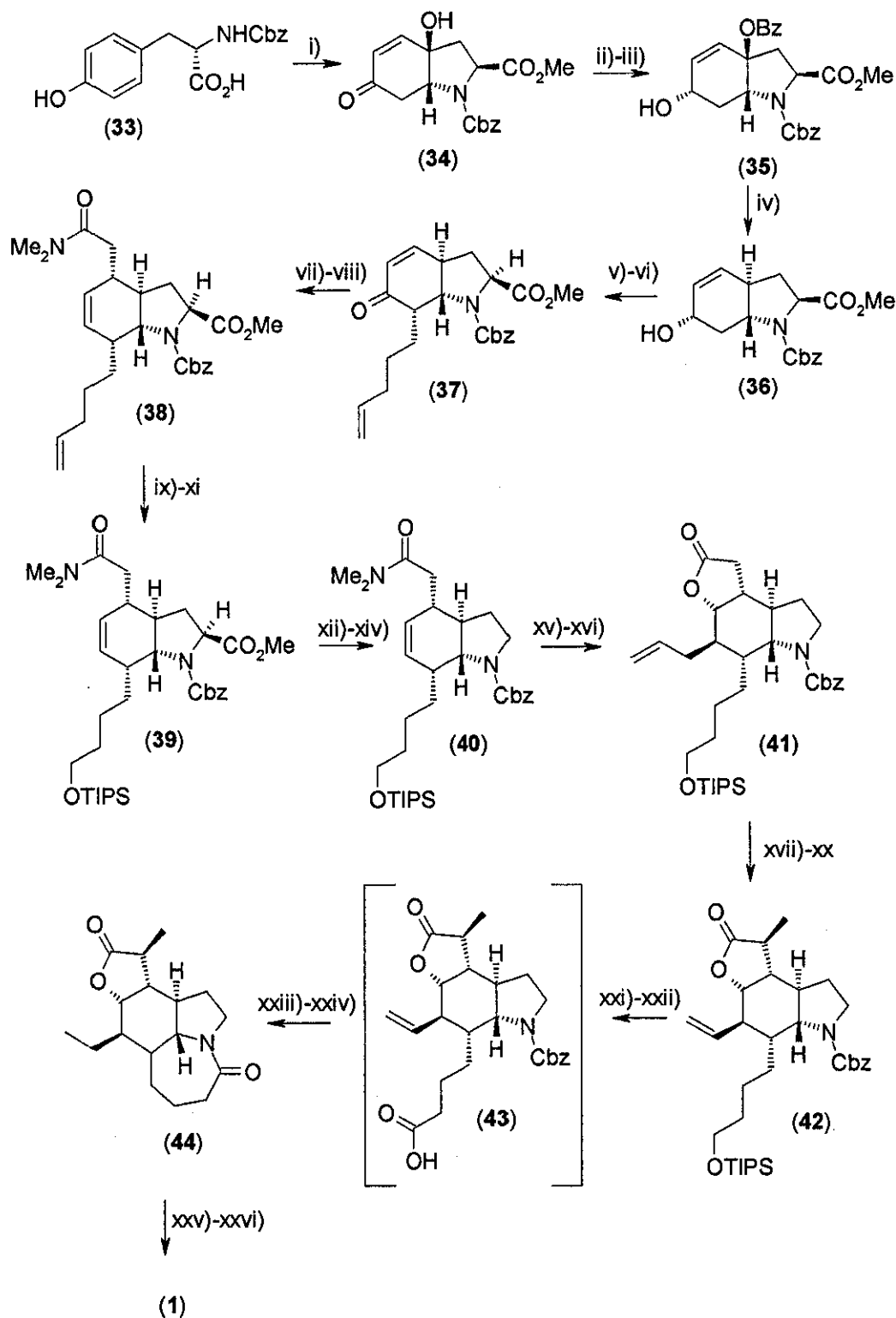
Padwa has reported using an intramolecular [4+2] cycloaddition of a 2-methylthio-5-amidofuran to create the azepinoindole skeleton in stenine (1).⁷ They incorporated the azepine ring at an early stage in the synthetic sequence, and used it as a template for setting the required stereochemistry. Caprolactam (18) was reacted with bis-(methylsulfanylacetaldehyde) followed by quenching with acetic anhydride to give amide (19). Acylation with *trans*-5-chlorocarbonyl-pent-3-enoic acid methyl ester gave imide (20). Methyl sulfenylation of one of the methylthio groups with DMTSF induced a thionium-promoted cyclisation. Loss of acetic acid from the resulting dihydrofuran, gave the desired furan (21). Rapid rearrangement of (21) at room temperature yielded azepinoindole (22). Removal of the methylthio group was accomplished by treating (22) with Raney-Nickel, and subsequent reduction under Luche conditions⁹ provided alcohol (23). Controlled hydrogenation of the enamide π -bond with a Crabtree catalyst system of [Ir(cod)pr(PCy₃)]PF₆/CH₂Cl₂/H₂ afforded (24) with the required *syn-anti* stereochemistry at the ring fusion sites.⁹ Alcohol (24) was converted to the corresponding mesylate, followed by treatment with DBU to yield alkene (25). Hydrolysis of the methyl ester followed by iodolactonisation, gave iodolactone (26). Subsequent Keck allylation with allyltributyl-stannane using the Hart/Wipf method^{6,10} gave (27), which was converted into aldehyde (28) *via* a Johnson-Lemieux oxidation. Treatment of the aldehyde with 1,2-ethanedithiol and BF₃.Et₂O gave (29). Conversion of the amide to the thioamide with Lawesson's reagent gave (30), followed by desulfurisation using Raney-Nickel, furnished (31) and finally methylation of the lactone enolate gave racemic stenine (1) in a 2% overall yield in 17 steps. The key step of the whole synthetic strategy was the intramolecular [4+2] cycloaddition of the amidofuran derivative (20), which constructed the azepinoindole skeleton in one step, allowing a series of reductions to set the *syn-anti* stereochemical relationship at the ring fusion sites (Scheme 2).



i) LDA, THF, -78°C to rt, 12 h; ii) $(\text{MeS})_2\text{CHCHO}$; iii) Ac_2O , (80%, 3 steps); iv) $\text{MeO}_2\text{CHCH}_2\text{CH}=\text{CHCH}_2\text{COCl}$, (85%); v) DMTSF, NEt_3 , (80%); vi) Raney-Ni, EtOH , (92%); vii) NaBH_4 , CeCl_3 , MeOH , (77%); viii) Crabtree's catalyst, H_2 , CH_2Cl_2 ; ix) MsCl , NEt_3 , DBU, (64%, 2 steps); x) LiOH , H_2O ; xi) I_2 , MeCN , (60%, 2 steps); xii) $\text{CH}_2=\text{CHCH}_2\text{SnBu}_3$, AIBN, (62%); xiii) OsO_4 , NaIO_4 ; xiv) $\text{HSCH}_2\text{CH}_2\text{SH}$, $\text{BF}_3\cdot\text{Et}_2\text{O}$, (48%, 2 steps); xv) Lawesson's reagent (73%); xvi) Raney-Ni; xvii) LDA, HMPA, MeI (93%, 2 steps).

Scheme 2: Padwa's synthesis of stenine.⁷

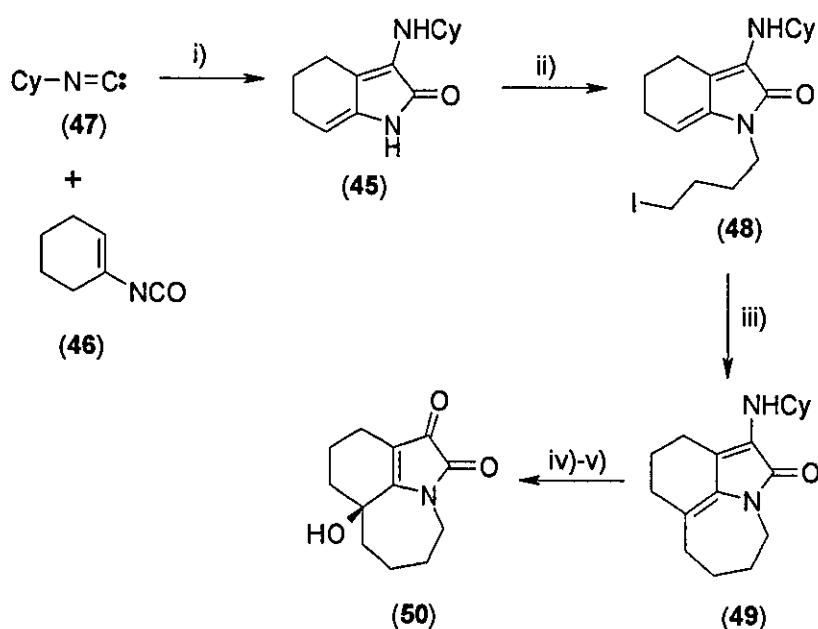
Wipf has developed a general synthetic strategy for the construction of the B, C ring system starting from L-tyrosine, and applied it to the total synthesis of stenine (1).¹⁰ Bicyclic (34) was prepared by treating L-tyrosine (33), with iodobenzenediacetate and NaHCO₃ in a one-pot procedure. Benzoylation of the tertiary alcohol, followed by reduction of the enone gave alcohol (35). The desired *trans*-hexahydroindole ring system (36) was accomplished by reduction of the π -allylpalladium complex of (35) at the more hindered tertiary carbon. Oxidation of the allylic alcohol of (36) with tetrapropylammonium perruthenate (TPAP) regenerated the enone which was deprotonated with KHMDSA. Subsequent alkylation with pentenyl triflate, gave enone (37). The alcohol was prepared *via* a 1,2-reduction of the enone, using NaBH₄/CeCl₃, followed by an Eschenmoser-Claisen rearrangement, which gave amide (38). Selective cleavage of the monosubstituted alkene was done using AD-mix- β , followed by sodium periodate cleavage of the resulting diol.¹¹ Reduction of the aldehyde and silylation of the primary alcohol gave triisopropylsilyl ether (39) and the ester was reductively decarbonylated to give (40). Iodolactonisation, followed subsequent Keck allylation in neat allyltributylstannane gave (41). Methylation of the lactone, followed by Johnson-Lemieux oxidation, reduction and Grieco-elimination provided tricycle (42).¹² Closure of the 7-membered azepine was achieved by desilylation of (42) and oxidation of the primary alcohol using Dess-Martin periodinane and sodium chlorite to the acid (43), which was directly hydrogenated and cyclised with pentafluorophenyl diphenylphosphinate (FDPP) to give lactam (44). Finally conversion of the amide to the thioamide with Lawesson's reagent and desulfurisation with Raney-Nickel provided (-)-stenine (1) in a 2% overall yield in 26 steps. The advantage of Wipf's synthetic strategy, was the key reduction step of the π -allylpalladium complex of (35), set the stereochemistry across the fused B, C rings very early on. This allowed relatively straight forward functional group manipulation to assemble the rest of the azepine core (Scheme 3).



i) $\text{PhI}(\text{OAc})_2$, NaHCO_3 , MeOH , (20-60%); ii) Bz_2O , NEt_3 ; iii) NaBH_4 , $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$, (89%); iv) $\text{Pd}_2(\text{dba})_3$, CHCl_3 , Bu_3P , $\text{HCO}_2\text{H}/\text{NEt}_3$; v) TPAP , NMO ; vi) KHMDSA , -80°C , $\text{HC}=\text{CH}(\text{CH}_2)_3\text{OTf}$, (46%); vii) NaBH_4 , $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$; viii) $\text{H}_3\text{CC}(\text{OMe})_2\text{NMe}_2$, (77%); ix) $\text{AD-mix } \beta$, NaIO_4 ; x) NaBH_4 ; xi) TIPS-Cl , DMAP , (76%); xii) LiOH , $\text{H}_2\text{O}/\text{THF}$; xiii) PhOPOCl_2 , NEt_3 , PhSeH ; xiv) Bu_3SnH , AIBN , (70%); xv) I_2 ; xvi) Allyl-SnBu_3 , AIBN , (77%); xvii) LDA , HMPA , MeI ; xviii) OsO_4 , NaIO_4 ; xix) NaBH_4 , -40°C ; xx) o -(NO_2) PhSeCN , Bu_3P , H_2O_2 , (47%); xxi) HF , MeCN ; xxii) Dess-Martin periodinane, NaClO_2 ; xxiii) $\text{Pd}(\text{OH})_2$, H_2 ; xxiv) FDPP , CH_2Cl_2 , (72%); xxv) Lawesson's reagent; xxvi) Raney-Ni, EtOH , (73%).

Scheme 3: Wipf's asymmetric synthesis of (-)-stenine.¹⁰

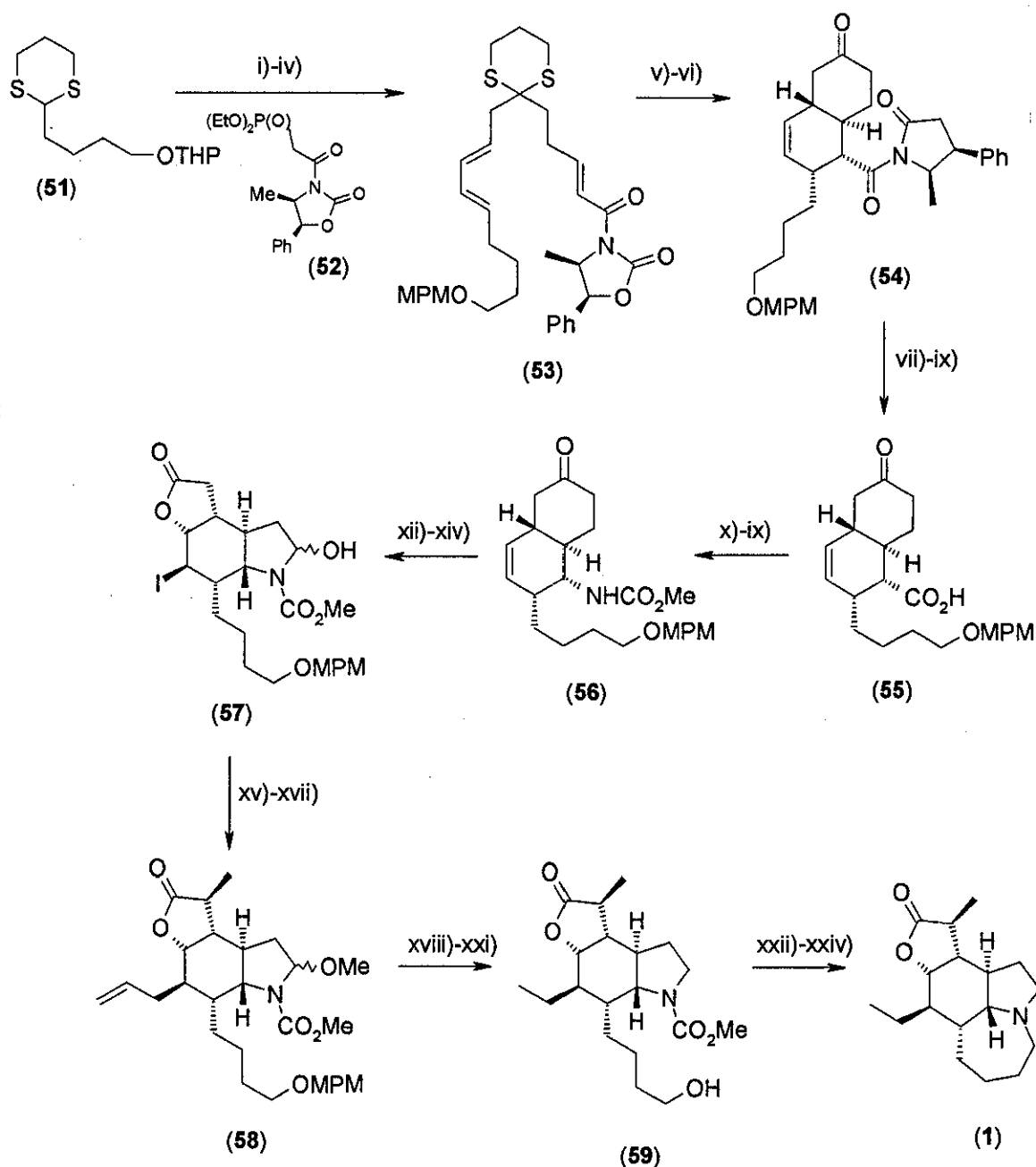
Rigby and co-workers have developed a synthetic strategy towards the construction of the azepinoindole skeleton, within the context of stenine (1) and tuberostemonine (2) as the target alkaloids.¹³ They looked at using a highly functionalised hydroindolone building block (45), formed by a [4+1] cycloaddition between an appropriate vinyl isocyanate (46) and alkyl isocyanate (47) serving as a nucleophilic 1,1-dipole equivalent. *N*-Alkylation with 1,4-diiodobutane gave the precursor (48) for the radical or metalloenamine based cycloheptannulation. Heating in the presence of EtMgBr afforded the desired tricyclic enamide (49). Hydrolysis of the enamide (49) followed by treatment with *m*-CPBA gave the desired oxidative product (50). The strategy developed by Rigby differs from most of the other approaches described, in that the stereochemistry around the azepine ring is set during the cycloheptannulation step. Most of the other strategies rely on the stereochemistry being set prior to closure of the seven membered ring on to the pyrrolidine nitrogen (Scheme 4).



i) rt, (83%); ii) NaH then I₂(CH₂)₄, (56%); iii) EtMgBr, diglyme, 120°C, (70%); iv) (COOH)₂, THF/H₂O, (60%); v) *m*-CPBA, CHCl₃, -15°C, (93%).

Scheme 4: Rigby's synthetic strategy towards the azepinoindole skeleton.¹³

Morimoto has accomplished an asymmetric synthesis of stenine (**1**), involving the intramolecular diastereoselective Diels-Alder reaction of the (*E, E, E*)-triene (**53**), prepared easily from readily available starting materials.¹⁴ Introduction of the nitrogen functionality was achieved by a modified Curtius rearrangement to give (**56**), followed by an *in situ* iodolactonisation to construct the A, B, C tricyclic ring system (**57**). Morimoto constructed the 7-membered azepine ring by removal of the methoxycarbonyl group of (**59**), followed by consecutive intramolecular *N*-Alkylation of the corresponding amine to afford (-)-stenine (**1**) in 20 steps. The key feature of Morimoto's synthesis being the intramolecular asymmetric Diels-Alder reaction of triene (**53**) to construct the B ring (Scheme 5).



i) *n*-BuLi, THF, 25°C; then (E,E)-MPMO(CH₂)₄CH=CHCH=CH-CH₂Cl, HMPA, -78°C-rt; ii) *p*-TsOH, H₂O, MeOH, THF, rt, (68%, 2 steps); iii) NaBH₄, CeCl₃·7H₂O, MeOH, THF, rt, (99%); iv) (52), Et₃N, LiCl, THF, 0°C-rt, (90%); v) Me₂AlCl, CH₂Cl₂, -20°C, (85%); vi) AgNO₃, *N*-chlorosuccinimide, CH₃CN-H₂O, 0°C, (80%); vii) LiSEt, THF, 0°C, (91%); viii) Et₃SiH, 10% Pd/C, acetone, 0°C-rt, (100%); ix) NaClO₂, NaH₂PO₄, 2-methylbut-2-ene, ^tBuOH, H₂O, 0°C-rt, (100%); x) (PhO)₂P(O)N₃, DMF, Et₃N, 60°C; xi) MeOH, CuCl (cat.), rt, (82%, 2 steps); xii) TMSCl, NaI, CH₃CN, Et₃N, 50°C; xiii) *m*-CPBA, hexane, CH₂Cl₂, -15°C-rt; xiv) H₅IO₆, THF, H₂O, rt then I₂, NaHCO₃, rt, (50%, 3 steps); xv) CSA, CH(OMe)₃, MeOH, CH₂Cl₂, rt, (90%); xvi) CH₂=CHCH₂SnBu₃, AIBN (cat.), toluene, 80°C, (80%); xvii) LDA, THF, HMPA, -78°C; then MeI, -78°C, (74%); xviii) Et₃SiH, BF₃·OEt₂, CH₃CN, 0°C, (82%); xix) OsO₄ (cat.), NaIO₄, THF, H₂O, rt, (75%); xx) HSCH₂CH₂SH, BF₃·OEt₂, CH₂Cl₂, -15°C, (81%); xxi) W2-Raney-Ni, EtOH, reflux, (80%); xxii) MsCl, Et₃N, CH₂Cl₂, 0°C, (88%); xxiii) NaI, acetone, reflux, (98%); xxiv) TMSI, CH₂Cl₂, rt then CH₃CN, reflux, (70%, 2 steps).

Scheme 5: Morimoto's synthesis of (-)-stenine.¹⁴

1.1.ii. The Stemoamide Group:

The stemoamide group is currently represented by 9 alkaloids, including stemoamide (60), stemonine (61), neostemonine (62) and tuberostemoamide (63) which all contain the tricyclic 2*H*-furo[3,2-*c*]pyrrolo[1,2-*a*]azepine, (A, D, C) ring system (Figure 4).

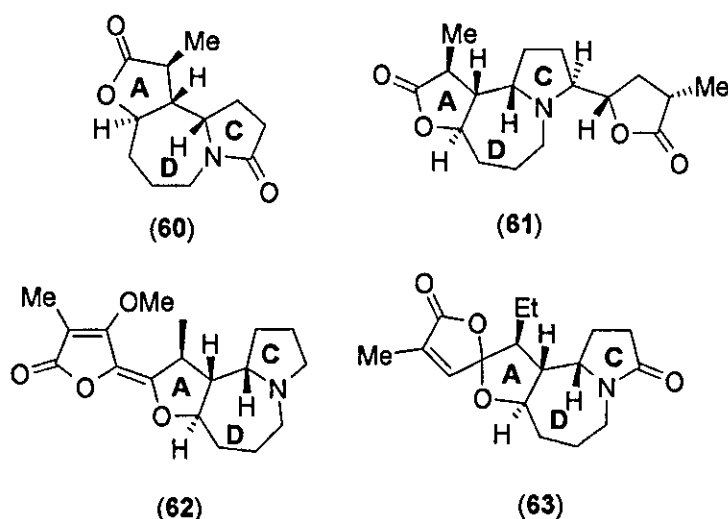
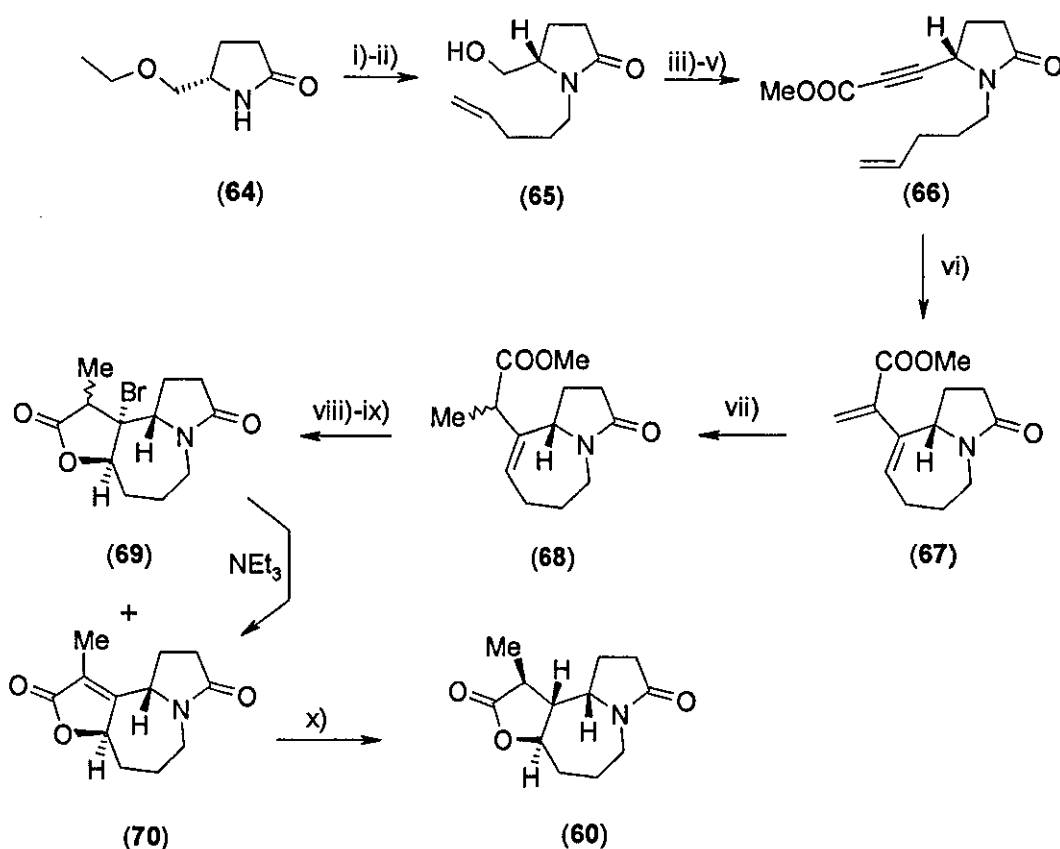


Figure 4: Representatives of the stemoamide group of *Stemona* alkaloids.

A total synthesis of stemoamide (60) has been achieved by Mori and co-workers.¹⁵ The total synthesis was accomplished in 14 steps, starting from (-)-pyroglutamic acid, using a ruthenium-catalysed enyne metathesis developed by Grubbs.¹⁶ The starting enyne was prepared from the alkylation of the amide (64), followed by deprotection to give alcohol (65). Oxidation of (65), followed by addition of CBr₄ and PPh₃ in a one pot reaction, gave the corresponding dibromoalkene, which was treated with base and an acid chloride to give enyne (66). Ruthenium catalysed metathesis of (66) gave the desired [5.3.0] bicyclic product (67), which was treated with NaBH₄ to give (68). Bromolactonisation gave products (69/70), with (69) easily converted to (70) by treatment with base.

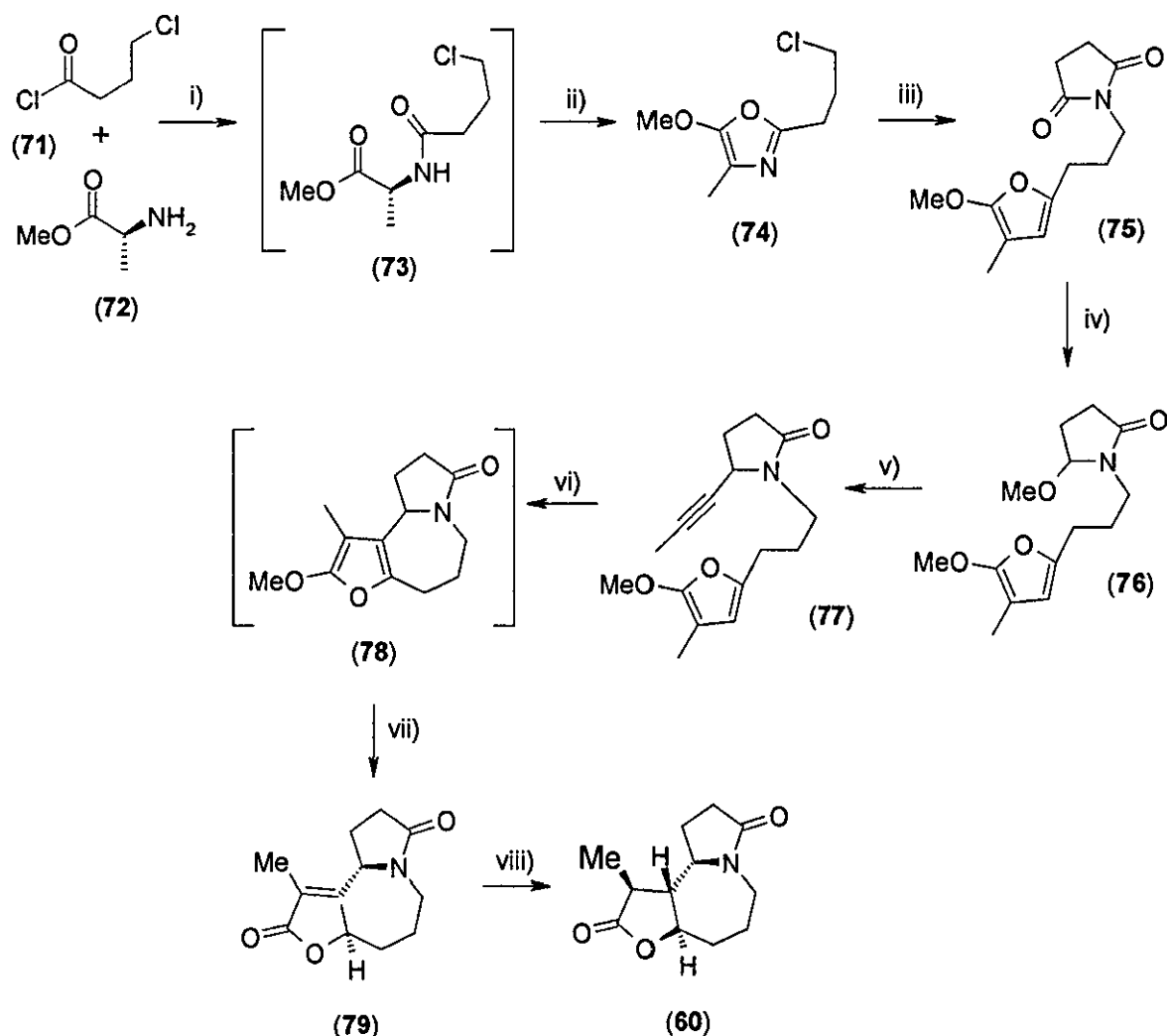
Treatment of enone (70) with NaBH₄ in the presence of NiCl₂·6H₂O in MeOH gave (-)-stemoamide (60) in an overall yield of 9 %. The key feature of this synthesis was the intramolecular enyne metathesis, which not only constructed the [5.3.0] bicyclic (C, D) ring system, but also left the alkylidene moiety in a position to be manipulated towards the lactone (A) ring, which makes Mori's synthesis a very elegant route (Scheme 6).



i) NaH, DMF, CH₂=CH(CH₂)₃Br, (89%); ii) TsOH, MeOH, (91%); iii) (COCl)₂, DMSO, Et₃N; iv) CBr₄, Ph₃P, (87%, 2 steps); v) BuLi, THF, -98°C, (72%) and LDA, HMPA, ClCOOMe (68%); vi) Ru catalyst (4-5 mol%), CH₂Cl₂, rt, (87%); vii) NaBH₄, MeOH, (85%); viii) NaOH, MeOH/H₂O; ix) CuBr₂ on Al₂O₃ (69, 25% and 70, 31%); x) NiCl₂·6H₂O, NaBH₄, MeOH, (76%).

Scheme 6: Mori synthesis of stemoamide.¹⁵

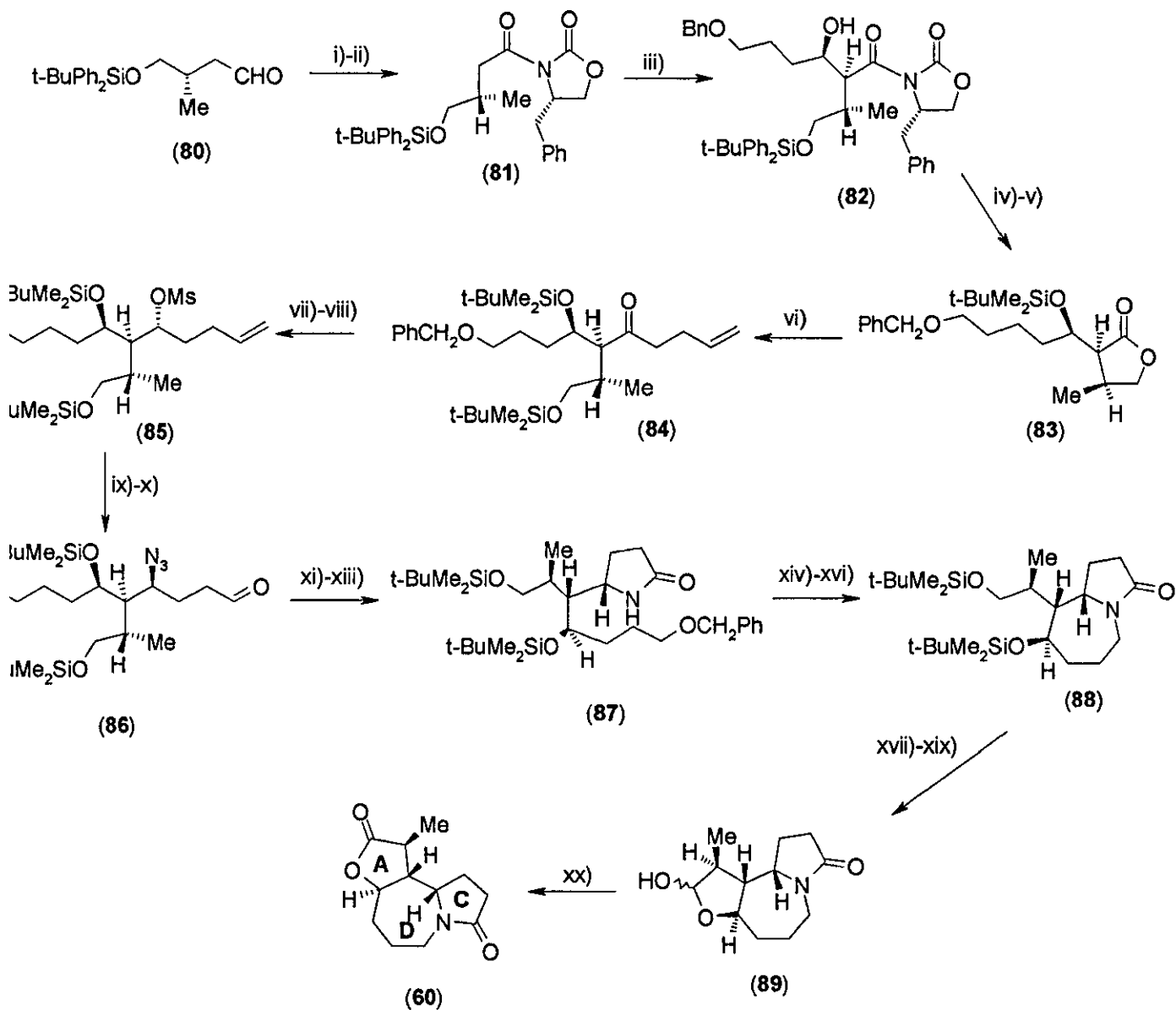
Jacobi's synthesis of (±)-stemoamide utilised a butenolide derivative (79), as an ideal precursor for establishing the *trans* relative stereochemistry.¹⁷ Oxazole (77) was identified as a logical precursor to butenolide (79). Firstly, acid chloride (71) was converted to the methoxyoxazole (74) by initial condensation with methyl alaninate, followed by cyclodehydration of the resultant amide (73) with P₂O₅, *N*-Alkylation of succinimide with (74) afforded oxazole imide (75). Selective reduction of (75) with NaBH₄ followed by treatment with MeOH/H⁺ afforded methoxylactam (76). Finally oxazole (77) was synthesised by a BF₃.Et₂O catalysed condensation of (76) with (*i*-propynyl)tributylstannane. Refluxing oxazole (77) in diethylbenzene gave (78) as the major product, which underwent rapid hydrolysis to the desired butenolide (79). A stereoselective *cis* reduction of (79) using a nickel-boride catalyst gave (±)-stemoamide (60) in 8 steps. The crucial step of this synthesis was the formation of the methoxyfuran (78), the precursor to the desired butenolide (79), achieved by an intramolecular Diels-Alder cyclisation (Scheme 7).



Scheme 7: Jacobi synthesis of (±)-stemoamide.¹⁷

Williams has reported a total synthesis of (-)-stemoamide.¹⁸ Aldehyde (80) was oxidised to the carboxylic acid, and then transformed to the imide (81). An Evans aldol reaction gave the *syn*-aldol derivative (82) specifically. Subsequent deprotection of the silyl ether, treatment with potassium carbonate to release the chiral auxiliary and hydride reduction, afforded compound (83). Condensation of the lactone and protection of the alcohol in a

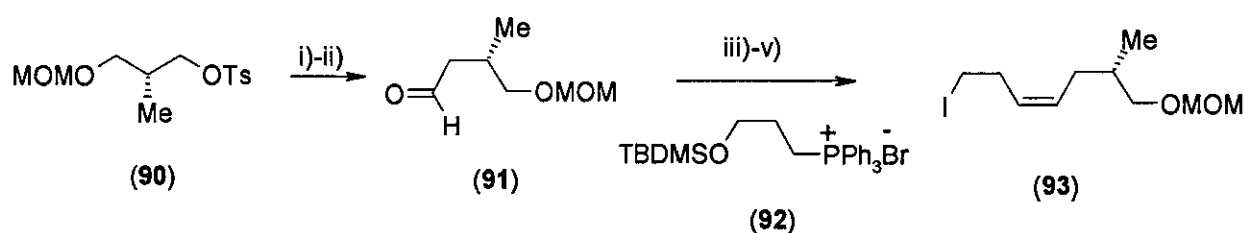
one pot procedure gave (84). Reduction of the ketone followed by mesylation gave (85), which was treated with sodium azide. Immediate ozonolysis afforded aldehyde (86). The stage was now set for the important sequential ring cyclisations to afford (-)-stemoamide (60). Firstly, sodium chlorite oxidation, then esterification of the resulting carboxylic acid to the methyl ester, followed by mild reduction of the azide moiety led to an *in situ* cyclisation affording (87) and the construction of the C ring. Hydrogenation and mesylation of the primary alcohol, followed by treatment with sodium hydride gave the aza-bicyclic structure (88) with rings C and D now in place. Deprotection of the primary silyl ether, and subsequent oxidation using Dess-Martin periodinane gave an intermediate aldehyde, which was immediately subjected to tetra-*n*-butylammonium fluoride to remove the final silyl ether and furnish lactol (89). Finally pyridinium dichromate oxidation of the lactol gave (-)-stemoamide (60). Within Williams' synthetic strategy, the construction of the D ring was the crucial step. It was achieved in an excellent yield of 71% and set the platform for the formation of the lactone ring with the relative stereochemistry already in place (Scheme 8).



i) 1M KMnO₄, 0.5 M NaH₂PO₄, *t*-BuOH, 15 min; ii) *t*-BuC(O)Cl, Et₃N, THF, 0°C to rt, cool to -78°C, (S)-4-(benzyl)-2-oxazolidinone, *n*-BuLi, THF, (94%); iii) *n*-Bu₂BOTf, CH₂Cl₂, -78°C, then Et₃N, then 4-benzyloxybutanal, (88%); iv) 48% aq HF, CH₃CN, then NaHCO₃, K₂CO₃, (82%); v) *t*-BuMe₂SiOTf, collidine, CH₂Cl₂, -78°C to rt, (97%); vi) 4-iodo-1-butene, *t*-BuLi, Et₂O, -100°C, 45 min, then add (83), then collidine, *t*-BuMe₂SiOTf, (78%); vii) LiEt₃BH, THF, -78°C to rt (91%); viii) MsCl, pyridine, rt, (96%); ix) NaN₃, HMPA, rt, 9 h; x) O₃, CH₂Cl₂/CH₃OH, -78°C, then Me₂S, -78°C to rt (49%, 2 steps); xi) NaClO₂, NaH₂PO₄·H₂O, CH₃CN, *t*-BuOH, H₂O, 2-methyl-2-butene, 0°C; xii) CH₂N₂, Et₂O, 0°C, (96%); xiii) PPh₃, THF/H₂O, reflux, 48 h, (87%); xiv) H₂, 10% Pd-C, EtOH, 24 h; xv) MsCl, pyridine, rt, 15 min; xvi) NaH, THF, rt, (71%, 3 steps); xvii) HF·NEt₃, CH₃CN, rt, 7 h, (63%); xviii) Dess-Martin periodinane, pyridine, CH₂Cl₂, rt, 30 min; xix) *n*-Bu₄NF, THF, rt, 15 min (94%, 2 steps); xx) PDC, CH₂Cl₂, reflux, 5 h, (80%).

Scheme 8: Williams total synthesis of (-)-stemomamide.¹⁸

Another member to be isolated within the stemoamide family is that of stemonine (**61**). Williams *et al.* have reported an enantioselective route towards this natural product. The two key transformations within this synthetic route involved a Staudinger-aza Wittig reaction to form the central perhydroazepine ring system and an iodine induced tandem cyclisation to construct the azepine core.¹⁹ Williams started from an acyclic precursor (**97**), synthesised from optically pure butyrolactone (**83**) and homoallylic iodide (**93**). Iodide (**93**) was prepared starting from tosylate (**90**), which was synthesised *via* hydroxyl protection, then hydride reduction of (*R*)-(-)-methyl-3-hydroxy-2-methyl propionate. Cyanide displacement, followed by reduction with DIBAL, gave aldehyde (**91**), which underwent a Wittig reaction to give the (*Z*)-olefin. Deprotection, followed by a Mitsunobu type reaction yielded iodide (**93**) (Scheme 6).

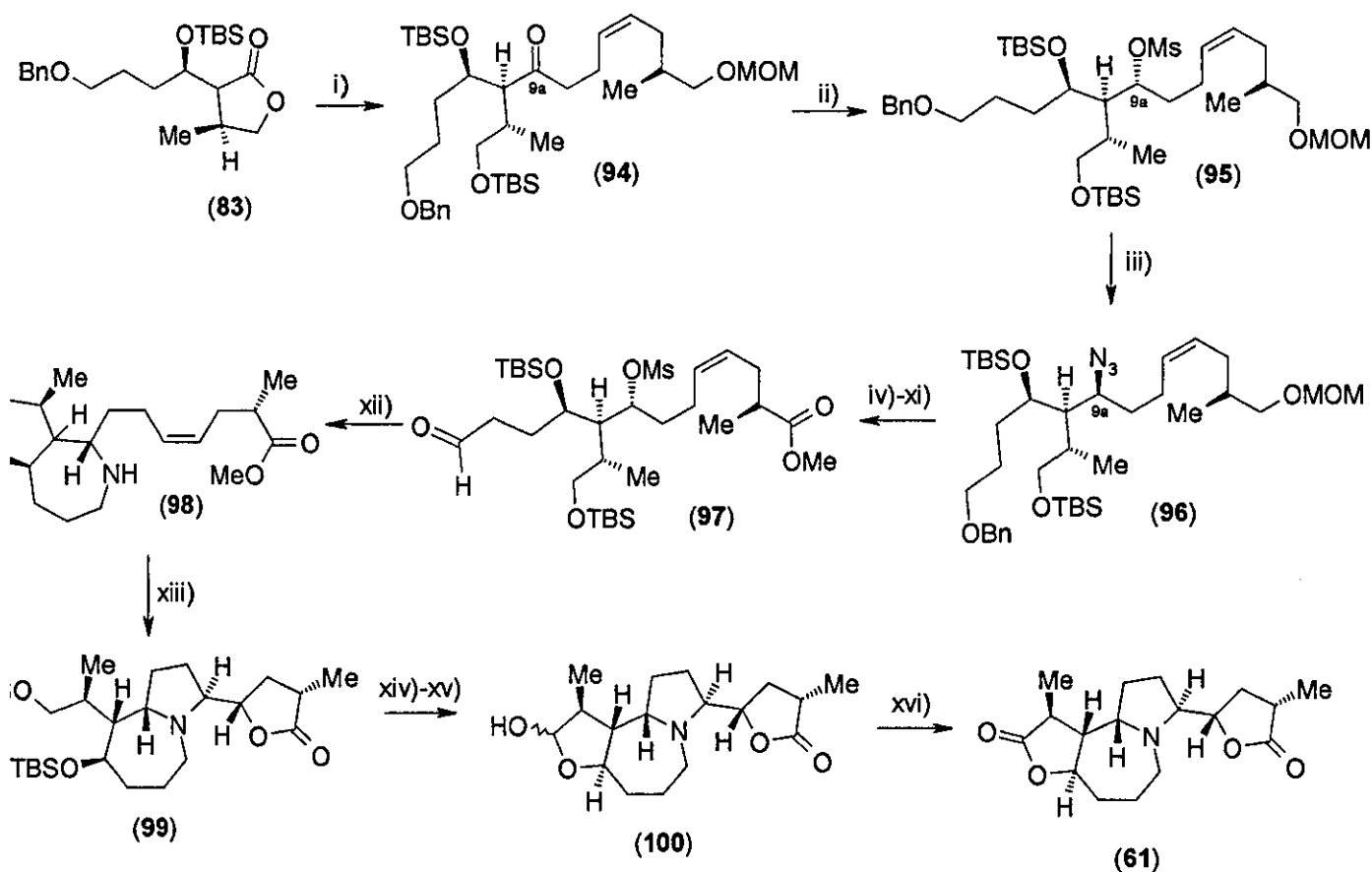


i) NaCN, DMSO, 70°C; ii) DIBAL, Et₂O, -78°C, H₃O⁺, (86%, 4 steps); iii) (**92**), KHMDS, Et₂O, -78°C, then (**91**); iv) TBAF, THF, 0°C-RT; v) PPh₃, I₂, imidazole, CH₂Cl₂, 0°C, (80%, 2 steps).

Scheme 6: Synthesis of homoallylic iodide (**93**).¹⁹

Quantitative metalation using BuLi in diethyl ether, followed by reaction with butyrolactone (**83**) gave the *t*-butyl-dimethylsilyl ether (**94**).²⁰ Reduction of (**94**) with lithium triethylborohydride followed by mesylation of the C9a alcohol gave (**95**). A stereocontrolled introduction of nitrogen was accomplished by azide displacement of the C9a mesylate to yield (**96**). Selective cleavage of the methoxymethyl ether moiety, followed by oxidation of the resulting alcohol to the methyl ester, then treatment with DDQ²¹ and subsequent Dess-Martin oxidation gave the desired acyclic aldehyde

precursor (97). The seven-membered ring was generated *via* a Staudinger reaction, to give (98), which was treated with iodine in a DCM/diethyl ether mixture, to afford (99). Finally deprotection of the TBS ethers, followed by Dess-Martin oxidation resulted in lactol (100), which was treated with Jones reagent to give (-)-stemonine (61) in 5 steps from (97) (Scheme 7).



i) 0.25M (93), -78°C, Et₂O, 0.5 h, then collidine, TBSOTf, -78°C to rt, (86%); ii) LiEt₃BH, THF, -78°C to rt, (94%); iii) MsCl, pyridine, rt, (95%); iv) NaN₃ (3 eq), 15-crown-5 (3 eq), HMPA, rt, (65%); v) TBSOTf, collidine, -78°C, (97%); vi) Me₂BBr, CH₂Cl₂, Et₃N, -78°C, (76%); vii) Dess-Martin periodinane, NaHCO₃, CH₂Cl₂, rt, (86%); viii) NaClO₂, NaH₂PO₄, t-BuOH, CH₃CN, 2-methyl-2-butene, 0°C; ix) CH₂N₂, Et₂O, (83%, 3 steps); x) DDQ, CH₂Cl₂, t-BuOH, H₂O, rt, (56%); xi) Dess-Martin periodinane, NaHCO₃, CH₂Cl₂, rt, (86%); xii) EtPPh₂, benzene, rt, 18h, concentrated *in vacuo*, then THF, NaBH₄, MeOH, (70%); xiii) I₂, CH₂Cl₂/Et₂O, rt, 48 h, (42%); xiv) TBAF, THF, rt, (77%); xv) Dess-Martin periodinane, NaHCO₃, CH₂Cl₂, rt, (69%); xvi) CrO₃, aq H₂SO₄, acetone, THF, rt, (68%).

Scheme 7: Williams enantioselective total synthesis of (-)-stemonine.¹⁹

1.1.iii. The Tuberostemonine Group:

The tuberostemospironine group of the *Stemona* alkaloids is characterised by a 2*H*-spiro[furan-2,9[9H]pyrrolo[1,2-*a*]azepin]-5-one nucleus, which displays a spiro γ -lactone at C-9 of the basic ring (Fig. 2). The group comprises of seven members including tuberostemospironine (101), croomine (102) and stemospironine (103) (Figure 5).

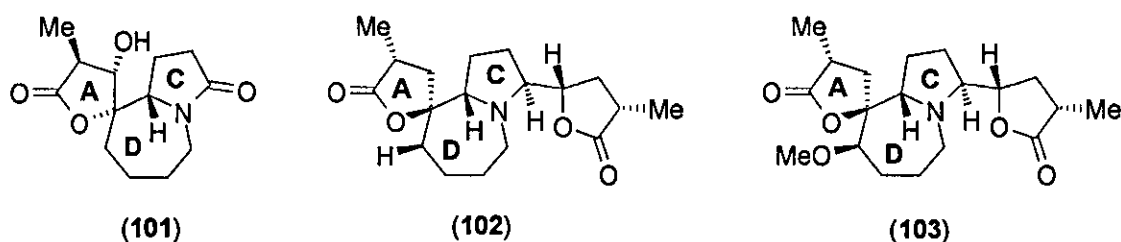
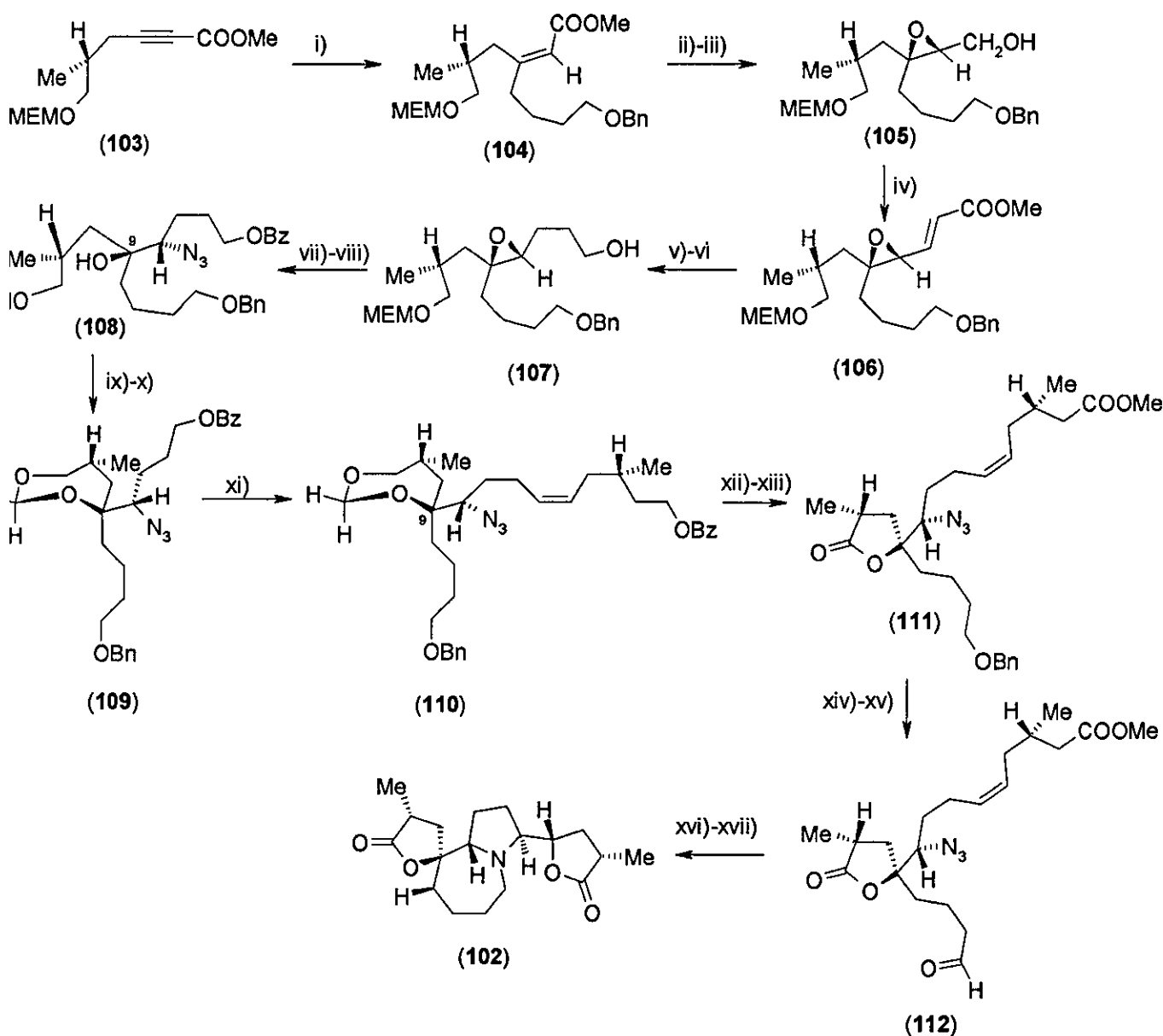


Figure 5: Representatives of the tuberostemospironine group of *Stemona* alkaloids.

Williams *et al.* reported the total synthesis of (+)-croomine (102) in 1988.²² They developed a strategy in which the preliminary construction of a branched acyclic carbon chain could be followed by consecutive ring closures of each heterocycle (A \rightarrow D \rightarrow C). The framework of croomine (102) was assembled *via* acylation of a terminal acetylene with methyl chloroformate, to give unsaturated ester (103). Conjugate *syn* addition to the acetylenic ester (103) using a pre-prepared Gilman reagent gave (104). DIBAL reduction followed by Sharpless epoxidation gave the desired β -epoxide (105). Oxidation of (105) followed by a Wittig reaction using solid (carbomethoxymethylene)triphenylphosphorane afforded α , β -unsaturated ester (106), which was treated with lithium borohydride to give an inseparable mixture of the desired product (107) and the corresponding (*E/Z*) allylic alcohols. Hydrogenation of the mixture with 5% rhodium completed the conversion to (107). Esterification of the alcohol (107), followed by treatment with lithium azide gave (108), which was converted to the saturated dioxepine (109) using boron trifluoride etherate, in order to protect the hindered tertiary alcohol at C9. Deprotection of the

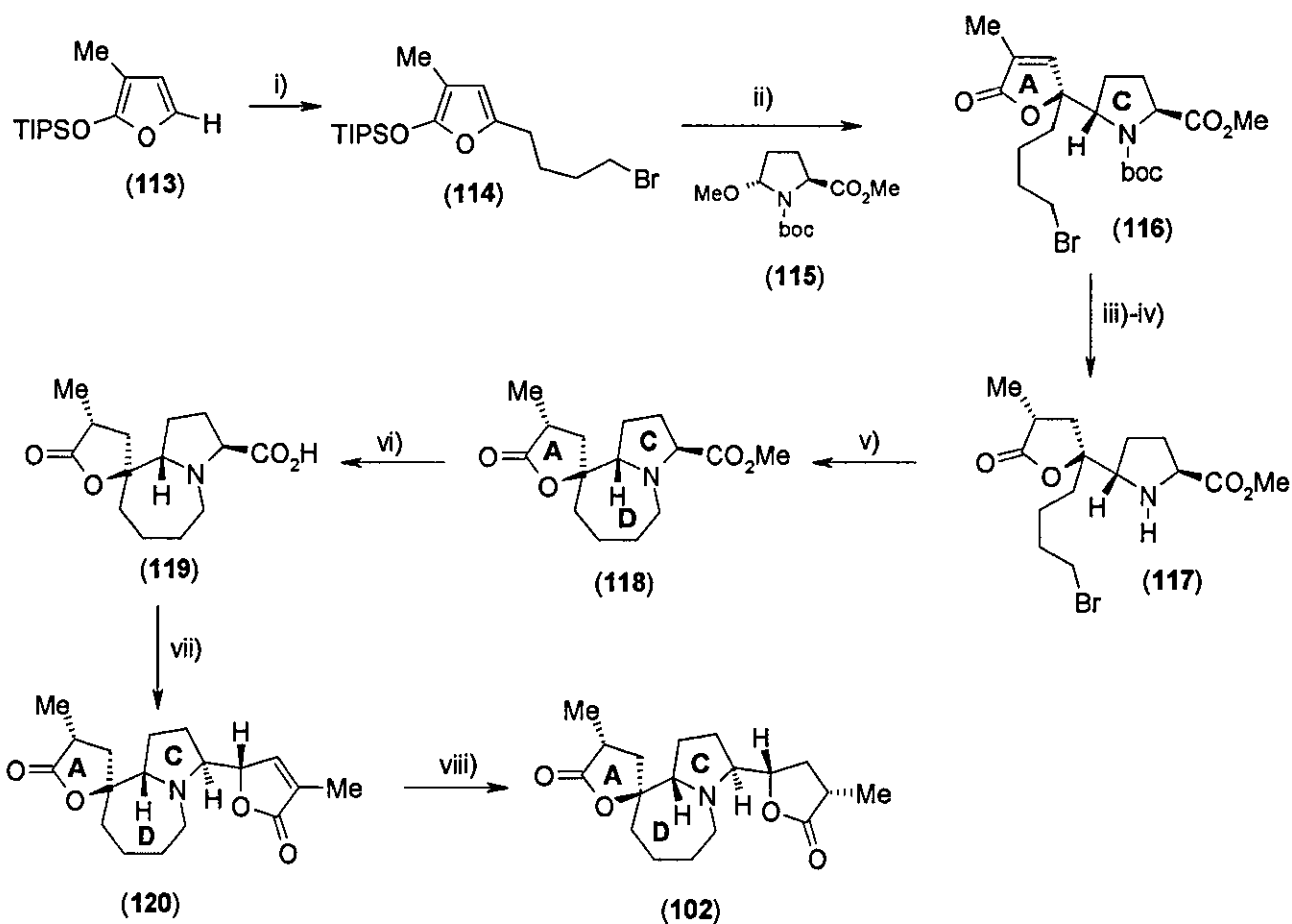
primary alcohol at C3, followed by saponification, Swern Oxidation and finally a Wittig olefination, gave the (Z)-alkene (110). Acid hydrolysis, basic saponification, addition of excess Jones reagent, followed by esterification with ethereal diazomethane gave the butyrolactone methyl ester (111). Removal of the benzyl ether and subsequent oxidation gave the aldehyde (112). A Staudinger reaction formed the seven membered ring, and the resulting amine was treated with iodide to give direct conversion to (+)-croomine (102) in 17 steps. This route was different to many other synthetic strategies towards the *Stemona* alkaloids, in that Williams chose to construct the carbon framework of the A, D, C ring system first, before sequential ring cyclisations, elegantly constructing the azepine core (Scheme 8).



i) $\text{BnOCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{MgBr}$, Et_2O , -78°C , DMS-CuBr , TMEDA , then (104), (95%); ii) DIBAL , CH_2Cl_2 , -78°C , (98%); iii) $\text{Ti}(\text{O}^i\text{Pr})_4$ (10 mol%), D-DIPT , (12 mol%), $t\text{-BuOOH}$ (3 eq), 4 Å sieves, CH_2Cl_2 at -50°C , (83%); iv) ClCOCOCi (1.2 eq), DMSO , (2.4 eq), CH_2Cl_2 , Et_3N , (2.5 eq), $\text{Ph}_3\text{P=CHCOOCH}_3$, (1.2 eq), (89%); v) LiBH_4 (1.2 eq), Et_2O , MeOH , (81%); vi) 5% $\text{Rh/Al}_2\text{O}_3$, H_2 , THF (62%); vii) BzCl , Et_3N , CH_2Cl_2 , (97%); viii) LiN_3 , DMPU , 110°C , (94%); ix) $\text{BF}_3\cdot\text{Et}_2\text{O}$, CH_2Cl_2 , 0°C , (81%); x) LiOH , THF , aq MeOH , (97%); xi) ClCOCOCi (1.2 eq), DMSO (2.4 eq), CH_2Cl_2 , Et_3N , (91%), then $\text{PPh}_3\text{=CHCH}_2\text{CH}(\text{CH}_3)\text{CHOBz}$, from KO^tBu , THF , -10°C , (70-81%); xii) aq. HBF_4 , CH_3OH , (72%); xiii) LiOH , THF , CH_3OH , H_2O (86%), then CrO_3 , 0°C then ethereal diazomethane, (78%); xiv) BCl_3 , CH_2Cl_2 , then MeOH , -78°C , (77%); xv) ClCOCOCi (1.2 eq), DMSO (2.4 eq), CH_2Cl_2 , Et_3N , (92%); xvi) PPh_3 , THF , then NaBH_4 , MeOH (90%); xvii) I_2 , CH_2Cl_2 , Et_2O , (25%).

Scheme 8: Williams total synthesis of (+)-croomine (102).²²

A concise route to (+)-croomine (**102**), utilising two vinylogous Mannich reactions has been developed by Martin.²³ Trialkylsilyloxy furan (**113**) was chosen as a common precursor for the formation of the A and D rings, using two separate Mannich reactions. Furan (**114**) was synthesised to set the stage for the first of these, by alkylation of the lithio derivative of (**113**) with 1,4-dibromobutane, (**114**) was then reacted with the chiral acyl iminium ion of (**115**) in the first vinylogous Mannich reaction, to give (**116**), which incorporated the A and C rings of (+)-croomine (**102**), with the correct stereochemistry, in a single step. Removal of the amine protecting group, followed by subsequent hydrogenation, gave compound (**117**), which was heated under reflux in DMF with *N*-methylmorpholine, to construct the seven membered B ring (**118**). Hydrolysis of (**118**) yielded carboxylic acid (**119**), which when treated with POCl₃, gave rise to the iminium salt. Furan (**113**) was introduced *in situ* and the subsequent vinylogous Mannich reaction afforded (**120**) with the introduction of the second lactone ring. Stereoselective hydrogenation gave (+)-croomine (**102**) in 8 steps (Scheme 9).

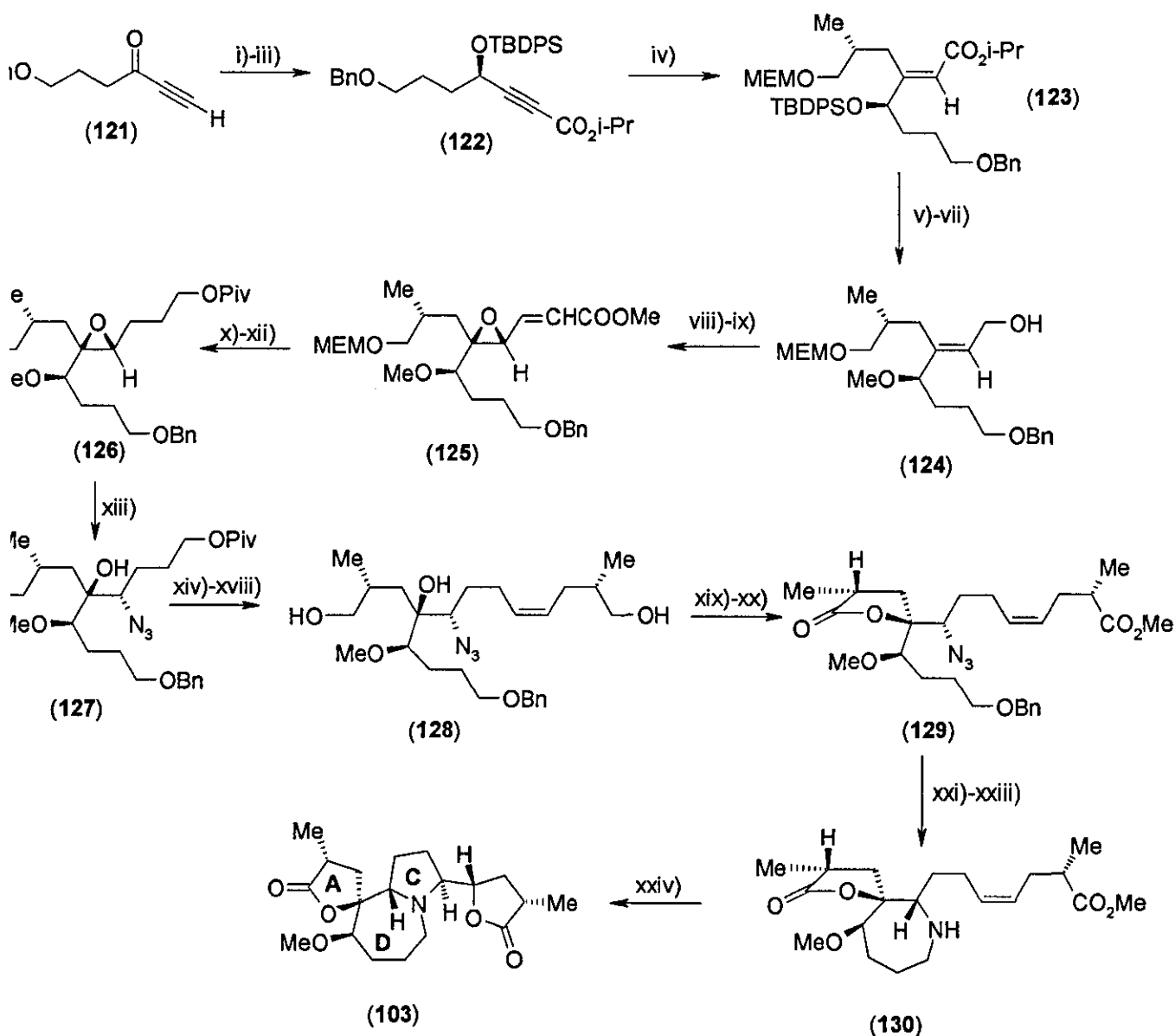


i) *s*-BuLi, TMEDA, THF, 0°C then BrCH₂(CH₂)₂CH₂Br, (83%); ii) 5% TIPSOTf, CH₂Cl₂, 0°C, (32%); iii) CF₃CO₂H, CH₂Cl₂, rt; iv) 3% Rh/C, H₂, EtOAc, EtOH, (96%, 2 steps); v) *N*-methylmorpholine, DMF, reflux; vi) 3M HBr (aq), 60°C, (74%, 2 steps); vii) POCl₃, DMF, rt then (113), (32%); viii) 10% Pd/C, H₂, 10% HCl-EtOAc, (85%).

Scheme 9: Martin's concise synthesis of (+)-croomine (102).²³

Williams has also reported a total synthesis of (-)-stemospirone (103), utilising a Staudinger reaction, leading to an aza-Wittig ring closure of the perhydroazepine system.²¹ Williams has shown the versatility of this chemistry, by also applying a similar route towards the total synthesis of (+)-croomine (102). Readily available ketone (121) underwent a Midland reduction with (*R*)-Alpine-borane, to give (122). Conjugate addition on to the acetylenic ester gave the *E*- α , β -unsaturated ester (123) exclusively. The silyl ether was removed using TBAF and then treated with methyl iodide and sodium hydride to give the required methyl ester, which was reduced to give alcohol (124). A Sharpless asymmetric epoxidation, followed by oxidation with Dess-Martin periodinane and a Wittig reaction using (carbomethoxymethylene)triphenylphosphorane gave methyl

ester (125). Reduction, then protection of the primary alcohol gave (126), which was treated with LiN_3 in DMPU to give azido alcohol (127). Saponification of the ester, followed by Swern oxidation gave an inseparable mixture of the lactol and hydroxyl aldehyde product in equilibrium. Treatment with triphenylphosphorane gave the desired alkene, then hydrolysis of the β -methoxyethyl ether, followed by removal of the primary benzoate, gave triol (128). Oxidation with Jones reagent, then treatment with ethereal diazomethane yielded the lactone methyl ester (129). Formation of azepine (130) occurred in similar fashion to previous alkaloid syntheses by Williams.^{18,19,20} Therefore cleavage of the benzyl ether followed by Dess-Martin oxidation of the resulting alcohol gave the azido-aldehyde intermediate. A Staudinger reduction gave the required azaylide, which underwent an intramolecular condensation reaction, followed by *in situ* reduction to give (130). Finally treatment with iodine yielded (-)-stemospironine (103) (Scheme 10).



i) (*R*)-Alpine borane, THF, -10°C to rt, (95%); ii) TBDPSCl, imidazole, CH₂Cl₂, rt, (80%); iii) *n*-BuLi, ClCO₂*i*-Pr, THF, -90°C, (90%); iv) CH₃OCH₂OCH₂CH₂CH(CH₃)CH₂MgBr, CuBr.DMS, THF, -78°C to rt, (70%); v) TBAF, THF, rt, (90%); vi) NaH, MeI, DMF, (85%); vii) DIBAL, CH₂Cl₂, -78°C, (92%); viii) Ti(O^{*i*}Pr)₄, CaH₂, SiO₂, (-)-DIPT, ^{*t*}BuOOH, CH₂Cl₂, -20°C, 72 h, (85-90%); ix) Dess-Martin oxidation, CH₂Cl₂, then Ph₃PC(H)CO₂CH₃, (60%); x) 5% Rh/Al₂O₃, H₂, THF, (85%); xi) LiBH₄, CH₃OH, Et₂O, (90%); xii) PivCl, Pyridine, DMAP, (91%); xiii) LiN₃, NH₄Cl, DMPU, 130°C, (83%); xiv) LiOH, THF, MeOH, H₂O, (94%); xv) ClCOCOC(1.2 eq), DMSO (2.4 eq), CH₂Cl₂, Et₃N, (97%); xvi) KO^{*t*}Bu, Ph₃PCH₂CH₂CH(CH₃)CH₂OCH₂Ph, THF, -10°C, (77%); xvii) HCl, THF, rt, (85%); xviii) LiOH, THF, H₂O, MeOH, (88%); xix) Jones Reagent, THF, -10°C; xx) CH₂N₂, Et₂O, 0°C, (80%, 2 steps); xxi) BCl₃, CH₂Cl₂, -78°C to -10°C, (60%); xxii) Dess-Martin oxidation, CH₂Cl₂, (80%); xxiii) PPh₃, THF then NaBH₄, CH₃OH, rt, (60%); xxiv) I₂, CH₂Cl₂, Et₂O, rt, 48 h, (30%).

Scheme 10: Williams' total synthesis of (-)-stemospirone.²¹

1.1.iv. The Stemonamine Group:

The stemonamine group contains a number of *Stemona* alkaloids, including stemonamine (131), stemonamide (132) and isostemonamide (133), all showing the characteristic spiro lactone ring at C-12 (Figure 6).

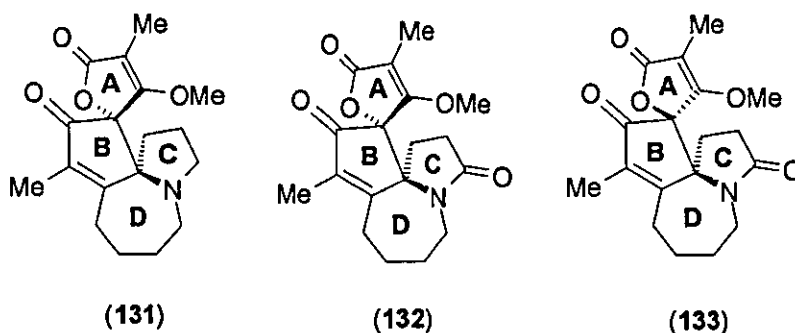
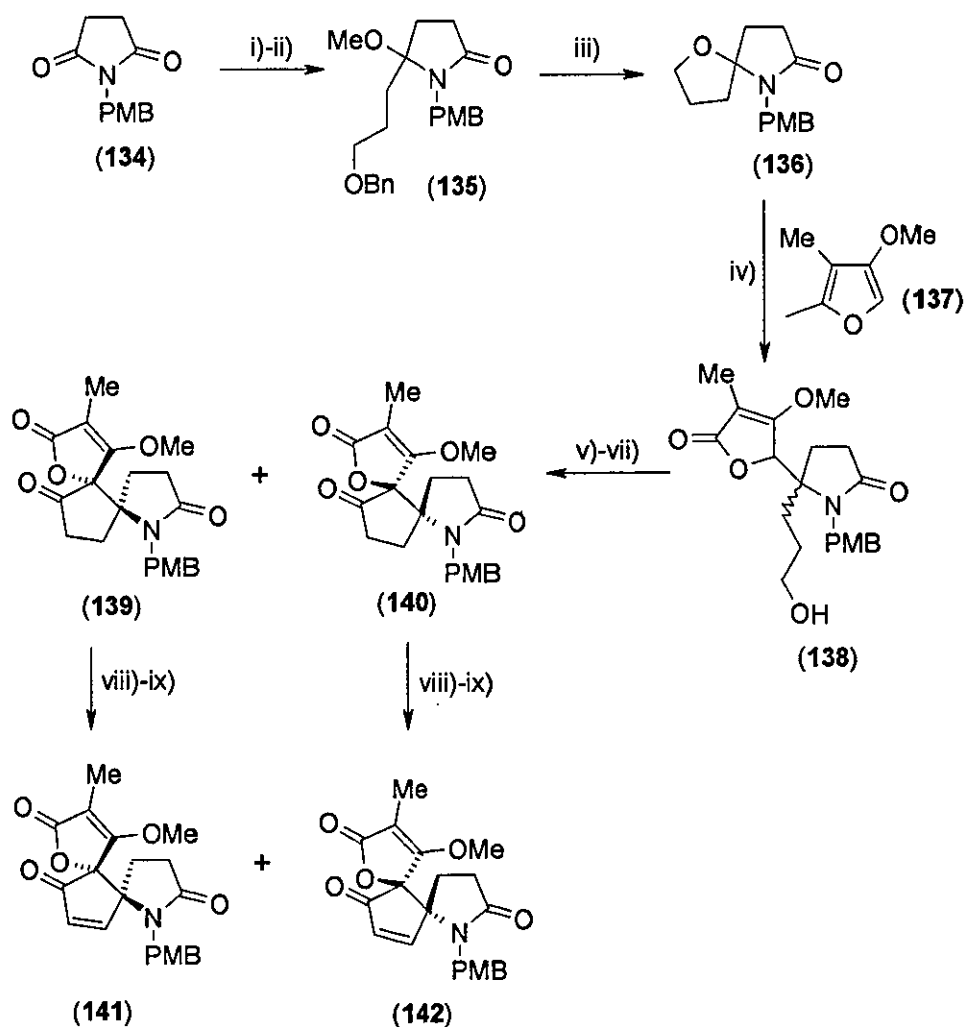


Figure 6: Representatives of the stemonamine group of *Stemona* alkaloids.

Kende has utilised acyliminium chemistry to perform the total synthesis of (±)-stemonamide (132) and (±)-isostemonamide (133).²⁵ The synthesis began with a Grignard addition of (3-benzyloxypropyl) magnesium bromide to succinimide (134). The resulting hemiaminal was protected as the methoxy derivative (135), which upon hydrogenolytic debenzylation gave the spiro compound (136). Addition of the silyloxyfuran (137) to the *N*-acyliminium ion generated from (136) created the first quaternary centre. A 1:2 mixture of diastereomeric alcohols (138) was produced, but a Swern oxidation produced the corresponding aldehydes, which were treated with DBU and cyclised to yield tricyclic aldol products. Further Swern oxidation converted the aldol products to a 1:1 mixture of tricyclic ketones (139) and (140). These were easily separated by column chromatography. Finally the enones required for the attempted total syntheses of stemonamide and isostemonamide were constructed by treatment with *tert*-

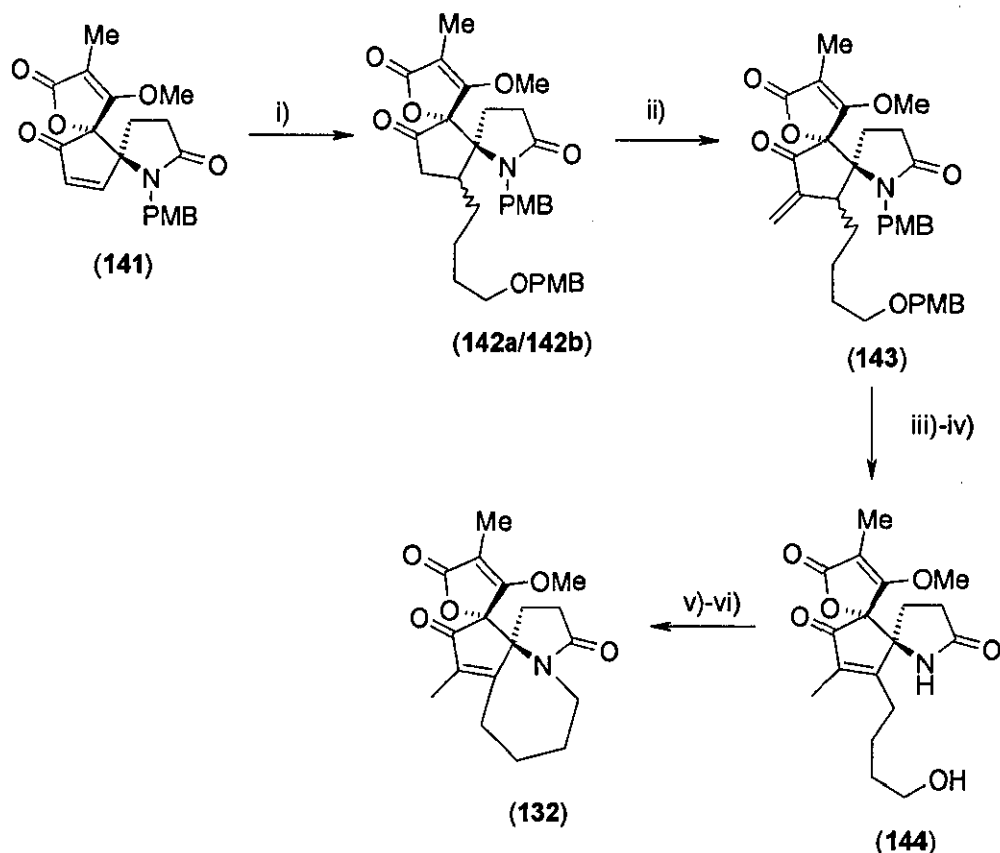
butyldimethylsilyl enyl ethers with $\text{Pd}(\text{OAc})_2$, to produce desired enones (**141**) and (**142**) (Scheme 11).



i) $\text{BnO}(\text{CH}_2)_3\text{MgBr}$, Et_2O , reflux, 30 min; ii) PPTS, MeOH , rt, 30 min, (90%, 2 steps); iii) H_2 , 5% Pd/C , 3h, (90%); iv) $\text{BF}_3 \cdot \text{Et}_2\text{O}$, CH_2Cl_2 , rt, 40 min, (82%); v) $(\text{COCl})_2$, DMSO , Et_3N , CH_2Cl_2 ; vi) DBU , CH_2Cl_2 , 12h, rt; vii) $(\text{COCl})_2$, DMSO , Et_3N , CH_2Cl_2 , (70%, 3 steps); viii) TBDSTf , collidine, toluene, 7h, 0°C to rt, (**139**, 80% and **140**, 68%); ix) $\text{Pd}(\text{OAc})_2$, O_2 , DMSO , 80°C , 24-48h, (**141**, 93% and **142**, 89%).

Scheme 11: Synthesis of the enone intermediate required for synthesis of stemonamide and isostemonamide by Kende.²⁵

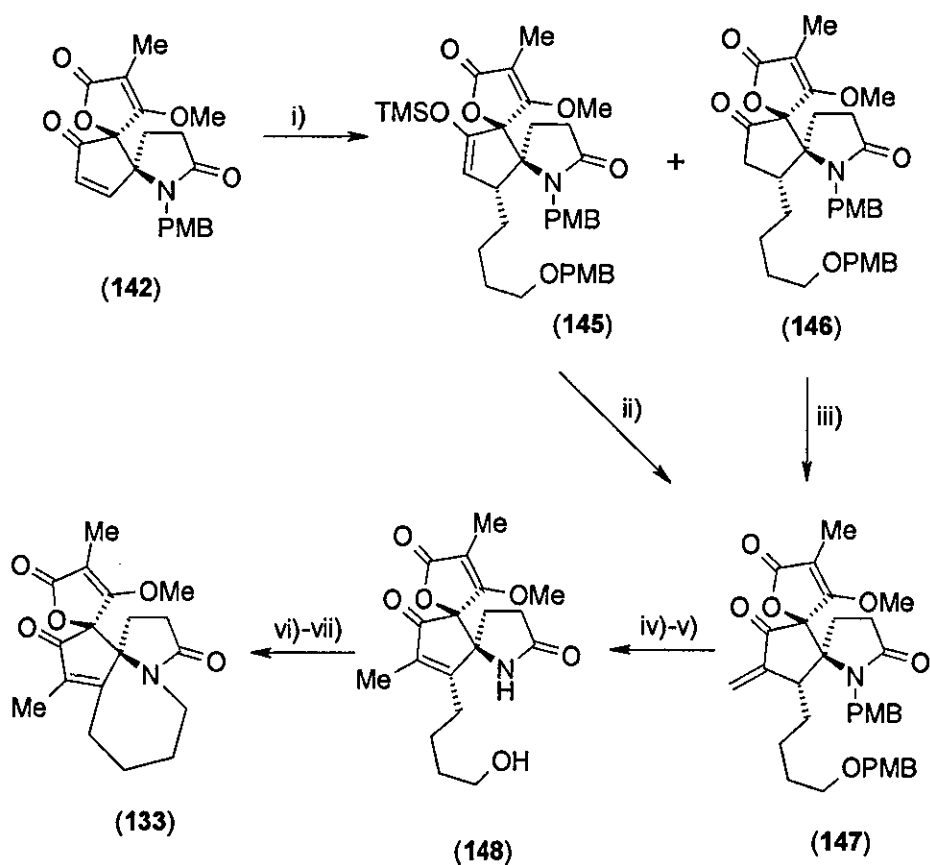
In the total synthesis of stemonamide (**132**), a conjugate Grignard addition to (**141**) in the presence of CuBr-Me₂S, gave the predominantly *anti* addition product to the C-N bond (**142a/142b**). A Mannich reaction installed the α -methyl group, unsaturation by deprotonation with KH and treatment with dimethylmethyleneammonium trifluoroacetate afforded ketone (**143**). Removal of the PMB groups allowed the unprotected lactam to undergo RhCl₃ mediated isomerisation to yield enone (**144**). Mesylation of the alcohol set the stage for the construction of the seven-membered ring, which was achieved *via* a nucleophilic displacement of the mesylate, by treatment with NaH, which produced racemic stemonamide (**132**) in an overall yield of 4 % from succinimide (**134**) (Scheme 12).



i) PMBO(CH₂)₄MgBr, 5% CuBr-Me₂S, TMSCl, HMPA, THF, -78°C, 30 min, (74%); ii) KH, Me₂N=CH₂⁺CF₃COO⁻, THF, overnight, (67%); iii) CAN, CH₃CN/H₂O, 2h (80%); iv) RhCl₃.H₂O, EtOH/H₂O,(10:1), reflux, 36h, (66%); v) MsCl, DMAP, pyridine, CH₂Cl₂, 0°C, 1 h; vi) NaH, THF, rt, 30 h.

Scheme 12: Synthesis of stemonamide (**132**) from the tricyclic enone intermediate (**141**).²⁵

Similarly the synthesis of (\pm)-isostemonamide (**133**) followed the same strategy. Thus, conjugate addition of the Grignard reagent to (**142**) in the presence of CuBr·Me₂S afforded (**145**) and (**146**). The TMS enol ether (**145**) was converted to (**147**) by direct treatment with the Mannich reagent, whereas ketone (**146**) underwent an identical Mannich reaction as previously described in the synthesis of (**143**). Finally RhCl₃ mediated isomerisation and azepine ring closure used identical methodology as described in the formation of stemonamide (**132**) to yield (\pm)-isostemonamide (**133**) in 7 % overall from succinimide (**134**) Scheme (13).



i) PMBO(CH₂)₄MgBr, 5% CuBr·Me₂S, TMSCl, HMPA, THF, -78°C, 30 min, (74%); ii) Me₂N=CH⁺CF₃COO⁻, CH₂Cl₂, rt, 3 h, (96%); iii) KH, Me₂N=CH⁺CF₃COO⁻, THF, overnight, (85%); iv) CAN, CH₃CN/H₂O, 2h (75%); v) RhCl₃·H₂O, EtOH/H₂O, reflux, 36 h, (69%); vi) MsCl, DMAP, pyridine, CH₂Cl₂, 0°C, 4 h; vii) NaH, THF, rt, 5 h.

Scheme 13: Synthesis of isostemonamide from the tricyclic enone intermediate (**143**).²⁵

1.1.v. The Parvistemoline Group:

The final group of the *Stemona* alkaloids is the parvistemoline group. These alkaloids are characterised by the lack of the D-B ring fusion and a hexahydro-2,6-dimethyl-5-oxofuro[3,2-*b*]furan-3-yl moiety attached to the azepine nucleus. To date there has been no formal synthesis of these alkaloids (Figure 7).

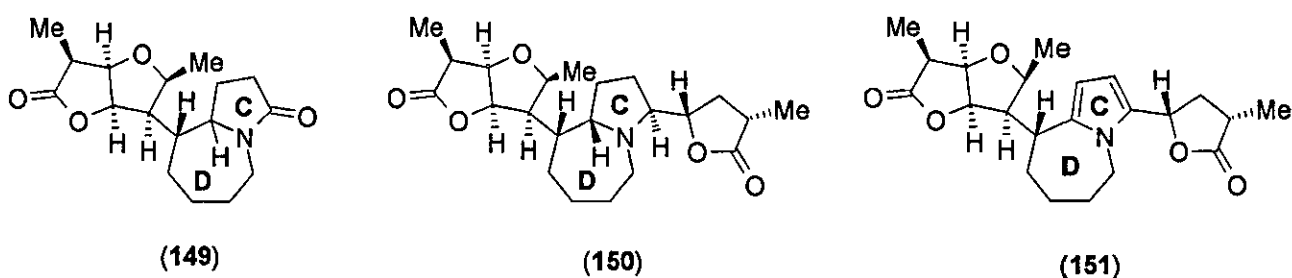


Figure 7: Representatives of the parvistemoline group of *Stemona* alkaloids.

1.2 Palladium catalysed [2+3] cycloaddition reactions involving methylenecyclopropanes:

A cycloaddition reaction is normally where two π bonds are lost and two σ bonds are introduced, usually in respect to forming five membered heterocycles. Various conditions can be used to optimise cycloaddition reactions, including heat, light, increasing pressure and Lewis acids. But one of the main areas of interest in promoting these types of reactions has come about by the use of transition metal catalysts. The use of these metal catalysts has facilitated the versatility, selectivity and reactivity of these cycloaddition reactions through complexation of the metal to the olefin. This enabled the rapid synthesis of highly functionalised heterocycles, many of which formed the templates required for complex total syntheses of natural product targets.²⁶

Cyclopropane (**152**) and its derivatives have been identified as useful building blocks for use in synthetic chemistry, due to its susceptibility to ring-opening reactions under a variety of different reacting species including electrophilic, nucleophilic and radical reagents, as well as other variables such as heat and light.²⁷ Unlike straight chain hydrocarbons, the C-C single bond of cyclopropane, is more characteristic of a C=C double bond. Due to the cyclic arrangement of the propane chain, there is significant angular (Bayer) strain, where the bond angles are in fact 60° instead of the desired 109.5° for sp³-hybridised systems. Coupled with the torsional (Pitzer) strain, as the co-planar carbon atoms forces the C-H bonds to be eclipsed. These factors show why cyclopropane units readily undergo ring-opening reactions, it is the relief of this ring strain that is the major driving force behind the reaction.²⁷

A powerful example of how useful these cyclopropane intermediates are in the synthesis of complex molecules can be seen through the palladium catalysed [2+3]-cycloadditions of methylene cyclopropane and its analogues. The exocyclic double bond further increases the ring strain, by forcing the bond angle at C-1 to increase, thus lengthening the C-2-C-3 bond (Figure 8).

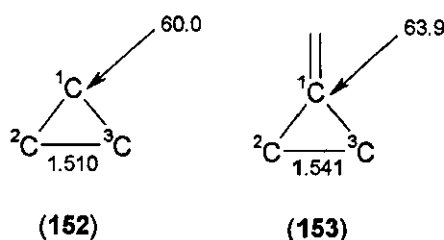
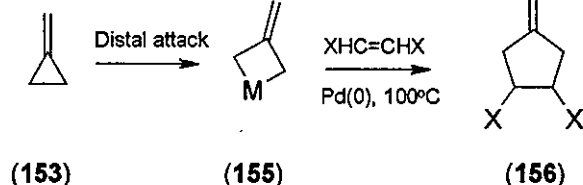
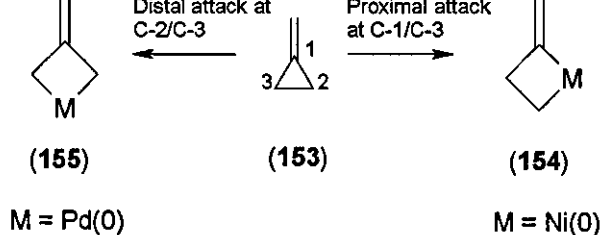


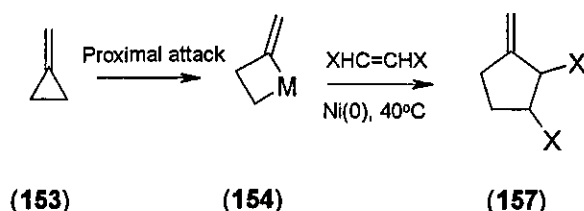
Figure 8: Cyclopropane and methylene cyclopropane.

Methylenecyclopropanes participate in reactions which are characteristic of olefins e.g. electrophilic additions, radical additions, addition to carbenes and nitrenes, various

There are a number of possible mechanistic pathways in which transition metals can react with methylenecyclopropanes. The metal can insert into the distal C-2/C-3 bond or the proximal C-1/C-2 bond, to form the metallacyclobutane.³⁰ (**Scheme 14**).



Alternatively the metallacyclobutane formed from proximal attack, can be reacted in the presence of Ni(0) to afford heterocycle (158), but this time the two carbon unit is introduced in the proximal position to the exo-cyclic double bond (Scheme 16).³¹



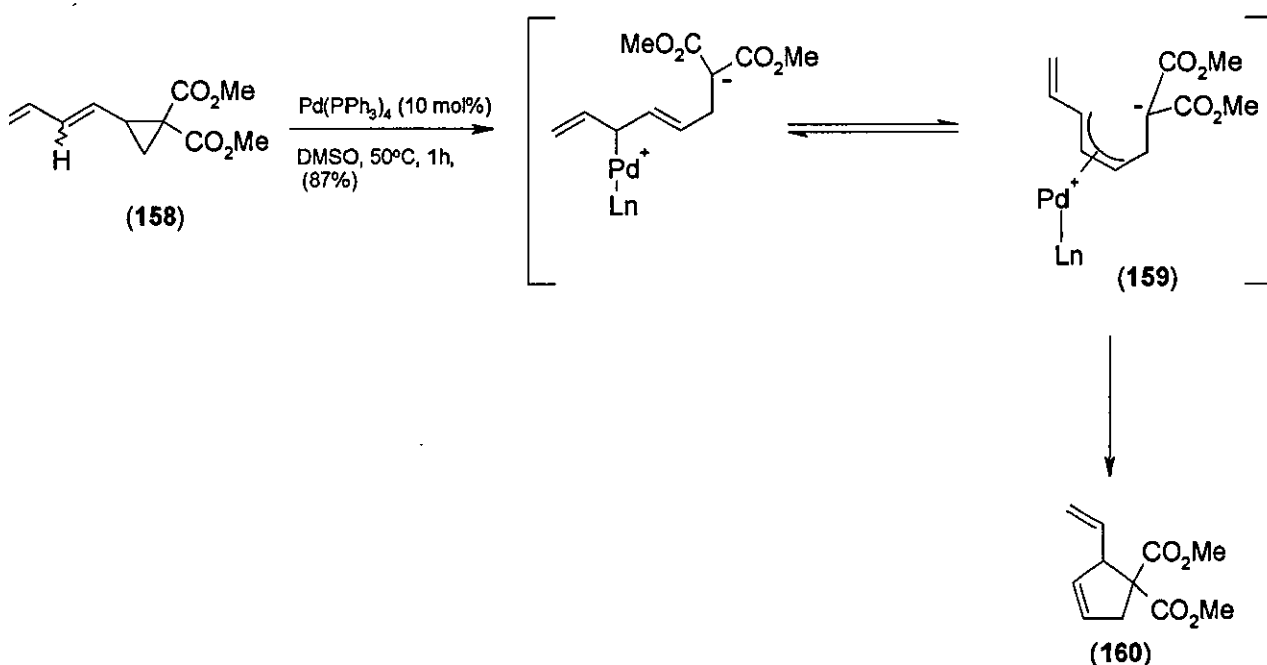
Scheme 16: Formation of carbocycle *via* proximal attack.³¹

Interestingly both cyclopentanes can be isolated in the presence of Ni(0), whereas only the heterocycle obtained *via* distal attack can be isolated when catalysed by Pd(0).³¹

1.3 Palladium catalysed [2+3] cycloaddition reactions involving vinylcyclopropanes.

The chemical properties of cyclopropanes are altered dramatically upon the incorporation of neighbouring electron-withdrawing groups (EWG). Early work within this area was carried out by Burgess, who investigated the effects of electron-withdrawing groups (EWG) on ring opening of the vinylcyclopropane, to form either the mono- and/or bis-alkylated conjugated product.³² He concluded that the ratio of mono- and bis-alkylated products depended not only on the concentration of starting materials, but also on the stabilising nature of the EWG present on the vinylcyclopropane, having to be greater or comparable to that of the EWG on the nucleophile.³²

In the early eighties, Morizawa and co-workers concentrated upon palladium catalysed [2+3]-cycloadditions using doubly activated vinylcyclopropanes (**158**), in which they reported could undergo formal retro-aldol rearrangement to 1,3-zwitterionic intermediates, which could then rearrange to afford varying cyclopentenenes (**Scheme 17**).³³

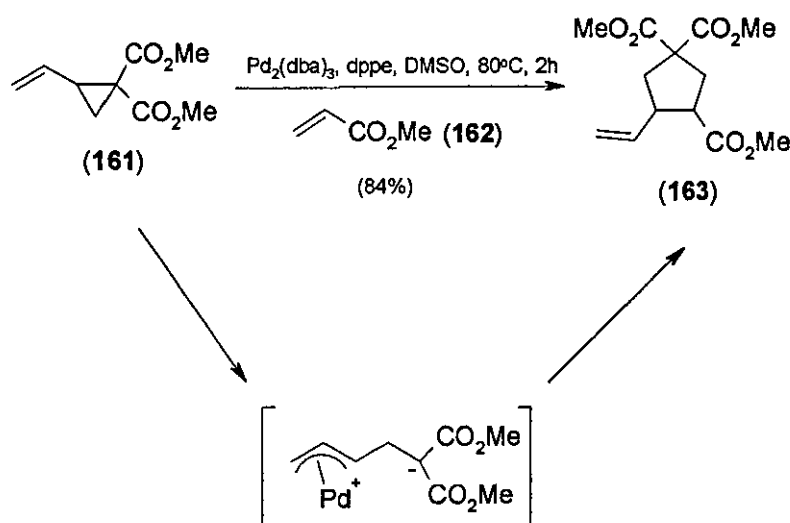


Scheme 17: Synthesis of functionalised cyclopentenenes.³³

Morizawa proposed that due to the oxidative addition of the Pd(0) species to the dienic group, a zwitterionic π -pentadienylpalladium intermediate (**159**) was generated. This ring opened the cyclopropane, and the subsequent anion was stabilised by the two EWG groups, which then collapsed to form the cyclopentene derivative (**160**).

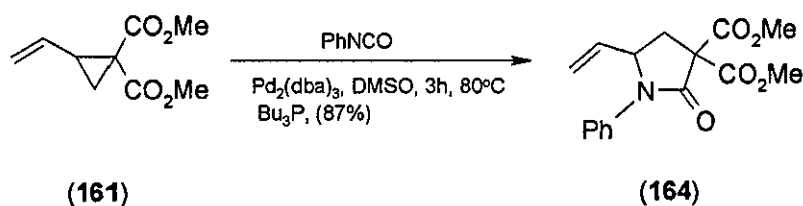
Further studies within this area have been conducted by Tsuji.³⁴ He has reported the synthesis of 5-membered carbo- (**163**) and heterocycles, using similar [2+3] palladium

catalysed methodology between doubly activated vinylcyclopropanes (**161**) and electron deficient olefins (**162**) (Scheme 18).



Scheme 18: Formation of 5-membered carbocycle (**163**).³⁴

Tsuji also believed that the palladium species added oxidatively into the vinyl double bond, ring opening the cyclopropane to form the π -allyl palladium complex. He viewed this intermediate as a 1,3 dipole equivalent, which could be trapped with a variety of electron-deficient olefins and activated vinylcyclopropanes to form the corresponding 5-membered rings (Scheme 19).^{34,35}

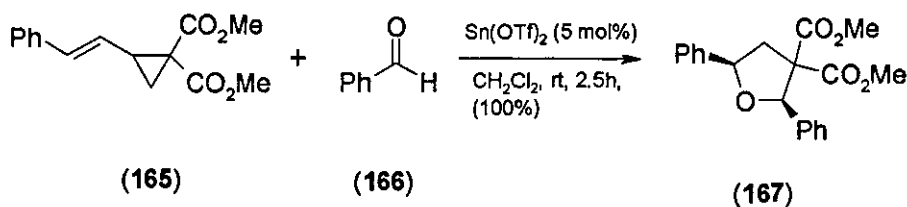


Scheme 19: Synthesis of 5-membered heterocycle (**164**).^{34,35}

This work provided a clear insight into the scope of this reaction. It provided an efficient route into highly functionalised 5-membered heterocycles, many of which could provide the building blocks in the synthesis of structurally complex and biologically important heterocycles. There were a few drawbacks within this route. The main cause for concern was the use of hexamethylphosphoramide (HMPA), a highly toxic solvent, to which an alternative would be desirable. It was thought that the reaction conditions could be modified to overcome these challenges. By using a variety of activated vinylcyclopropanes and electrophiles, a powerful pathway towards highly functionalised heterocycles could be developed.

1.3.i Lewis acid mediated cycloaddition reactions involving vinylcyclopropanes:

A recent addition within this field of work was proposed by Pohlhaus and Johnson.³⁶ They reported the synthesis of 2,5-disubstituted tetrahydrofuran (**167**) from donor acceptor cyclopropane (**165**), and trapping these with benzaldehyde (**166**) in the presence of a catalytic amount of $\text{Sn}(\text{OTf})_2$ (Scheme 20).³⁶

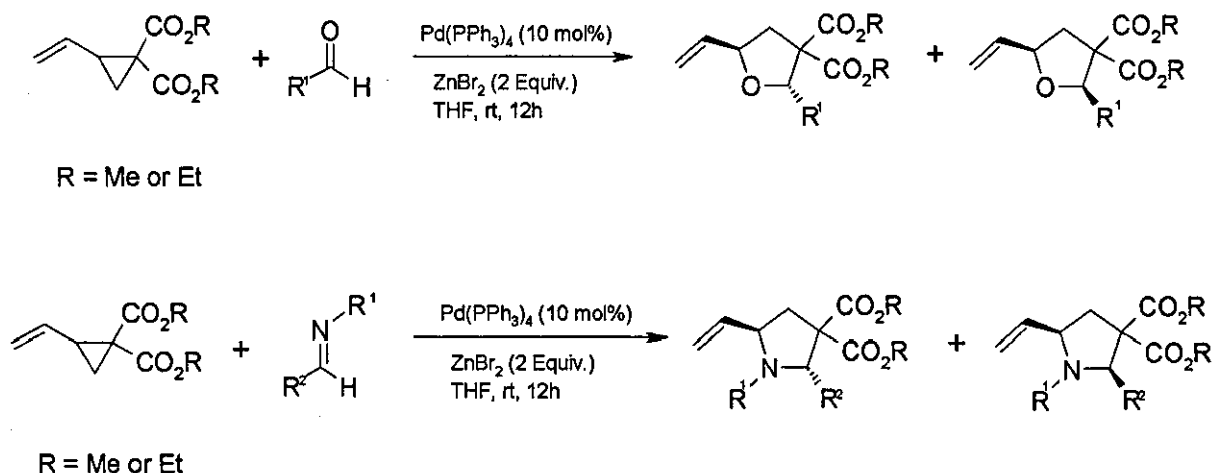


Scheme 20: Synthesis of functionalised tetrahydrofuran.³⁶

They used a wide range of cyclopropanes, including phenyl, 2-furyl and 4-nitrobenzaldehyde derivatives. These were all successfully cyclised with benzaldehyde in excellent yields (89-100%), though 3 equivalents of benzaldehyde were required. The reaction mainly favoured the *cis* isomer, though a range of diastereomeric ratios were observed. They proposed that the Lewis acid chelated to the electron withdrawing groups of the vinylcyclopropane, to facilitate ring opening and subsequent trapping of the benzaldehyde, to give the 5-membered heterocycles.

1.4 Previous group work:

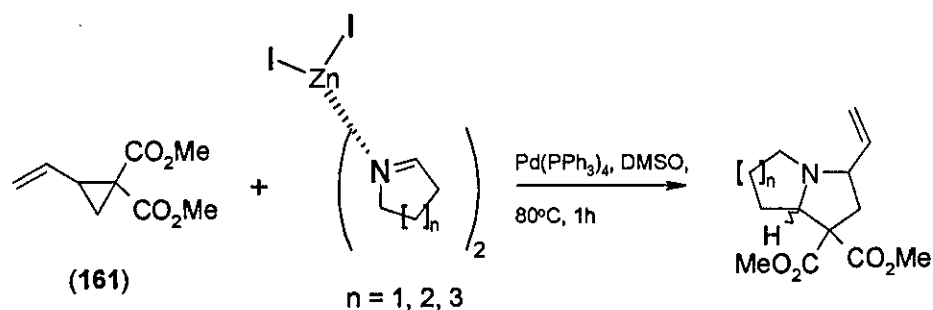
Investigations carried out expanding on Tsuji's work were started by Tang.³⁷ He concentrated on developing the palladium catalysed [2+3] cycloaddition reactions involving the doubly activated vinylcyclopropane, towards synthesising functionalised, novel heterocycles. Tang reported using a variety of trapping agents, including different imines and aldehydes, to give a selection of pyrrolidines and tetrahydrofurans. Crucially Tang was able to synthesise these heterocycles using different conditions to those first reported by Tsuji. The conditions Tang optimised involved using a stoichiometric amount of vinylcyclopropane and electrophile, 10 mol% Pd(PPh₃)₄, two equivalents of Lewis acid (ZnBr₂); the solvent used was THF, moving away from the highly toxic HMPA traditionally used by Tsuji (**Scheme 21**).



Scheme 21: Synthesis of functionalised heterocycles.³⁷

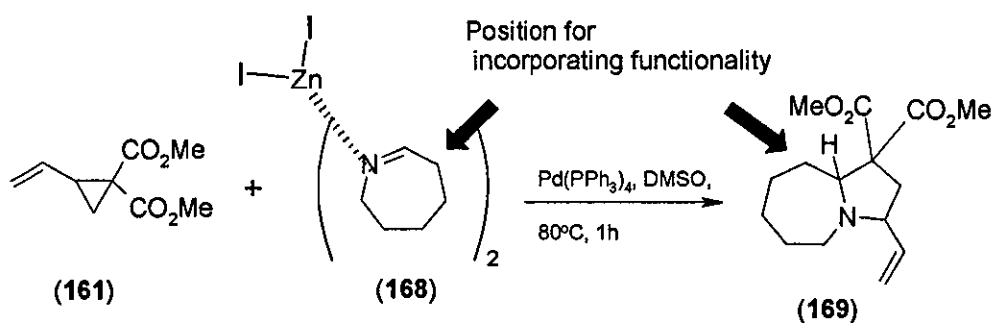
From his studies, Tang was able to identify a full range of functional groups which tolerated these conditions and used this methodology to generate a range of precursors which could potentially be used to construct a wide variety of biologically interesting compounds, work which has been investigated further within the group.^{38,39}

More recently the group has concentrated on using the [2+3] cycloaddition chemistry to access the azepine core at the heart of the *Stemona* alkaloids.^{40,41,42} One area under development is the synthesis of ring fused derivatives such as pyrrolizidines, indolizidines and azepines. The stereochemical outcome of the reaction may be affected by the ring size of the cyclic imine used, allowing control over two stereogenic centres in just one step. These types of fused heterocycles are present in not only the *Stemona* alkaloids but in a large range of biologically active compounds, making it a very powerful synthetic strategy (**Scheme 22**).⁴⁰



Scheme 22: Synthesis of ring-fused heterocycles.⁴⁰

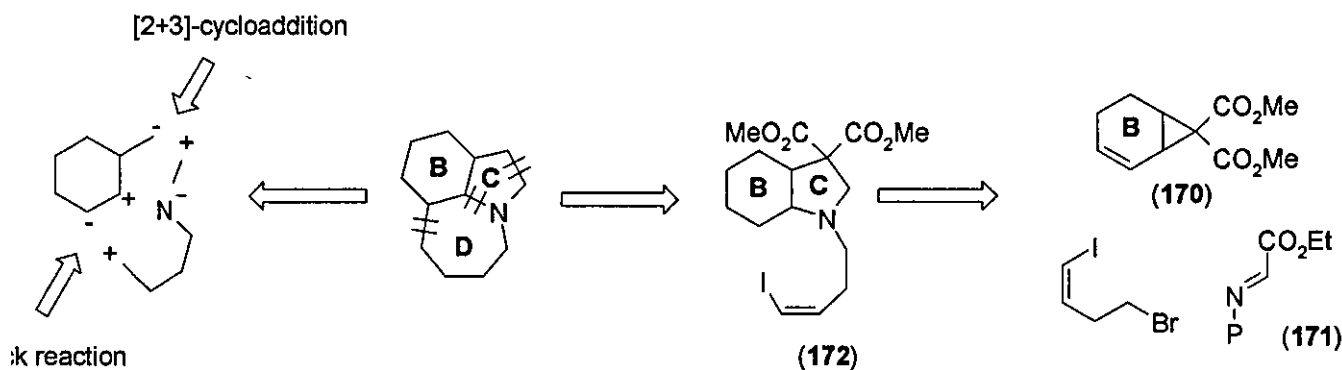
Interestingly with this particular route, if a 7-membered cyclic imine (**168**) was used, the group's palladium catalysed [2+3]-cycloaddition methodology would open up a synthetic pathway into the *Stemona* alkaloids containing the 1-azabicyclo[5.3.0]decane system. Importantly, the cyclic imine can easily be manipulated into incorporating some functionality at C-3, which would open up a possible route towards the azepine core of the stenine group of alkaloids (**Scheme 23**).⁴⁰



Scheme 23: Possible route into the azepine core of the *Stemona* alkaloids.⁴⁰

1.4.1 Previous group work towards the azepinoindole core of the *Stemona* alkaloids:

Work towards the tricyclic core of the *Stemona* alkaloids had previously been undertaken by Leybourne.⁴² He investigated the viability of using bicyclic cyclopropane (**170**) and the group's [2+3] cycloaddition methodology to construct pyrrolidine (**172**) by trapping the bicyclic cyclopropane with a suitable imine, followed by *N*-Alkylation, this would construct the B, C rings of the azepinoindole core. Finally, an intramolecular Heck cyclisation would construct the seven-membered ring and form the tricyclic skeleton of the alkaloid stenine (**1**) (Scheme 24).⁴²

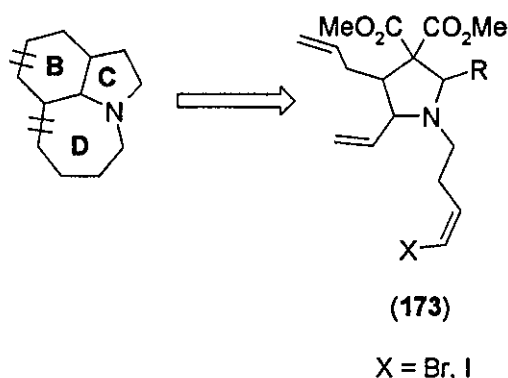


Scheme 24: Retrosynthesis of proposed route to tricyclic core of stenine.⁴²

Throughout his studies, Leybourne never managed to obtain the tricyclic skeleton he desired, but some of the methodologies he developed, particularly those involving the selective cyclopropanation of a variety of 1,3 dienes, would prove valuable in our pursuit of the azepinoindole core.

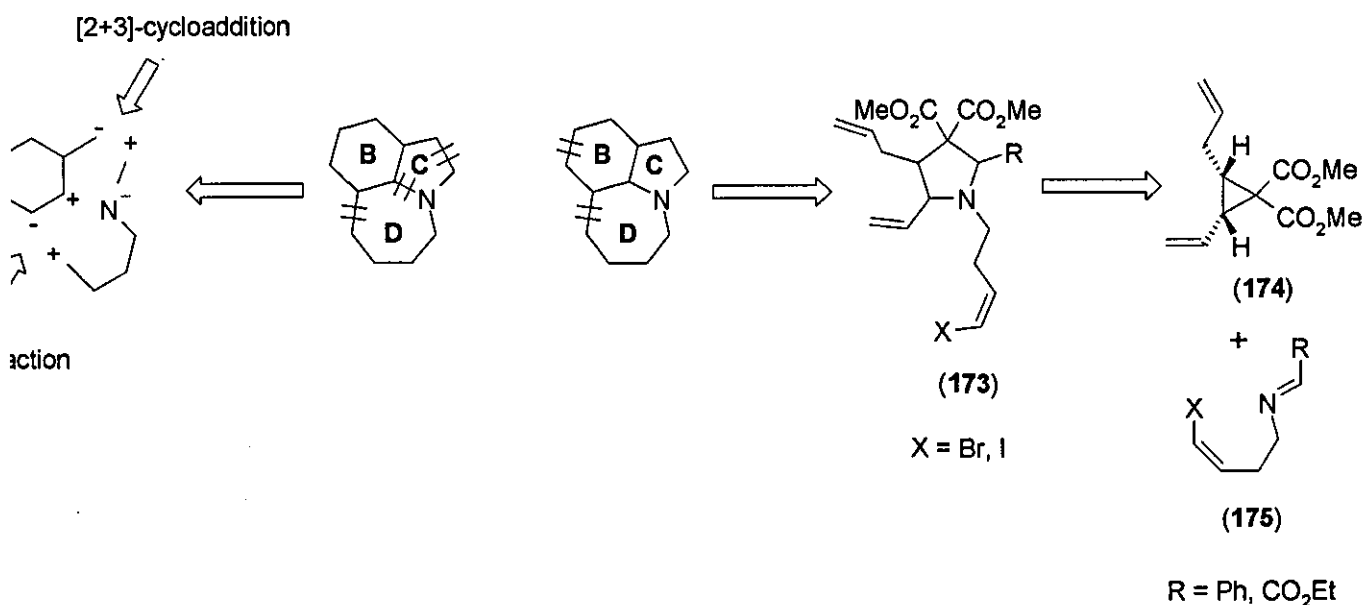
1.4.ii. The proposed route towards the azepinoindole core:

Within this investigation, we were keen to explore a route towards generating the azepinoindole core. At the heart of this methodology was again the group's palladium catalysed [2+3] cycloaddition chemistry. Throughout his studies, Leybourne had investigated the potential of using bicyclic cyclopropanes in order to immediately construct the B, C rings of the tricyclic core. We decided to look at an alternative route. Though initially we would use the methodology set out by Leybourne involving the bicyclic cyclopropanes, we would in fact use an elegant Heck/carbopalladation cascade reaction, to construct the seven membered D ring and then the six membered B ring in one step (Scheme 25).



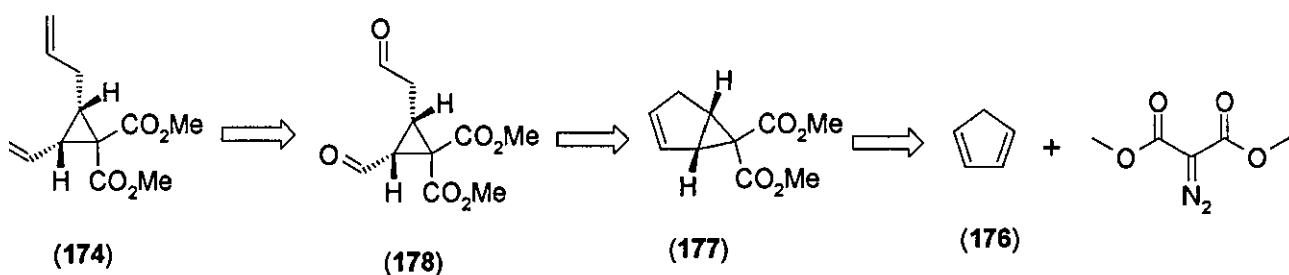
Scheme 25: Proposed precursor to the azepinoindole core

Pyrrolidine (173) was chosen as an ideal precursor for this cascade reaction towards the azepinoindole core. We envisaged that allylvinylcyclopropane (174), when reacted with a suitable imine (175) under the palladium catalysed [2+3] cycloaddition methodology set out by the group, would yield us our desired pyrrolidine target (Scheme 26).



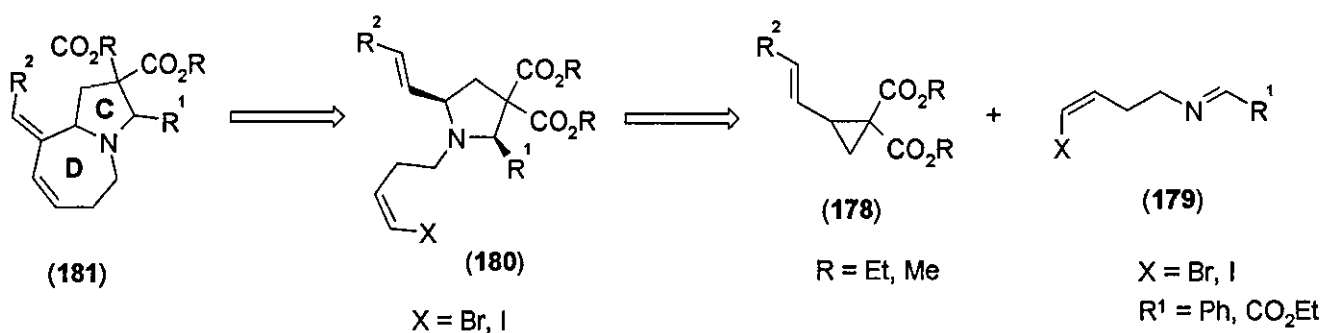
Scheme 26: Retrosynthesis of proposed route to azepinoindole core.

The allylvinylcyclopropane (**174**) would be generated using the methodology set out by Leybourne involving the selective cyclopropanation of 1,3-dienes.⁴² We envisaged that selectively cyclopropanating 1,3-cyclopentadiene (**176**) would yield us the [3.1.0] bicyclic cyclopropane (**177**). This could then be subjected to an ozonolysis reaction to give the di-aldehyde (**178**) and then a Wittig reaction would deliver us the required allylvinylcyclopropane (**174**) (Scheme 27).



Scheme 27: Proposed route towards allylvinylcyclopropane (174)

We were also keen to explore the potential of applying this chemistry in constructing the aza-bicyclic core of the alkaloids present in the stemoamide group. We envisaged the palladium catalysed [2+3] cycloaddition of vinylcyclopropane (178) and its analogues, with a suitable imine trapping reagent (179), would allow us to construct pyrrolidines (180) capable of undergoing an intramolecular Heck cyclisation, to form the [5.3.0] bicyclic core. This would leave us with the key D, C rings in place, and plenty of scope for further manipulation towards natural product targets (**Scheme 28**).



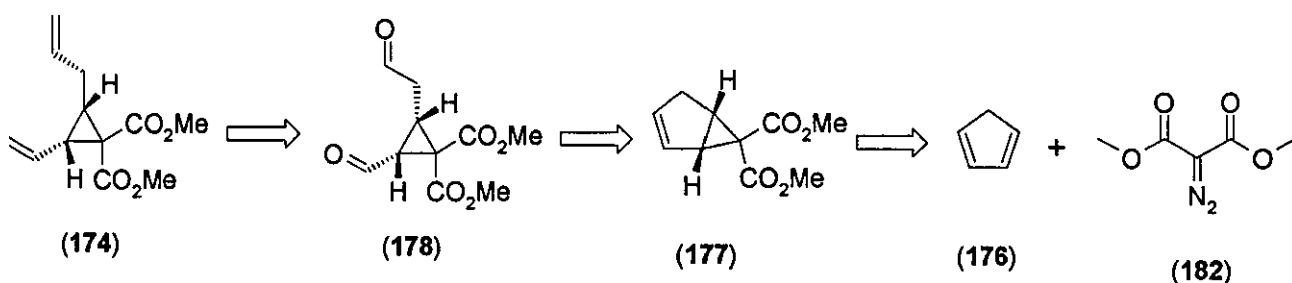
Scheme 28: Retrosynthesis of proposed route to bicyclic core

This report describes the work undertaken towards achieving these objectives.

Chapter 2 – Work towards the azepinoindole core.

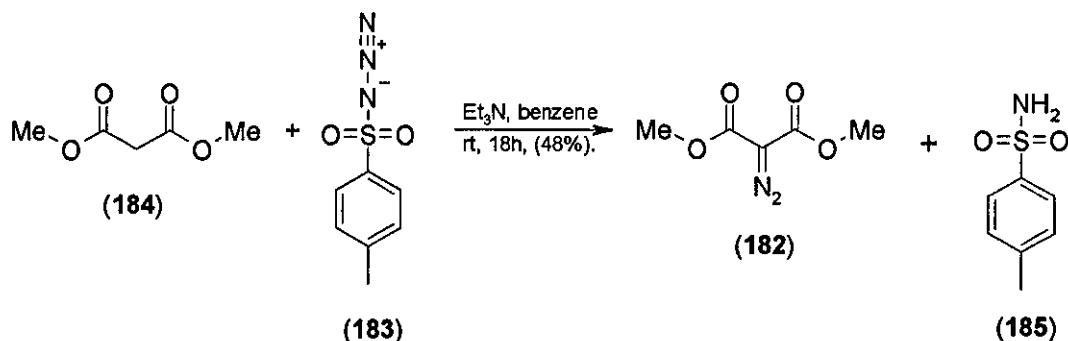
2.1 Synthesis of allylvinylcyclopropane - Part I:

The key intermediate in our attempt at constructing the azepinoindole core was the allylvinylcyclopropane (174) derivative. We envisaged that this precursor could be prepared from a Wittig reaction on di-aldehyde (178), which in turn could be prepared from an ozonolysis of bicyclic cyclopropane (177). Work previously undertaken in the group had looked at synthesising a variety of bicyclic cyclopropanes⁴² and we hoped to apply this methodology to synthesise bicyclic cyclopropane (177) (Scheme 29).



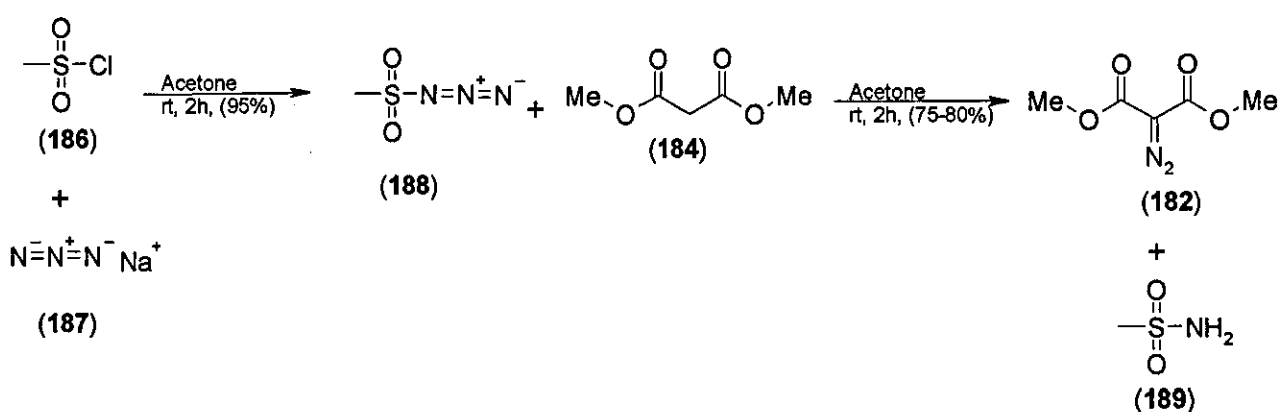
Scheme 29: Proposed route towards allylvinylcyclopropane (174)

Formation of dimethyl diazomalonate (182) followed a procedure previously investigated within the group.⁴² Reaction of tosyl azide (183) (easily prepared from reacting tosyl chloride with sodium azide in acetone)⁴³ with dimethyl malonate afforded dimethyl diazomalonate (182) in average yields (Scheme 30).^{44,45}



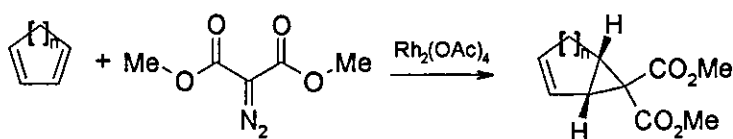
Scheme 30: Preparation of dimethyl diazomalonate (182).^{44,45}

Low yields were a problem with this reaction, with a large amount of tosyl amide by-product being isolated from the reaction and causing a problem. Not only did this reduce the yield but made purification extremely difficult. With this in mind we decided to explore other options. Danheiser *et al.* reported that mesyl azide (**188**) was a viable alternative to the tosyl azide we had originally been using.⁴⁶ The key advantage with using mesyl azide, was that a simple wash with 10% NaOH removed all of the mesyl amide by-product to yield the dimethyl diazomalonate in high yields and in no need of further purification (**Scheme 31**).⁴⁶




Scheme 31: Preparation of dimethyl diazomalonate using mesyl azide.⁴⁶

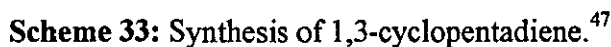
We could now synthesise the dimethyl diazomalonate (**182**) efficiently and in high yields which meant we could turn our attention to the construction of the bicyclic cyclopropane (**177**). Extensive work had already been undertaken within the group, looking at cyclopropanating a variety of 1,3-cyclodienes of varying ring size (**Scheme 32**).⁴²



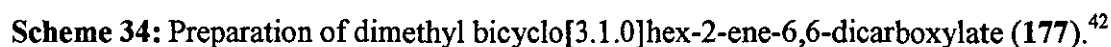
Scheme 32: Selective cyclopropanation of 1,3-cyclodienes.⁴²

We wanted to concentrate our efforts on the 5-membered analogue, which would provide us with the ideal bicyclic cyclopropane to achieve our allylvinylcyclopropane target. The





Nevertheless, we decided to carry on and synthesise the bicyclic cyclopropane (**177**) using the optimum conditions set out by Leybourne (**Scheme 34**).⁴²



To our dismay we found that using these conditions the best we could achieve was a 17% yield on a 0.250 g reaction. The yield decreased further when we tried to increase the scale, something that Leybourne had noted too. With the reaction being done neat, it meant that purification was a real problem. The crude product was a very gummy solid, which meant column loading was extremely difficult and could have contributed to the reduced yield. With this in mind, we decided to investigate other conditions which would hopefully increase the yield (Table 1).

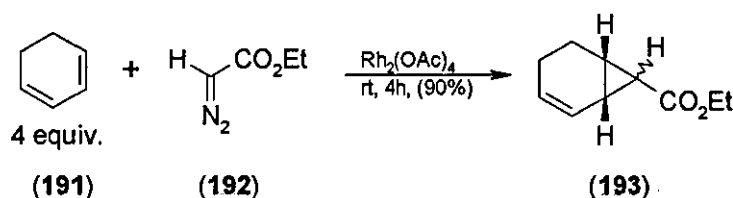
Equiv. (182 diazo)	Catalyst (10 mol %)	Solvent	Temperature	Time	Yield
1.0	Rh ₂ (OAc) ₄	DCM	Reflux	3h	17%
2.0	Rh ₂ (OAc) ₄	DCM	Reflux	3h	13%
5.0	Rh ₂ (OAc) ₄	DCM	Reflux	3h	6%
1.0	Rh ₂ (OAc) ₄	CH ₃ CN	Reflux	3h	10%
2.0	Rh ₂ (OAc) ₄	CH ₃ CN	Reflux	3h	12%
1.0	Rh ₂ (OAc) ₄	DCM	Reflux	24h	Trace
1.0	Rh ₂ (OAc) ₄	CH ₃ CN	Reflux	24h	N/A
1.0	Rh ₂ (OAc) ₄	DCM	RT	3h	No Reaction
1.0	Rh ₂ (OAc) ₄	DCM	RT	24h	No Reaction
1.0	Rh ₂ (OAc) ₄	CH ₃ CN	RT	24h	No Reaction
1.0	Cu(OTf) ₂	Neat	Reflux	3h	No Reaction
5.0	Cu(OTf) ₂	Neat	Reflux	3h	No Reaction
1.0	Cu(OTf) ₂	Neat	Reflux	24h	No Reaction
1.0	Cu(OTf) ₂	DCM	Reflux	3h	No Reaction
1.0	Cu(OTf) ₂	CH ₃ CN	Reflux	3h	No Reaction

Table 1: Attempts at synthesising dimethyl bicyclo[3.1.0]hex-2-ene-6,6-dicarboxylate (177).

Much to our frustration we found that we could not increase the yield towards anywhere near an acceptable level. We also looked into slow addition of the dimethyl diazomalonate using a syringe pump, but this had little effect on the reaction yields. Use of another catalyst to facilitate the cyclopropanation was also briefly investigated. Copper(II) triflate was investigated due to reports in the literature that it can also catalyse these types of cyclopropanations.⁵¹ Unfortunately we saw no sign of cyclopropanation, and starting materials were generally recovered. Another alternative we did not look at

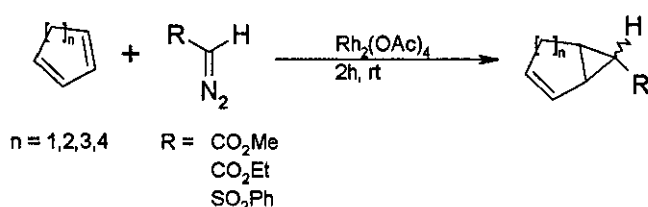
was diluting the reaction. By using increased amount of solvent in the reaction, it may have reduced the competing dimerisation reaction and increased the yields. Obviously this would have an effect on the length of time the reaction took to occur.

This was a slight set-back in our attempts to synthesis the allylvinylcyclopropane (174), but undeterred we decided to revise our route slightly. Research into the literature revealed work had been reported using rhodium-stabilised carbenoid chemistry with diazo-carbonyl compounds, to synthesise bicyclic [4.1.0] ethylester mono-substituted cyclopropanes (193) (Scheme 35).^{49,50}



Scheme 35: Cyclopropanation of 1,3-cyclohexadiene.⁴⁹

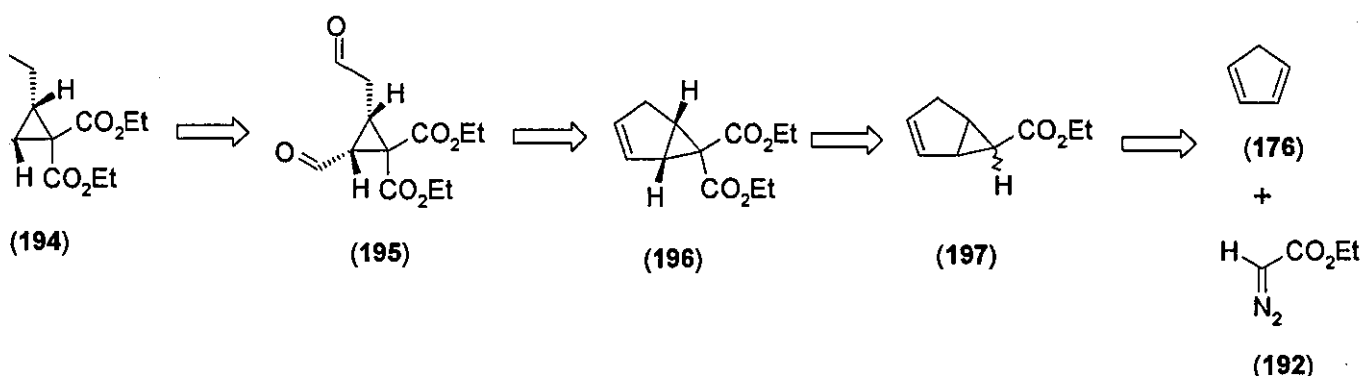
Previous work within this area had also been explored within the group. Leybourne had again investigated the viability of selectively cyclopropanating a variety of different ring sized 1,3-cyclodienes based on the reaction carried out initially by Demonceau (Scheme 36).⁵²



Scheme 36: Cyclopropanation of 1,3-cyclodienes.⁵²

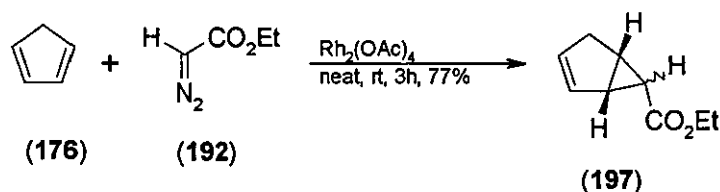
We decided to apply the methodology set-out by Leybourne, towards achieving our target compound. He had already seen a vast increase in yields when forming the mono-ethylester derivative, compared with the problems faced when synthesising the dimethyl ester analogue. The allylvinylcyclopropane (194) would be constructed from a Wittig reaction of the di-aldehyde (195), which would be prepared from an ozonolysis of the bicyclic cyclopropane (196). We envisaged a rhodium catalysed cyclopropanation of 1,3-

cyclopentadiene (176) with ethyl diazoacetate (192), would form the mono ethyl ester derivative (197) and allow an acylation reaction to insert the second ethyl ester group to form the desired bicyclic system (196). Though we had formed the ethyl esters instead of the original methyl ester analogue, this would still leave us ideally placed to convert it to the di-acid followed by decarboxylation at a later stage to move towards a natural product target if we desired (Scheme 37).



Scheme 37: Revised route towards allylvinylcyclopropane (194).

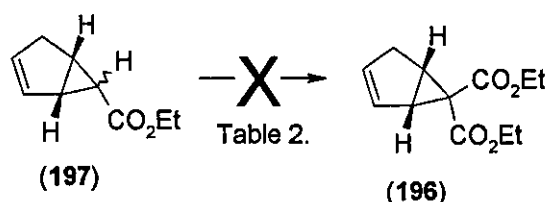
With the revised route in place, the first target was to synthesise bicyclo[3.1.0]hex-2-ene-6-carboxylic acid ethyl ester (197) (Scheme 38).



Scheme 38: Synthesis of bicyclo[3.1.0]hex-2-ene-6-carboxylic acid ethyl ester (197).

We were delighted to find the yields were significantly increased and they were not affected by an increase in the scale of the reaction. The major drawback with the reaction was that it was extremely exothermic and therefore potentially explosive. We found though by careful and slow addition of the α -diazoester (192) using a syringe, reduced the threat of explosion and gave consistent, repeatable results.

With the fused cyclopropane in place, we decided to investigate the insertion of the second ethyl ester group (**Scheme 39**).



Scheme 39: Attempted acylation of bicyclo[3.1.0]hex-2-ene-6-carboxylic acid ethyl ester (196).

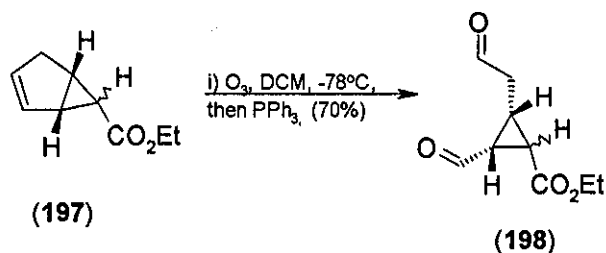
Frustratingly, we found that we were unable to insert the second ethyl ester moiety. Only starting material was recovered from all of our attempts. Because of this fact, we believed that maybe it was due to the bulky LDA base failing to deprotonate the acidic hydrogen; hence we were seeing no addition to the electrophile. An experiment we could do to test this theory, would be to react the material with D₂O after the attempted deprotonation with LDA. We could then clearly see in the ¹H NMR spectra whether or not the hydrogen had been removed, by seeing if the signal appeared in the spectra. This would confirm whether or not deprotonation was actually occurring (**Table 2**).

Base	Electrophile	Temperature	Time	Solvent	Yield
LDA	Diethyl carbonate	rt	3h	THF	Starting Material
LDA	Diethyl carbonate	rt	24h	THF	Starting Material
LDA	Diethyl carbonate	rt	3h	DCM	Starting Material
LDA	Diethyl carbonate	rt	24h	DCM	Starting Material
LDA	Ethyl chloroformate	rt	3h	THF	Starting Material
LDA	Ethyl chloroformate	rt	24h	THF	Starting Material
LDA	Ethyl chloroformate	rt	3h	DCM	Starting Material
LDA	Ethyl chloroformate	rt	24h	DCM	Starting Material
2,3,6,6-tetramethyl piperidine	Diethyl carbonate	rt	3h	THF	Starting Material
2,3,6,6-tetramethyl piperidine	Ethyl chloroformate	rt	3h	DME	Starting Material

Table 2: Attempts to synthesise diethyl bicyclo[3.1.0]hex-2-ene-6,6-dicarboxylate (196).

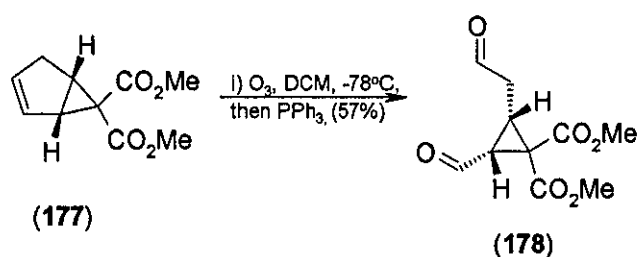
Though we were disappointed at not being successful in inserting the second ethyl ester moiety, we envisaged to insert it later. With this in mind, it was decided to press on and form the di-aldehyde required for the crucial Wittig reaction.

The ozonolysis was tried on the mono-ester derivative first (**Scheme 40**).



Scheme 40: Synthesis of 2-formyl-3-(2-oxoethyl)-cyclopropanecarboxylic acid ethyl ester (**198**)

Due to the challenges we faced when synthesising the dimethyl ester derivative, we had limited material to work with, but there was enough to investigate the viability of the subsequent ozonolysis reaction (**Scheme 41**).

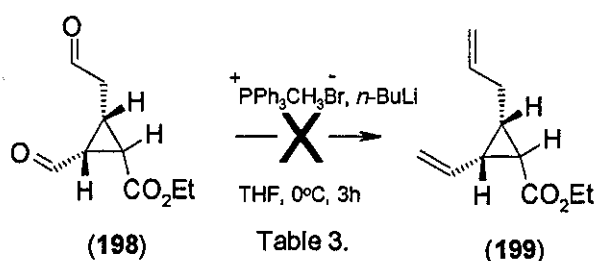


Scheme 41: Synthesis of 2-formyl-3-(2-oxoethyl)-cyclopropane-1,1-dicarboxylic acid dimethyl ester (**178**).

Average yields were obtained with the dimethyl ester derivative, and at first we obtained relatively low yields with the ethyl ester analogue. These were increased significantly though, by quenching the ozonolysis reaction with dimethyl sulfide (DMS) instead of using triphenylphosphine. This eliminated the need to use column chromatography for

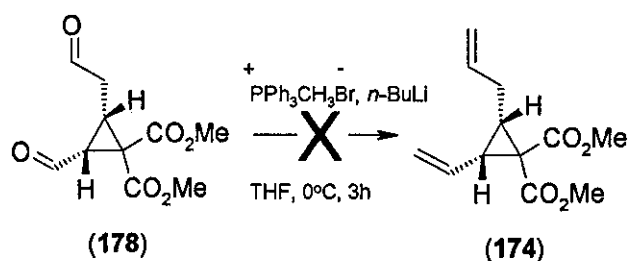
purification as the DMS could easily be removed by washing the crude product with copper(II) sulphate and brine, during work-up and increased the yields from 40 % to 70 %.

We were now just one step away from obtaining our first desired target. The Wittig reaction was the crucial step in the synthesis. Methyltriphenylphosphonium bromide and *n*-BuLi in THF were the reagents chosen to perform the reaction (**Scheme 42**).⁵³



Scheme 42: Attempted synthesis of allylvinylcyclopropane (199).

We also tried the Wittig reaction on the small amount of the 2-formyl-3-(2-oxoethyl)-cyclopropane-1,1-dicarboxylic acid dimethyl ester (178) we had previously formed (**Scheme 43**).



Scheme 43: Attempted synthesis of allylvinylcyclopropane (174).

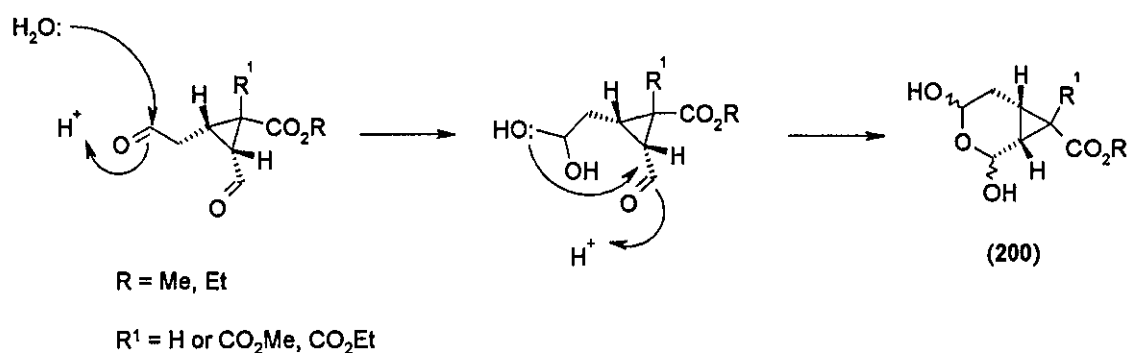
With both the mono ethyl ester and the dimethyl ester derivative, we saw no sign of our desired compound (**Table 3**).

Equiv. Wittig Reagent	Base	Equiv Base	Temperature	Time	Solvent	Yield
2	<i>n</i> -BuLi	2	0°C	3h	THF	Starting Material
2	<i>n</i> -BuLi	2	0°C	24h	THF	Decomposed
2	<i>n</i> -BuLi	2	-78°C	3h	THF	Decomposed
3	<i>n</i> -BuLi	3	0°C	3h	THF	Decomposed
3	<i>n</i> -BuLi	3	-78°C	24h	THF	Decomposed
3	<i>n</i> -BuLi	3	-78°C	20 min	THF	Starting Material
1	<i>n</i> -BuLi	1.2	-78°C	3h	THF	Starting Material
2	DBU	2	Reflux	3h	THF	Decomposed
2	DBU	2	Reflux	24h	THF	Decomposed

Table 3: Attempts at the Wittig reaction of the di-aldehyde (198).

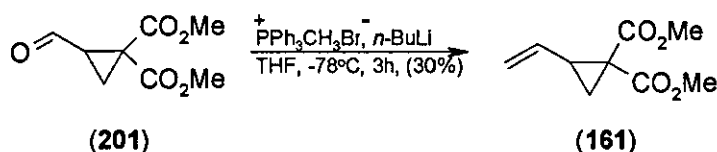
This proved to be a disappointing outcome for us. Numerous conditions were attempted and we investigated extensively different methods of forming the Wittig reagent *in situ*. The main problem we found was that under most conditions we saw almost complete degradation of starting material, with at best 5-10% being recovered, but no sign of the allylvinylcyclopropane target. We tried addition of 1 equivalent of the Wittig reagent, to investigate whether the reaction would occur on the most reactive alkene, but again we saw no reaction.

Due to the structure of the di-aldehyde compound we were using, we began to consider why the Wittig reaction may have been failing. We hypothesised that the di-aldehyde could in fact be forming the hydrated structure (200), with the presence of water. The formation of this structure could explain why we saw no sign of the desired allylvinylcyclopropane target. Though we had no spectroscopic data to support the formation of this product, it was a reasonable explanation for the failure of the Wittig reaction (Scheme 44).



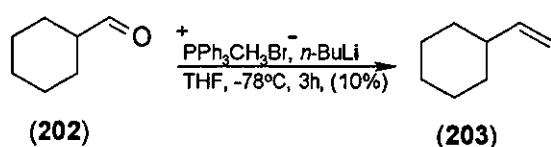
Scheme 44: Proposed formation of hydrated structure (200).

Though we had failed in our attempts to synthesise the allylvinylcyclopropane (**199**), we decided to look at the Wittig reaction in more detail. We wanted to be sure that the problem was with the substrate we were using and not with the methodology. With this in mind, we took simple vinylcyclopropane (**161**) and formed the mono-aldehyde derivative (**201**) *via* an ozonolysis reaction. We then looked to perform the Wittig reaction using the conditions we had previously investigated (**Scheme 45**).



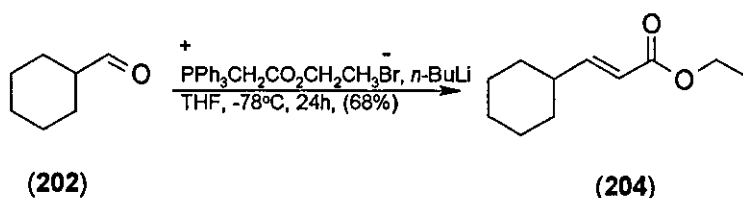
Scheme 45: Wittig reaction on simple mono-aldehyde (**201**).

We managed to isolate the Wittig product, but in a low yield of 30 %. So even though we managed to isolate the Wittig product, even on the simpler substrate we faced challenges. Next we decided to try the Wittig reaction on a more stable substrate, and chose cyclohexanecarboxaldehyde (**202**), as it was cheap, easy to handle and commercially available (**Scheme 46**).⁵⁴



Scheme 46: Wittig reaction of cyclohexanecarboxaldehyde (202).⁵⁴

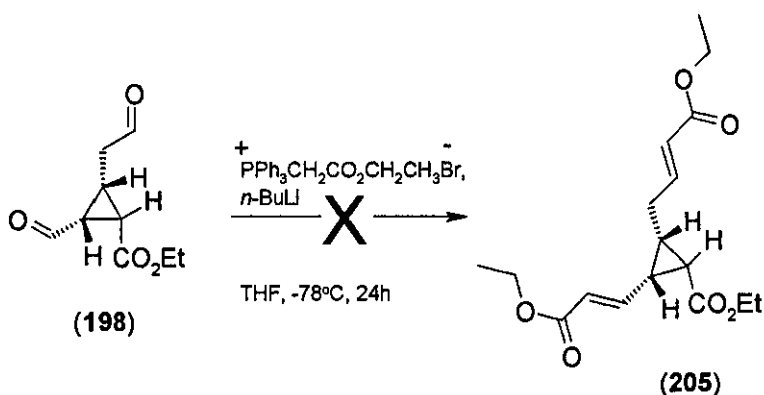
Disappointingly the highest yield we managed to obtain was only 10%. Again we investigated a variety of conditions, but were unable to increase the yield any higher. We decided to look at one more variable and that was the Wittig reagent itself. With all the previous reactions we had used an un-stabilised Wittig reagent and we were interested to see whether this was the reason for the low yields. We decided to try the reaction again using (carbethoxymethyl)triphenylphosphonium bromide, a stabilised Wittig reagent (Scheme 47).⁵⁵



Scheme 47: Wittig reaction of cyclohexanecarboxaldehyde using a stabilised Wittig reagent.⁵⁵

Through optimisation of the reaction conditions, we managed to isolate (204) in average yields of 68%. This was substantially higher than any of our previous attempts using the un-stabilised Wittig reagent.

Due to the success with the stabilised Wittig reagent, we decided to try this on the dialdehyde substrate (198) (Scheme 48).

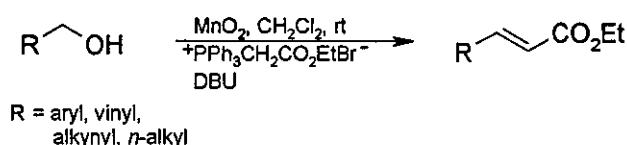


Scheme 48: Attempted Wittig reaction of 2-formyl-3-(2-oxoethyl)-cyclopropanecarboxylic acid ethyl ester (198)

Our initial attempts at this reaction again provided us with negative results. We recovered no starting material and there was no trace of the Wittig product. We concluded that a combination of the type of Wittig reagent used and also the substrate we were trying to perform the reaction on, contributed to our failed attempts at synthesising the allylvinylcyclopropane and we decided to look at an alternative route.

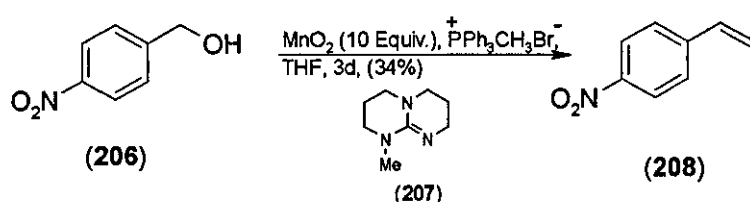
2.2 Synthesis of allylvinylcyclopropane – Part II:

Although disappointed that our original method had failed to yield us our desired target, research into the literature presented us with another possible route. Richard Taylor *et al.* had done extensive research in the area of *in situ* alcohol oxidation-Wittig reactions, being catalysed by manganese dioxide.^{56,57,58} They showed that this methodology could be applied to semi-activated and also un-activated alcohols, using stabilised phosphoranes (**Scheme 49**).⁵⁶



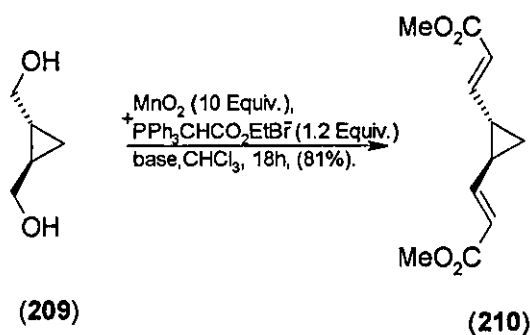
Scheme 49: Oxidation-Wittig reactions with stabilised phosphoranes.⁵⁶

Further research in this area by Taylor *et al.* found that the methodology could be applied to un-stabilised phosphoranes. They utilised previous work undertaken by Simoni *et al.*, where they had used a variety of guanidines to promote *in situ* Wittig reactions between non-stabilised phosphoranes and aldehydes.⁵⁹ Taylor *et al.* decided to use 1-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD) (**207**) in their *in situ* oxidation-Wittig reaction, and discovered that the reaction proceeded in a 34% yield, where in the absence of MTBD (**207**), the reaction had not yielded any of the desired product (Scheme 50).⁵⁶



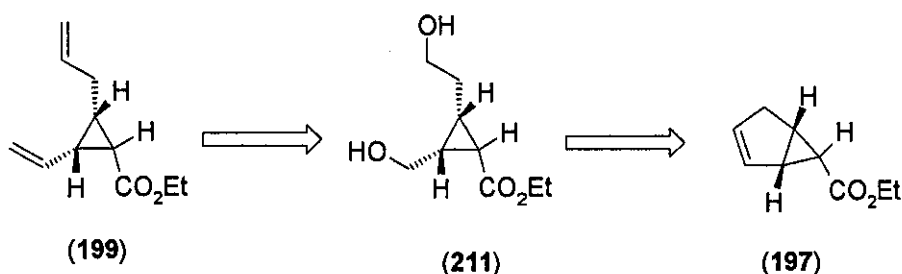
Scheme 50: Oxidation-Wittig reaction with un-stabilised phosphoranes.⁵⁶

What really interested us was the fact that this type of reaction had been successful on a variety of cyclopropane derivatives (Scheme 51).⁵⁷



Scheme 51: Oxidation-Wittig reactions of cyclopropanes.⁵⁷

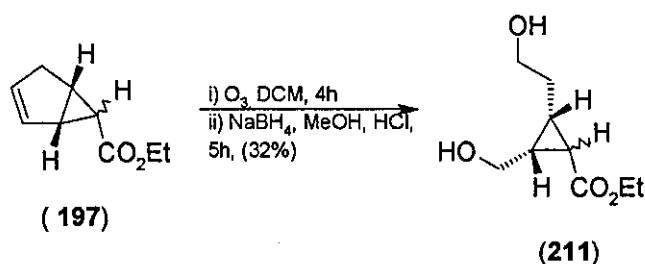
Though the reactions on the cyclopropanes had only been done using stabilised phosphoranes, we were keen to apply this methodology into our attempts of synthesising allylvinylcyclopropane (**199**) (Scheme 52).



Scheme 52: Proposed synthesis of allylvinylcyclopropane (199)

We hypothesised that we could do an ozonolysis on the bicyclic cyclopropane, but this time convert it to the diol (211), rather than the di-aldehyde. Then by using the methodology described by Taylor *et al.*, we would convert the diol into the target molecule. Even though Taylor *et al.* described using only stabilised phosphoranes on their cyclopropanes, we believed that we could perform the oxidation-Wittig reaction using the un-stabilised phosphorane in the presence of the guanidine derivative (207), which had been described by Taylor *et al.* to facilitate this particular reaction.^{56,57,58}

The first stage was to form the diol (211) (Scheme 53).

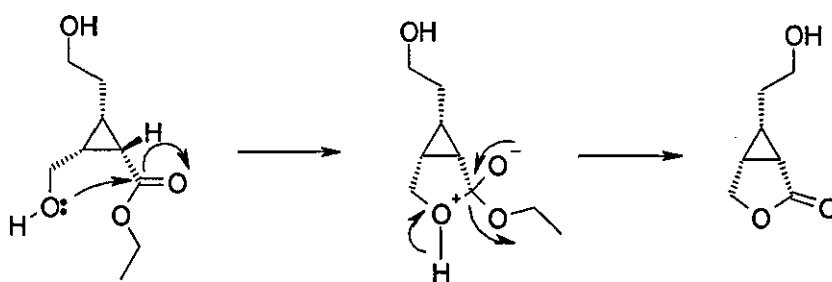


Scheme 53: Synthesis of 2-(2-hydroxyethyl)-3-hydroxymethyl-cyclopropanecarboxylic acid ethyl ester (211).

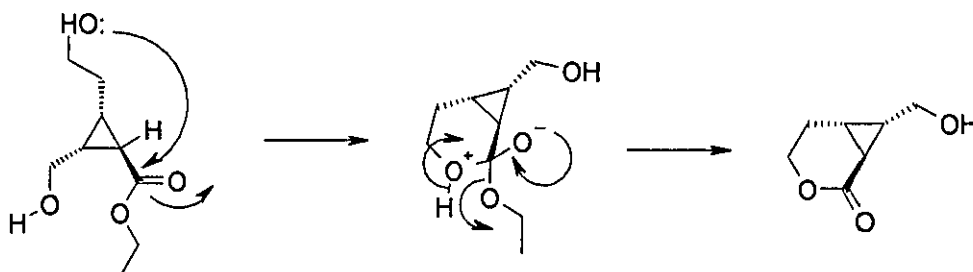
Frustratingly we found the yields of our desired compound were relatively low, particularly as we expected the reaction to proceed quantitatively. We investigated a variety of conditions, including altering the reaction time and looked at using ethanol in the work up instead of methanol, but this had no real effect on increasing the yield. Closer inspection of the ^1H NMR data led us to believe that there was a competing reaction occurring. The loss of the normal CH_3CH_2 splitting pattern we observed for the

ethyl ester and an appearance of a stretch in the IR at 1755cm^{-1} , suggested to us that the diol, once formed, was undergoing a lactonisation reaction, which would explain why we were seeing lower yields than we expected. The size of the lactone ring would be determined by the stereochemistry at the cyclopropane ring. If the diol was *cis*, we would see the formation of a 5-membered lactone ring, but if the stereochemistry was *trans*, we would see the formation of a 6-membered lactone ring (**Scheme 53**).

5-Membered Lactone:

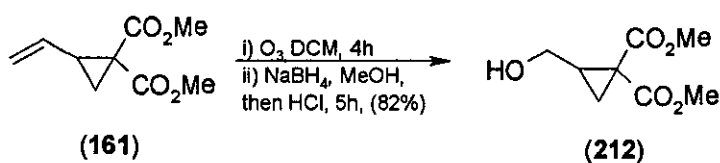


6-Membered lactone:



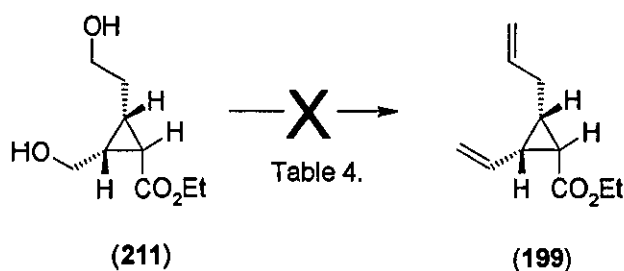
Scheme 53: Proposed lactonisation of 2-(2-hydroxyethyl)-3-hydroxymethyl-cyclopropanecarboxylic acid ethyl ester (**211**).

We decided to test our theory that it was the competing lactonisation causing the low yields, by doing a test reaction on the simpler analogue. We took vinylcyclopropane (**161**), performed the ozonolysis, and again treated this with NaBH_4 and methanol and saw a dramatic increase in yield (**Scheme 54**).



Scheme 54: Test reaction on vinylcyclopropane (161).

Though the yields of the diol substrate were low, we decided to press on and investigate the oxidation-Wittig reaction (**Scheme 55**).



Scheme 55: Attempted synthesis of allylvinylcyclopropane (199).

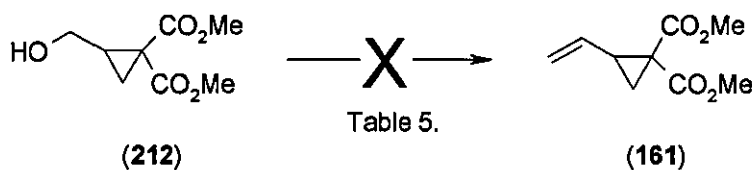
To our disappointment we were unable to synthesise our desired target, often with complete degradation of starting material to an unidentifiable black oil (**Table 4**).

Solvent	Base	Temperature	Time	Yield
CHCl ₃	Guanidine (207)	Reflux	18h	N/A
CHCl ₃	Guanidine (207)	Reflux	6h	N/A
CHCl ₃	Guanidine (207)	Reflux	3h	15% SM
CHCl ₃	Guanidine (207)	RT	18h	SM
CHCl ₃	Guanidine (207)	RT	3d	N/A
DCM	Guanidine (207)	Reflux	18h	N/A
DCM	Guanidine (207)	Reflux	6h	N/A
CHCl ₃	DBU	Reflux	18h	N/A
DCM	DBU	Reflux	18h	N/A
THF	DBU	RT	18h	SM
THF	DBU	RT	3d	N/A

Table 4: Attempted *in situ* oxidation-Wittig reaction.

A variety of conditions were looked at, mostly based around the work already done by Taylor *et al.*^{56,57,58} Even though they had not specifically done the reaction on our substrate, we were still hopeful of applying their methodology to our specific cyclopropane derivative. The initial conditions of refluxing for 18 hours saw complete decomposition of starting material and no sign of our desired target. Even after 3 hours of reflux, we recovered <15% of the starting material, with the rest of the starting material being decomposed. This led us to believe that the diol was particularly sensitive, so we decided to try the reaction at room temperature. After 18 hours, we recovered only starting material, so decided to leave the reaction time longer. Though after 3 days there was complete decomposition of starting material and no trace of our desired target.

We decided to test the viability of the oxidation-Wittig reaction on a much simpler substrate, to see if it was the more complex diol that was causing the reaction not to work. We decided to look at 2-hydroxymethyl-cyclopropane-1,1-dicarboxylic acid dimethyl ester (**212**), due to its structural similarities but distinct difference being just the mono-alcohol (**Scheme 56**).



Scheme 56: Attempted oxidation-Wittig reaction.

Interestingly, even on the simpler substrate we were still unable to yield the vinylcyclopropane. Again complete decomposition of starting material was observed (**Table 5**).

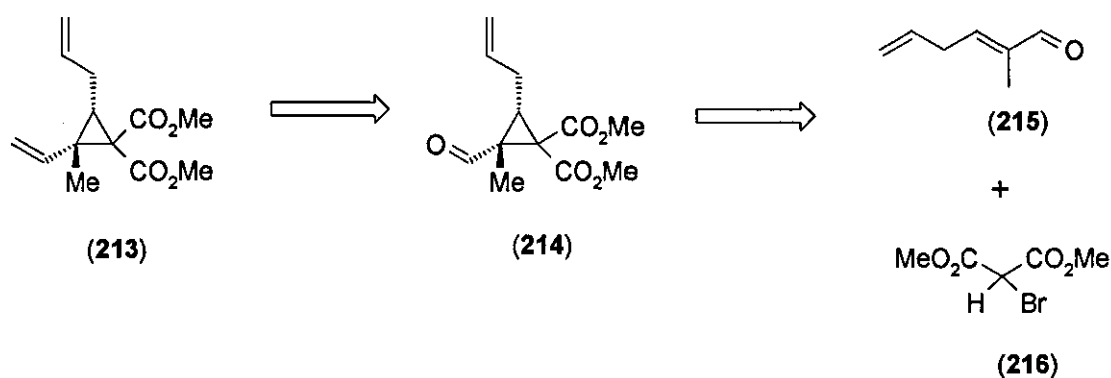
Solvent	Base	Temperature	Time	Yield
CHCl ₃	Guanidine (207)	Reflux	18h	N/A
CHCl ₃	Guanidine (207)	Reflux	6h	N/A
CHCl ₃	Guanidine (207)	Reflux	3h	26% SM
CHCl ₃	Guanidine (207)	RT	3d	35% SM
DCM	Guanidine (207)	Reflux	18h	N/A
CHCl ₃	DBU	Reflux	18h	N/A
DCM	DBU	Reflux	18h	N/A

Table 5: Attempted *in situ* oxidation-Wittig reaction.

Though we did not look into this reaction as extensively as we had done on the diol substrate, the conditions we tried gave us a clear picture that this route towards the allylvinylcyclopropane (**199**) was not going to be successful. It was decided that an alternative route towards our desired target should be looked at.

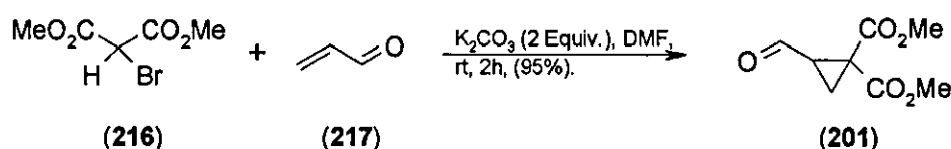
2.3 Synthesis of allylvinylcyclopropane – Part III:

We decided to look at a different approach in our pursuit of the allylvinylcyclopropane target. We believed that allylvinylcyclopropane derivative (**213**) would be an ideal target. Not only would the presence of the methyl group leave us in an ideal position to prevent dehydropalladation occurring early when it came to looking at the cascade reaction, but we hoped the mono aldehyde derivative would prove less problematic when it came to the Wittig reaction. We believed the target could be prepared by a Wittig reaction of the mono aldehyde derivative (**214**). We would construct this mono aldehyde derivative by doing a selective cyclopropanation *via* a Michael addition reaction of dimethyl bromomalonate (**216**) on alkadienal (**215**) (Scheme 57).



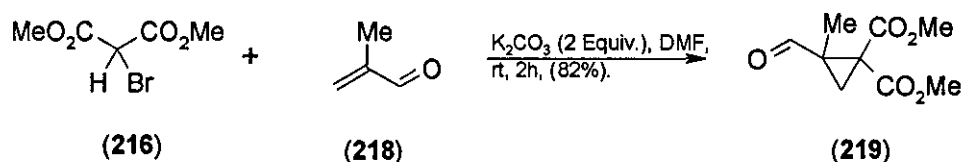
Scheme 57: Proposed synthesis of allylvinylcyclopropane derivative (213).

Research into the literature revealed methods of selectively cyclopropanating conjugated alkenes *via* a Michael addition reaction.⁶⁰ We re-tried the literature methodology and achieved excellent yields, particularly by using an excess of acrolein, which ensured all the dimethylbromomalonate was used in the reaction and due to the high volatility of acrolein, any excess was removed *in vacuo* to yield the pure product (Scheme 58).⁶⁰



Scheme 58: Synthesis of 2-formylcyclopropane-1,1-dicarboxylic acid dimethyl ester (201).⁶⁰

The literature also reported selective cyclopropanations of conjugated systems where the methyl group we required was present. Again we were able to re-produce the results reported, obtaining excellent yields (Scheme 59).⁶⁰



Scheme 59: Synthesis of 2-Formyl-2-methyl-cyclopropane-1,1-dicarboxylic acid dimethyl ester (219).⁶⁰

Spangler *et al.* had reported an efficient method into synthesising alkadienals, valuable intermediates in a variety of synthetic applications.⁶¹ In particular they had synthesised 2-methylhexa-2,5-dienal (**220**) (Figure 9). This was the ideal substrate for us to investigate the Michael addition reaction and construct the mono aldehyde derivative (**214**) we required.

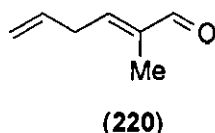
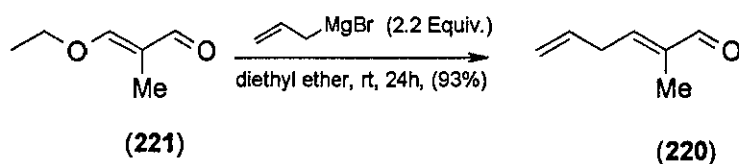


Figure 9: 2-methylhexa-2,5-dienal (**220**).

Our first step was to synthesise the alkadienal. This was achieved by reacting 3-ethoxymethacrolein (**221**) with a suitable Grignard reagent (Scheme 60).⁶¹



Scheme 60: Synthesis of 2-methylhexa-2,5-dienal (**220**).⁶¹

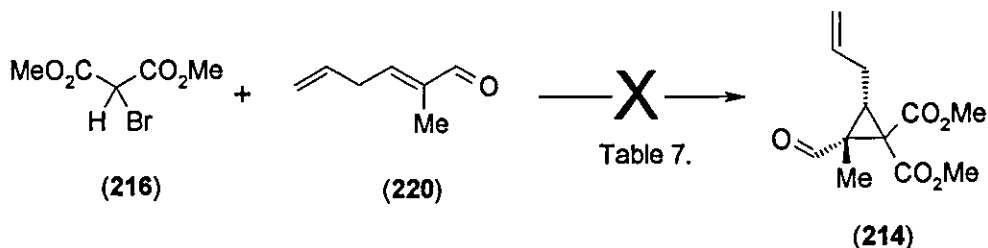
Initially we tried the reaction on small scales and we observed unacceptable low yields. We discovered that by increasing the scale of the reaction and freshly preparing the Grignard reagent *in situ*, led to the reaction yields rising to an excellent 93% of the alkadienal on a 5 g scale (Table 6).

Scale	Equiv Grignard	Solvent	Time	Yield
200 mg	1.1	THF	15 min	N/A
200 mg	1.1	Ether	15 min	20%
200 mg	2.2	Ether	24 h	N/A
500 mg	2.2	Ether	24 h	7 %
500 mg	2.2	Ether	24 h	21% ^a
200 mg	2.2	Ether	24 h	16% ^a
5.00 g	2.2	Ether	24 h	93% ^a

a: Grignard reagent was prepared fresh. See experimental for procedure.

Table 6: Attempted synthesis of 2-methylhexa-2,5-dienal (**220**).

Next our attention turned towards the Michael addition of dimethyl bromomalonate (**213**) and 2-methylhexa-2,5-dienal (**220**) (Scheme 61).⁶⁰



Scheme 61: Attempted synthesis of 3-allyl-2-formyl-2-methylcyclopropane-1,1-dicarboxylic acid dimethyl ester (**214**).⁶⁰

We were unable to isolate our desired target. The table below summarises the attempted synthesis (Table 7).

Equiv (220)	Equiv Nucleophile	Base	Equiv Base	Solvent	Time	Yield
1	1.1	K ₂ CO ₃	1	Acetone	4h	SM
1	1.1	K ₂ CO ₃	1	Acetone	24h	SM
1	1.1	K ₂ CO ₃	1	DMF	4h	SM
1	1.1	K ₂ CO ₃	1	DMF	24h	SM
1	1.1	K ₂ CO ₃	1	CH ₃ CN	24h	SM
1	1.1	K ₂ CO ₃	1	DCM	24h	SM
1.2	1	K ₂ CO ₃	2	Acetone	24h	SM
1.2	1	K ₂ CO ₃	2	DMF	24h	SM
1.2	1	K ₂ CO ₃	2	DCM	24h	SM
1.2	1	K ₂ CO ₃	2	DMF	24h	SM ^a
1.2	1	K ₂ CO ₃	2	Acetone	24h	SM ^a
1.2	1	K ₂ CO ₃	2	DCM	24h	SM ^a
1.2	1	DBU	2	DMF	24h	SM
1.2	1	DBU	2	Acetone	24h	SM
1.2	1	DBU	2	DCM	24h	SM
1.2	1	Et ₃ N	2	DMF	24h	SM
1.2	1	Et ₃ N	2	DCM	24h	SM
1.2	1	NaOMe	2	DMF	24h	SM
1.4	1	NaOMe	2	DMF	24h	SM
1.2	1	K ₂ CO ₃	1	Acetone	48h	SM
1.2	1	K ₂ CO ₃	1	DCM	48h	SM
1.2	1	NaOMe	2	DMF	48h	SM
1.4	1	NaOMe	2	DMF	48h	SM

a: Reaction carried out with 1.2 equiv of Lewis Acid (ZnCl₂).

Table 7: Attempted synthesis of allylcyclopropane derivative (214).

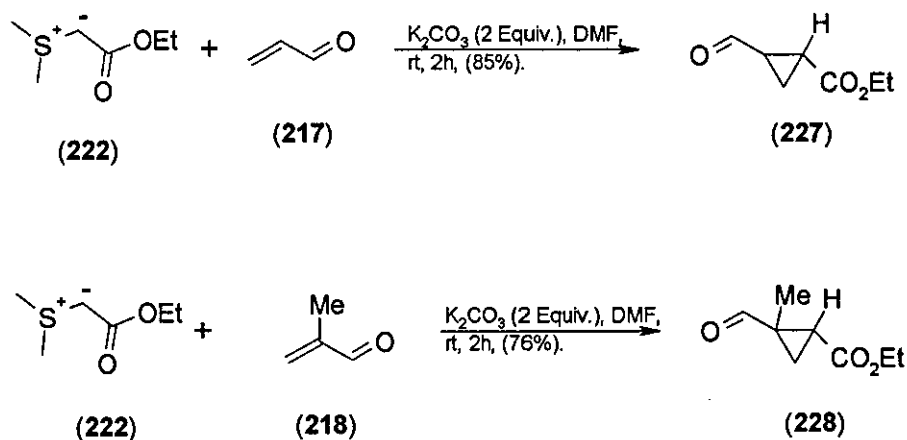
We investigated several variables in an attempt to construct the mono aldehyde target. Several bases were investigated to explore the possibility that deprotonation of the dimethyl bromomalonate was not occurring.^{62,63} This had no effect on the reaction, with starting material still being recovered. We also looked at including a Lewis acid into the reaction. The theory behind this was that we thought it would co-ordinate to the methyl ester groups of dimethyl bromomalonate (216) and make the hydrogen even more acidic and help facilitate deprotonation. Unfortunately this did not have the desired effect either.

Having seemingly exhausted all of our options, we thought about the possibility of using a sulphur ylide derivative⁶⁴ in place of the dimethyl bromomalonate. We decided to use the mono ethyl ester sulphur ylide derivative (**222**), as the di-methyl ester sulphur ylide, derived from malonate, would be far too stable, due to the negative charge being readily stabilised through resonance and hinder the nucleophilic addition we required (**Scheme 62**).



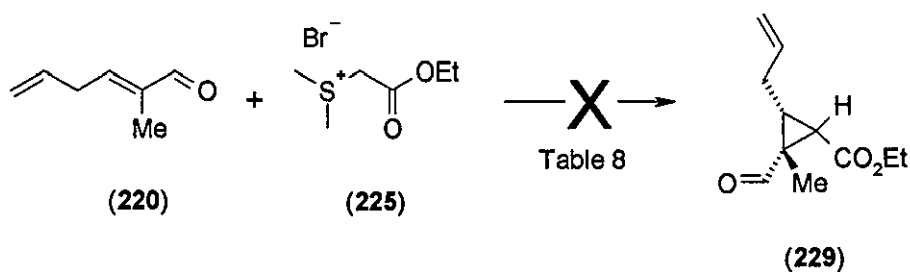
(226) $\xrightarrow[\text{rt, 22h, (90\%)}]{\text{DMS, acetone}}$ (225)

We tested the viability of this alternative by first trying the cyclopropanation reaction on acrolein and methacrolein (**Scheme 64**).



Scheme 64: Selective cyclopropanation using sulphur ylide (222) on acrolein (217) and methacrolein (218).

With the sulphur ylide successfully cyclopropanating on the simpler substrates, we attempted the conjugate addition reaction on the alkadienal (Scheme 65).



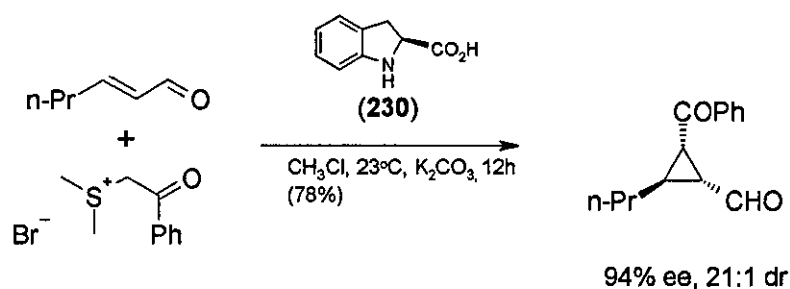
Scheme 65: Attempted conjugate addition reaction using ethoxycarbonylmethyl-dimethylsulfonium (225).

Again we saw no sign of the conjugate addition product and like before with dimethyl bromomalonate as the nucleophile, starting material was recovered. The table below summarises our attempts at this reaction (Table 8).

Equiv (220)	Equiv Nucleophile	Base	Equiv Base	Solvent	Time	Yield
1	1.1	K ₂ CO ₃	1	Acetone	4h	SM
1	1.1	K ₂ CO ₃	1	Acetone	24h	SM
1	1.1	K ₂ CO ₃	1	DMF	24h	SM
1	1.1	K ₂ CO ₃	1	CH ₃ CN	24h	SM
1	1.1	K ₂ CO ₃	1	DCM	24h	SM
1.2	1	K ₂ CO ₃	2	DMF	24h	SM
1.2	1	K ₂ CO ₃	2	DCM	24h	SM
1.2	1	DBU	2	DMF	24h	SM
1.2	1	DBU	2	DCM	24h	SM
1.2	1	Et ₃ N	2	DMF	24h	SM
1.2	1	NaOMe	2	DMF	24h	SM

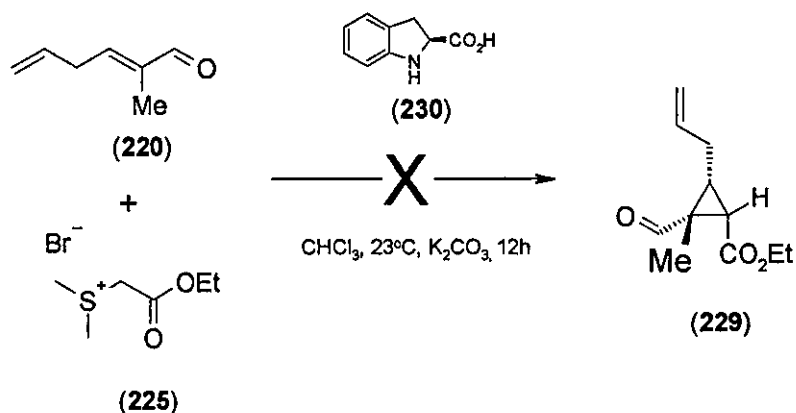
Table 8: Attempts at conjugate addition reaction.

By this time it seemed we had seemingly exhausted all of our options, but a paper came to our attention where they had been looking at similar conjugate addition reactions involving sulphur ylides and had used 2-carboxylic acid dihydroindole (**230**) to catalyse these reactions (Scheme 66).⁶⁵



Scheme 66: Conjugate addition reaction catalysed by 2-carboxylic acid dihydroindole.⁶⁵

With this in mind we decided to have one final attempt at the conjugate addition reaction, using the sulphur ylide (Scheme 67).

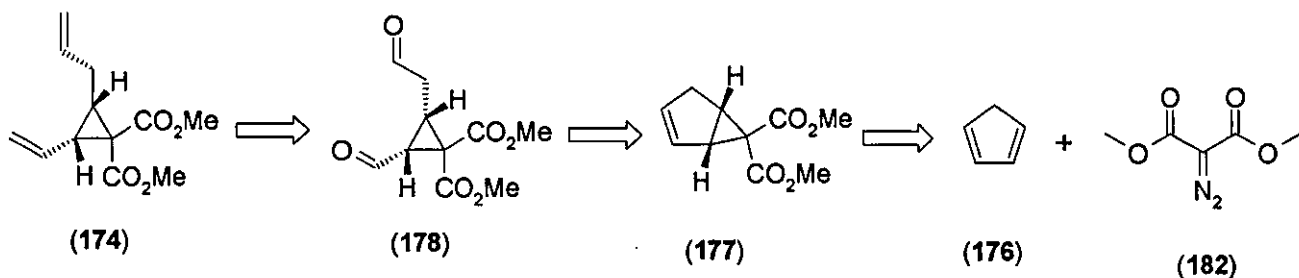


Scheme 67: Attempted synthesis of allylvinylcyclopropane skeleton (229).

Again we found the reaction was not successful. Only starting material was recovered. At this stage we decided we had exhausted most of our options in trying to synthesise the allylvinylcyclopropane target. We found no conclusive evidence as to why the methods we tried failed on our chosen substrates, though we have shown the methodology in most cases does work, by applying it to simpler analogues.

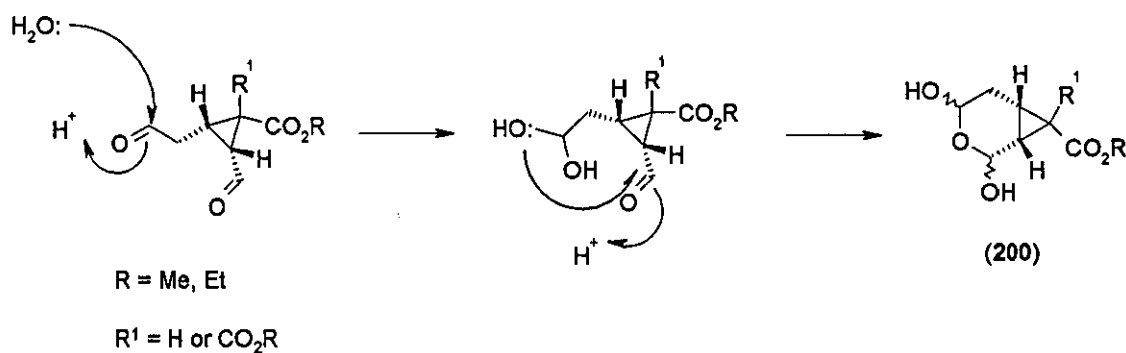
2.4 Conclusion:

We have investigated several different routes towards our allylvinylcyclopropane target. In the original route we first proposed, we faced huge challenges with the di-aldehyde compound (178) not undergoing the desired Wittig reaction to form allylvinylcyclopropane (174) (Scheme 68).



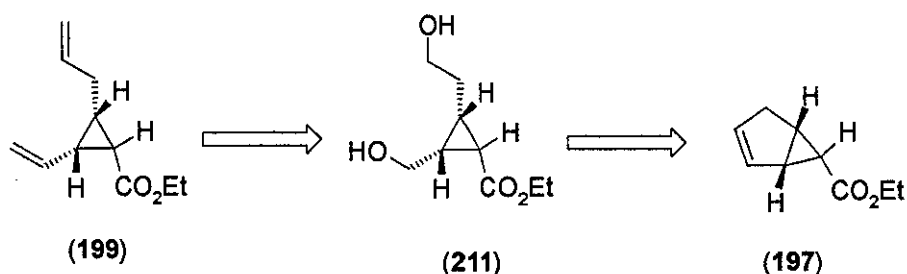
Scheme 68: Original route towards allylvinylcyclopropane (174).

We proposed the formation of a hydrated structure (200) as a possible explanation as to why the Wittig reaction failed (Scheme 69).



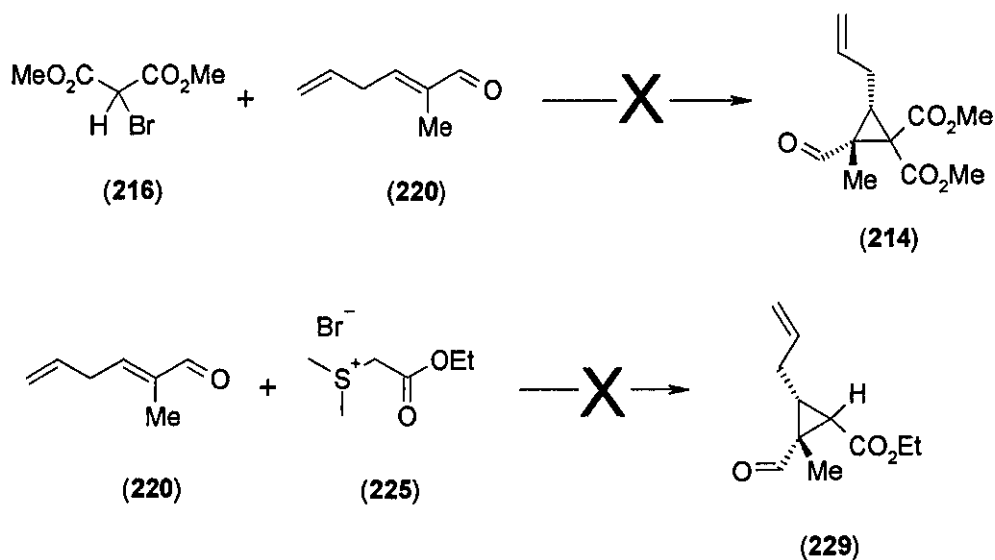
Scheme 69: Formation of hydrated structure (200).

Investigations into forming diol (211) instead of the di-aldehyde also proved fruitless. With the proposed oxidation-Wittig reaction going from diol (211) to the allylvinylcyclopropane derivative (199) in one step not yielding us our desired target. A competing lactonisation reaction involving the diol compound was another factor we proposed as to why the reaction may have been failing (Scheme 70).



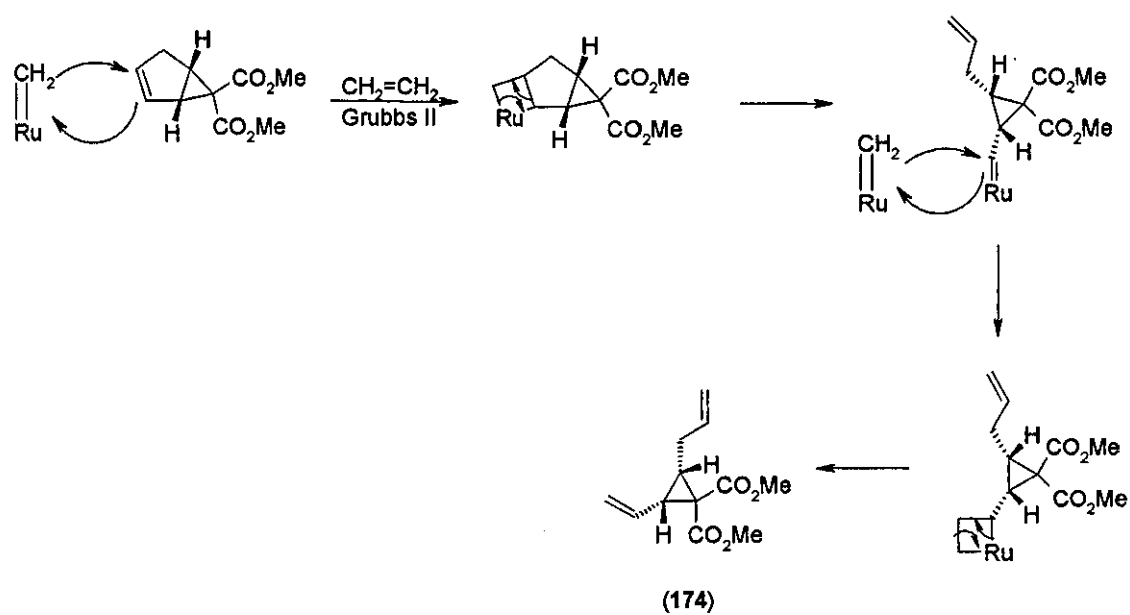
Scheme 70: Proposed route towards allylvinylcyclopropane target (199).

A third route involving a conjugate addition reaction of dimethyl bromomalonate onto an alkadienal, also proved fruitless. Only starting material was recovered, despite several options being investigated (**Scheme 71**).



Scheme 71: Attempts at the conjugate addition to form cyclopropane targets.

Within this investigation we had looked into a variety of alternative routes towards our target. Though we had been unsuccessful in our attempts, there were still other options available for constructing the allylvinylcyclopropane. One of these options was olefin metathesis utilising Grubb's second generation catalyst. We could start from the bi-cyclic cyclopropanes (177 or 197) and then use Grubb's catalyst to perform a ring opening metathesis reaction and deliver us our desired target allylvinylcyclopropane (174 or 199) (**Scheme 72**).

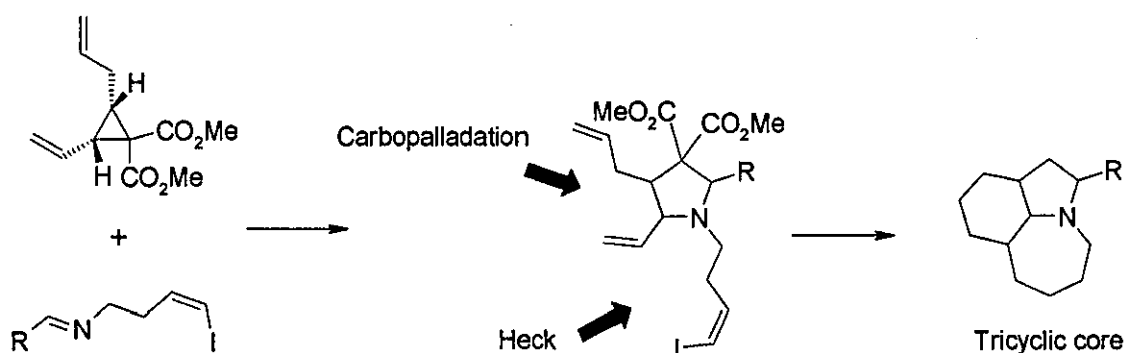


Scheme 72: Proposed formation of allylvinylcyclopropane (174) by olefin metathesis.

Chapter 3 - Carbopalladation/Heck Chemistry.

3.1 Investigations into the cascade reaction:

Though we were disappointed that we had faced serious challenges in our pursuit of the allylvinylcyclopropane, which meant that we could not look directly at synthesising the azepinoindole core, we were still very interested in investigating the key Heck/carbopalladation cascade step. In the original route towards the tricyclic core, this was the key stage of the synthesis that would construct the 7 and 6 membered rings in a single step (Scheme 73).



Scheme 73: Original route towards the tricyclic core involving a Heck/carbopalladation cascade step.

We decided to investigate this cascade step by constructing a suitable substrate that would allow us to explore the viability of this reaction. We chose 2-(2-bromophenyl)-1-(2-methylallyl)-5-vinylpyrrolidine-3,3-dicarboxylic acid dimethyl ester (**231**) (Figure 10) as an ideal precursor to the cascade step. The presence of the methyl group on the allyl moiety would prevent dehydropalladation from occurring early, and hopefully drive the carbopalladation step to completion, thus synthesising two rings in a single step. The size of the rings constructed would obviously depend on whether the Heck/carbopalladation steps, proceeded *endo* or *exo*. This would provide an excellent insight into the viability of this one-pot procedure.

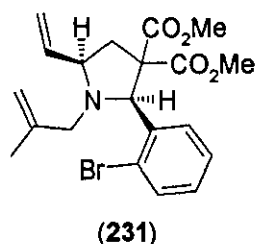
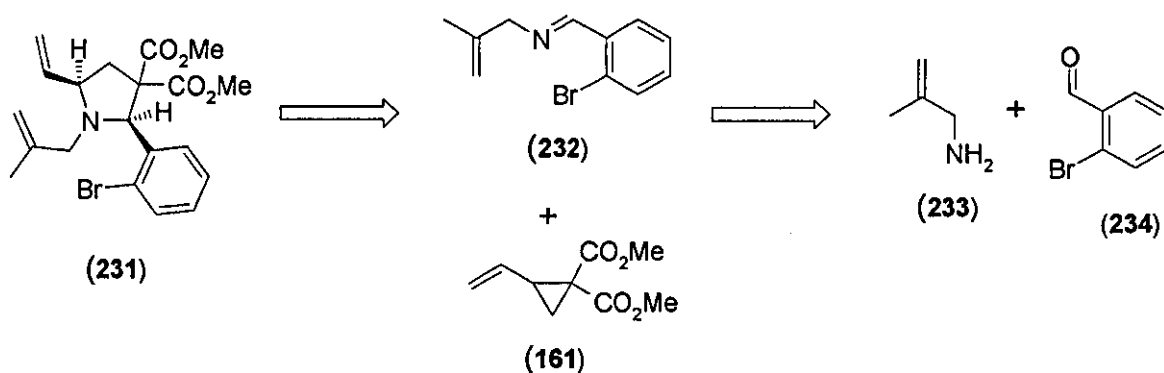


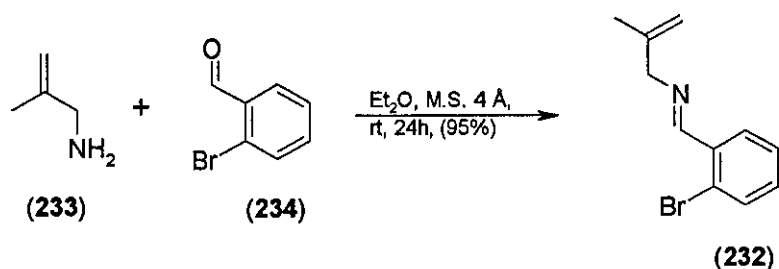
Figure 10: Substrate chosen to investigate viability of cascade reaction.

We envisaged utilising the palladium catalysed [2+3] cycloaddition chemistry previously developed within the group to construct pyrrolidine (231).^{37,38,39,42} With this in mind, preparing imine (232), from simple building blocks such as bromo-benzaldehyde (234) and methylallylamine (233) and reacting this with vinylcyclopropane (161) would achieve the target molecule. The imine derived from methylallylamine (233) was chosen because the inclusion of the methyl group on the allyl moiety would stop dehydropalladation from occurring early, when it came to investigating the cascade reaction (Scheme 74).



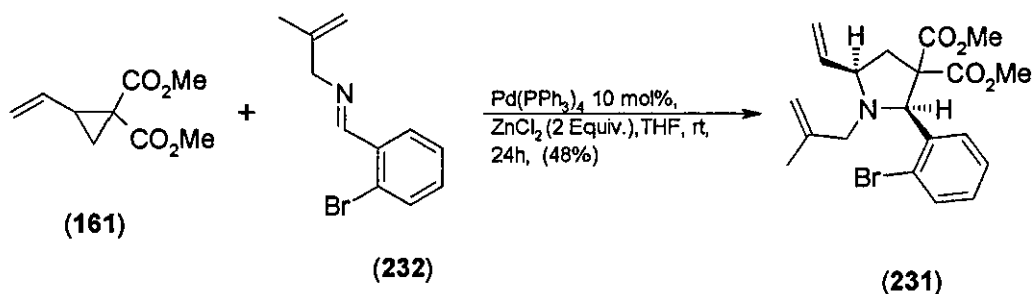
Scheme 74: Proposed synthesis of pyrrolidine (231).

The first step in the synthesis was to prepare the imine using conditions that had been optimised previously within the group.^{38,39} This condensation reaction between an amine and aldehyde was a simple high yielding procedure (Scheme 75).



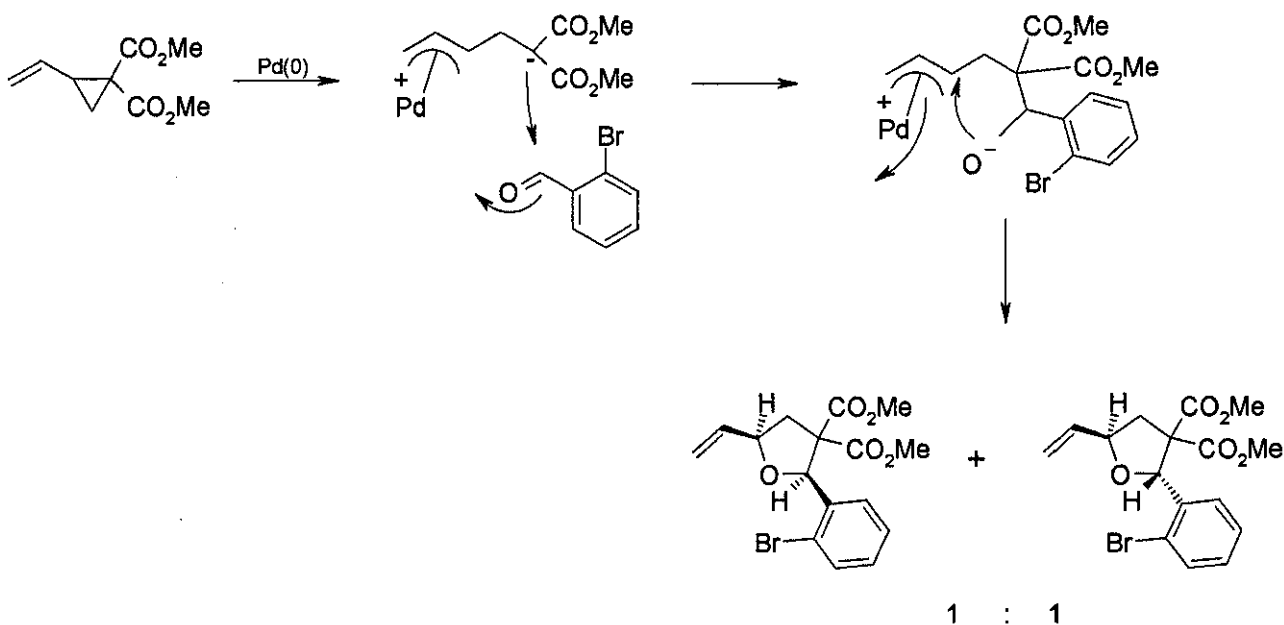
Scheme 75: Preparation of (2-bromobenzylidene)-(2-methylallyl)amine (232).

The next stage was to react imine (232) with vinylcyclopropane (161), using the palladium catalysed [2+3] cycloaddition chemistry developed within the group, to deliver us our desired pyrrolidine target (231) (Scheme 76).



Scheme 76: Synthesis of 2-(2-bromophenyl)-1-(2-methylallyl)-5-vinylpyrrolidine-3,3-dicarboxylic acid dimethyl ester (231).

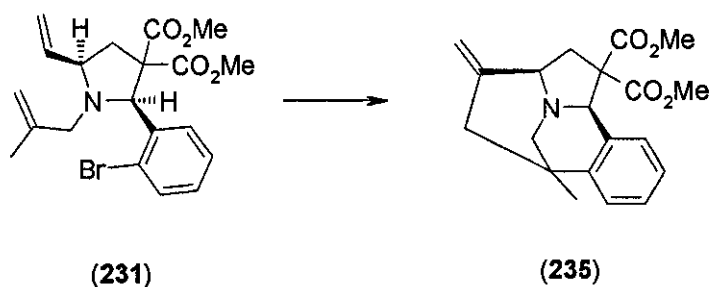
We were pleased to see that the reaction was stereoselective and yielded us the *cis* isomer exclusively. The yield was relatively low though and this was because the imine was hydrolytically sensitive and readily reverted back to the starting material benzaldehyde and amine. This meant that the 2-bromobenzaldehyde was in direct competition with the imine and we were isolating approximately 30-40% of the furan product as well as the required pyrrolidine (231) (Scheme 77).



Scheme 77: Formation of furan by-product when vinylcyclopropane trapped with 2-bromobenzaldehyde.

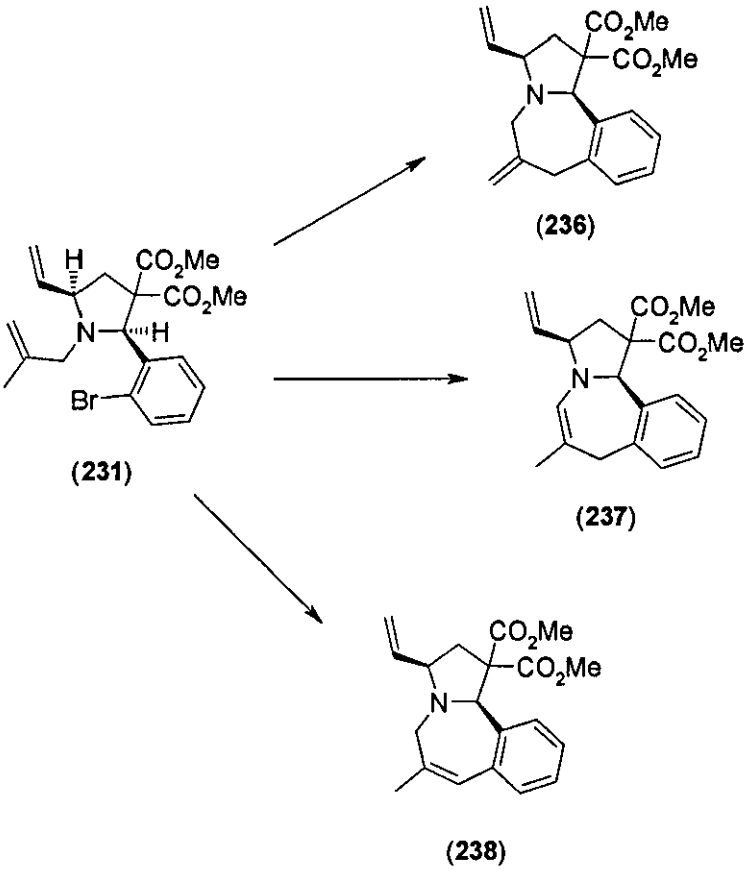
The hydrolytically sensitive nature of the imine highlighted the need for it to be freshly prepared and used in the [2+3] cycloaddition reaction immediately, in order to reduce the competing reaction that occurs with 2-bromobenzaldehyde, when the imine begins to hydrolyse back to the starting materials.

Now that we had usable amounts of the pyrrolidine compound in hand, our attention turned towards the cascade reaction. If the cascade reaction was successful, we would isolate compound (**235**), which would see the formation of two 6-membered rings in a single step (**Scheme 78**).



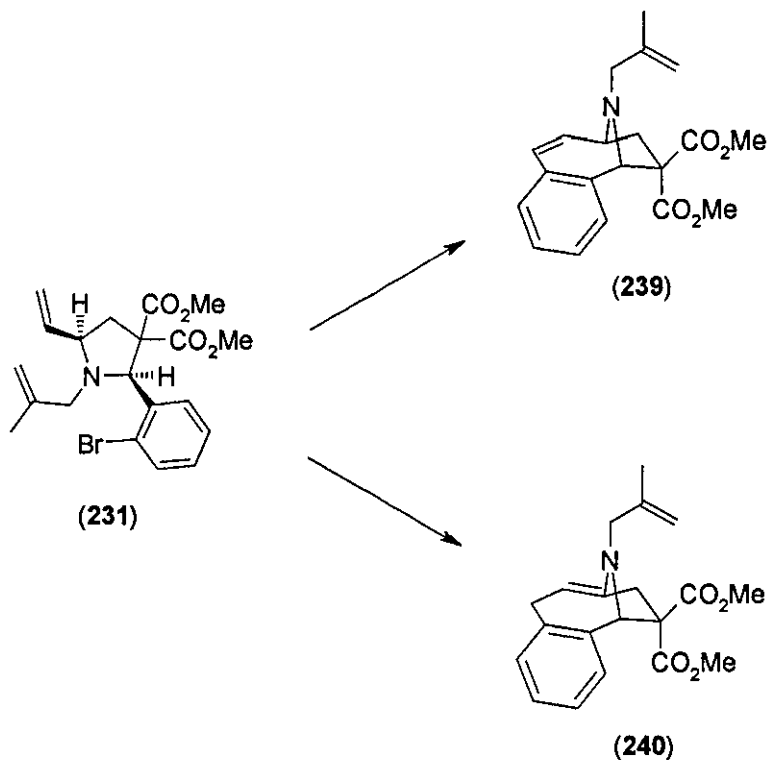
Scheme 78: Proposed formation of cascade compound (**235**).

But due to the complexity of the reaction, there were also a number of different possible compounds that could be isolated, depending on which alkene the palladium would react with first. There was a chance that the palladium could insert into the allyl alkene moiety and for dehydropalladation to occur early, despite the presence of the methyl group to prevent this and give rise to 3 possible structures (Scheme 79).



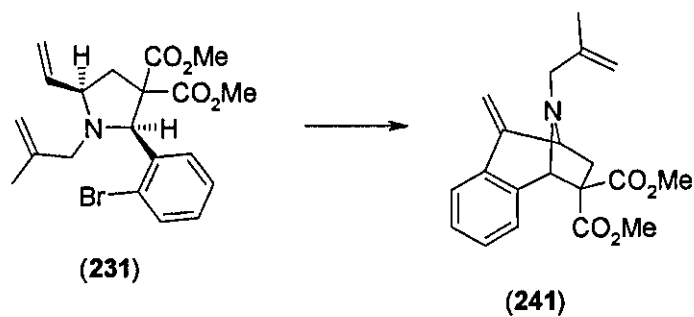
Scheme 79: Structural possibilities if Heck cyclisation occurs *via* a 7-endo trig pathway on the allyl alkene moiety.

There was also the possibility of the Heck cyclisation occurring *via* the same 7-*endo trig* pathway, but this time reacting with only the vinyl moiety and giving rise to another 2 possible structural outcomes (**Scheme 80**).



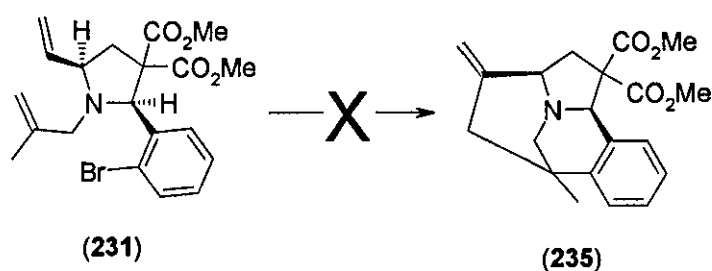
Scheme 80: Structural possibilities if Heck cyclisation occurs *via* a 7-*endo trig* pathway on the vinyl moiety.

Finally the Heck cyclisation could again react with the vinyl group solely, but this time follow a 6-*exo trig* pathway and give yet another product (**Scheme 81**).



Scheme 81: Structural possibility if Heck cyclisation occurs *via* a 6-*exo trig* pathway on the vinyl moiety.

As highlighted above, this reaction was never going to be a simple procedure and as we might have expected we faced challenges and our initial attempts did not yield us our desired cascade product (**Table 9**).



Pd (0) Source	Base	Equiv Base	Solvent	Temperature	Time	Yield
Pd(PPh ₃) ₄	NEt ₃	-	-	90°C	24 h	SM
Pd(PPh ₃) ₄	NEt ₃	-	-	90°C	48 h	SM
Pd(PPh ₃) ₄	NEt ₃	-	-	90°C	72 h	SM
Pd(PPh ₃) ₄	NEt ₃	-	-	120°C	24 h	SM
Pd(PPh ₃) ₄	NEt ₃	-	-	120°C	48 h	SM
Pd(PPh ₃) ₄	NEt ₃	-	-	120°C	72 h	SM
Pd(PPh ₃) ₄	NEt ₃	2	CH ₃ CN	120°C	48 h	SM
Pd(PPh ₃) ₄	NEt ₃	2	DMF	120°C	48 h	SM
Pd(PPh ₃) ₄	NEt ₃	5	CH ₃ CN	120°C	48 h	SM
Pd(PPh ₃) ₄	NEt ₃	5	DMF	120°C	48 h	SM
Pd ₂ (dba) ₃ .CHCl ₃	NEt ₃	-	-	120°C	24 h	SM
Pd ₂ (dba) ₃ .CHCl ₃	NEt ₃	2	CH ₃ CN	120°C	48 h	SM
Pd ₂ (dba) ₃ .CHCl ₃	NEt ₃	2	DMF	120°C	48 h	SM
Pd ₂ (dba) ₃ .CHCl ₃	NEt ₃	5	DMF	120°C	48 h	SM
Pd ₂ (dba) ₃ .CHCl ₃	NEt ₃	5	DMF	120°C	72 h	SM
Pd(OAc) ₂	^t PrNEt ₂	2	DMF	200°C	24 h	SM
Pd(OAc) ₂	^t PrNEt ₂	2	DMF	200°C	48 h	SM

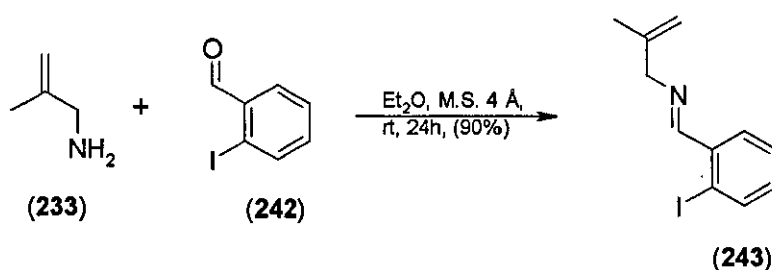
Note: 10 mol% of Pd(0) was used in all reactions.

Table 9: Attempted Heck/carbopalladation reaction.

We investigated various reaction conditions in an attempt to achieve the one pot cascade reaction. Due to the huge number of variables involved in the Heck reaction itself, we could not possibly investigate every single factor that might have had an effect on the reaction, but chose to concentrate on what we felt might have a decisive outcome on the reaction. With this in mind we concentrated on looking at the Pd(0) source, time, temperature and base and solvent combinations.⁶⁶ Unfortunately altering these had no impact on the success of the reaction, and we still recovered starting material, even after 3 days of reflux in some cases.

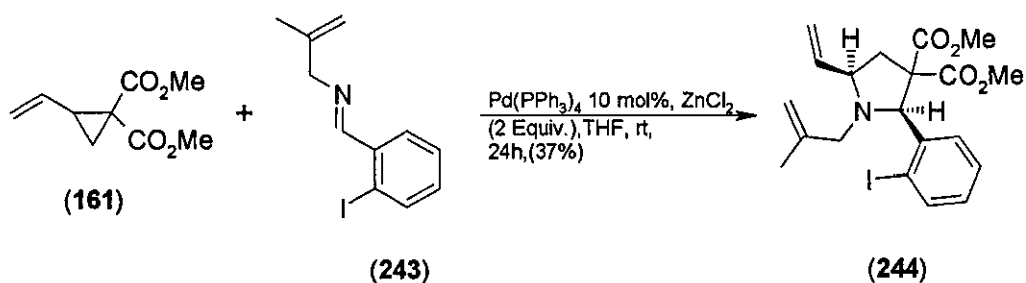
At this stage we felt it would be more worthwhile to look at other options instead of spending time investigating the endless list of potential reaction conditions we could use. With this in mind, we decided to make a slight alteration to our chosen substrate, and instead of the bromine pyrrolidine derivative, we would construct the iodine analogue. The thought being that the palladium would insert easier into a C-I bond than a C-Br bond.⁶⁶ The fact that we were recovering starting material from all of our reactions, led us to believe that the palladium may not be inserting into the C-Br bond and that this alteration to the substrate might lead us to a more positive outcome.

As with the previous synthesis of pyrrolidine (**231**) we would follow the exact same route. Therefore imine (**243**) was freshly prepared from 2-methylallylamine (**233**) and 2-iodobenzaldehyde (**242**) (Scheme 82).



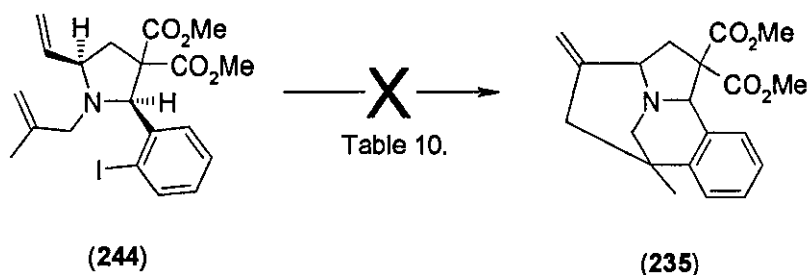
Scheme 82: Synthesis of 2-methylallyl-(2-methylbenzylidene)-amine (**243**).

As before the imine formation was a simple, high yielding reaction. Due to our past experience with these types of compounds and their hydrolytically sensitive nature, we immediately reacted the imine with vinylcyclopropane (**161**) to form the desired pyrrolidine analogue (**244**) *via* the group's palladium catalysed [2+3] cycloaddition reaction (Scheme 83).



Scheme 83: Synthesis of 2-(2-iodophenyl)-1-(2-methylallyl)-5-vinylpyrrolidine-3,3-dicarboxylic acid dimethyl ester (**244**).

We found the yield again was relatively low and this was still to do with the competing reaction that occurred with 2-iodobenzaldehyde (**242**) to form the undesired furan product (See Scheme 77). Even though we used the imine immediately, we isolated the furan by-product in yields of 40-50%. Despite this we decided to press on and try the cascade reaction again (Scheme 84).



Scheme 84: Attempted Heck/carbopalladation cascade reaction.

Much to our disappointment we were frustrated again in our attempts (Table 10).

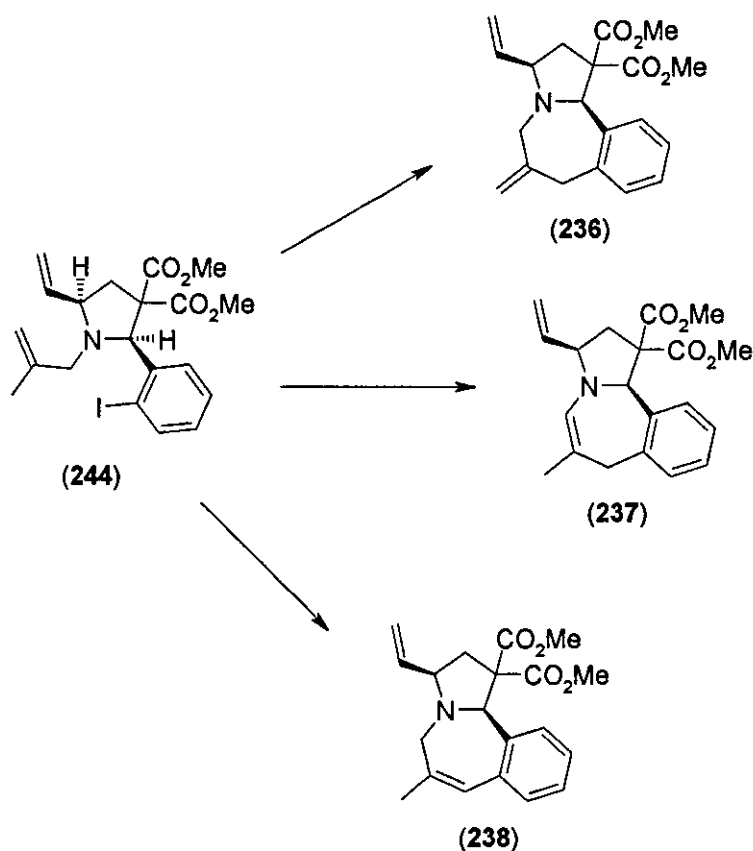
Pd (0) Source	Base	Equiv Base	Solvent	Temperature	Time	Yield
Pd(PPh ₃) ₄	NEt ₃	-	-	90°C	48 h	SM ^a
Pd(PPh ₃) ₄	NEt ₃	-	-	120°C	72 h	SM ^a
Pd(PPh ₃) ₄	NEt ₃	2	CH ₃ CN	120°C	48 h	SM ^a
Pd(PPh ₃) ₄	NEt ₃	2	DMF	120°C	48 h	SM ^a
Pd(PPh ₃) ₄	NEt ₃	5	CH ₃ CN	120°C	48 h	SM ^a
Pd(PPh ₃) ₄	NEt ₃	5	DMF	120°C	48 h	SM ^a
Pd ₂ (dba) ₃ .CHCl ₃	NEt ₃	2	CH ₃ CN	120°C	48 h	SM ^a
Pd ₂ (dba) ₃ .CHCl ₃	NEt ₃	2	DMF	120°C	48 h	SM ^a
Pd(OAc) ₂	ⁱ PrNEt ₂	2	DMF	200°C	48 h	SM ^a
Pd(PPh ₃) ₄	NEt ₃	2	CH ₃ CN	Microwave	40 min	SM ^a
Pd(PPh ₃) ₄	NEt ₃	2	DMF	Microwave	40 min	SM ^b
Pd(PPh ₃) ₄	NEt ₃	2	DMF	Microwave	1 h	cf text ^b

a: 10 mol % Pd(PPh₃)₄ used.

b: 20 mol % Pd(PPh₃)₄ used.

Table 10: Attempted Heck/carbopalladtion cascade reaction.

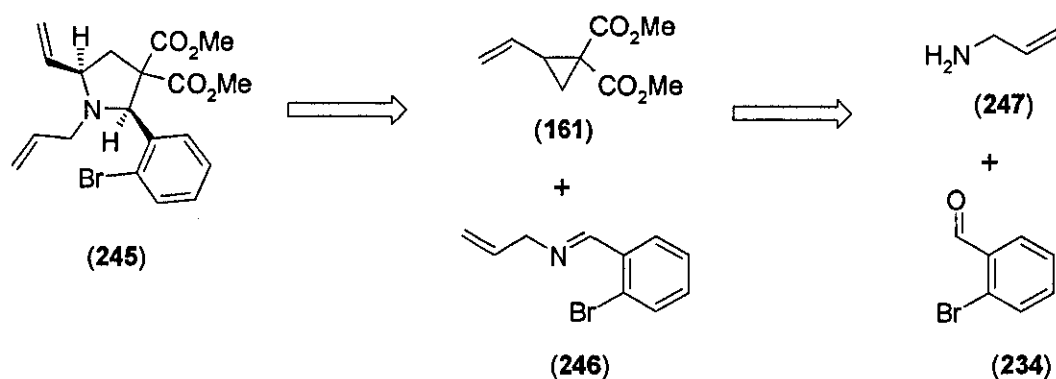
Much like before with the bromine derivative, we found that starting material was recovered, and from crude ¹H NMR data, there were no clear signs that our desired product had been formed or a hint that something may have occurred within the reaction. Unlike our previous attempts though, we decided to investigate the use of the microwave to try and promote this cascade reaction.⁶⁷ From the final attempt in the table, it can be seen that trying the cascade reaction using the microwave, actually provided us with an interesting outcome. From crude ¹H NMR data, we could clearly see that it was not starting material we had recovered, but due to the complexity of the ¹H NMR data we were unable to isolate anything clearly. One explanation could be that the reaction was proceeding *via* a 7-*endo trig* route instead of the desired 6-*exo trig* pathway. This would explain the appearance of the new alkene peaks in the ¹H NMR data, but also explain the fact that we still saw characteristic signs that the vinyl group was still intact. We hypothesised before actually attempting the cascade reaction, that the formation of these compounds could be a distinct possibility and that if the Heck was proceeding *via* a 7-*endo trig* pathway, the 7-membered ring would be formed instead. This would also explain why we were isolating such a complex and impossible to separate, mixture of products (Scheme 85).



Scheme 85: Proposed structures that may be forming if reaction proceeds *via* a 7-*endo trig* pathway.

Based on this theory, it was decided to attempt the Heck reaction on a simpler substrate, to determine whether the Heck reaction was actually proceeding, and if so, what was the more favourable pathway.

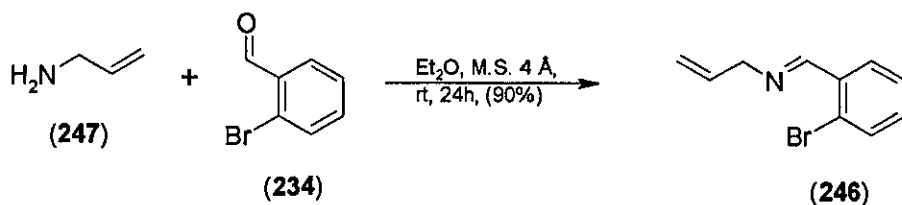
The allylpyrrolidine (245) was chosen as the ideal substrate, and it was envisaged that this could be prepared from vinylcyclopropane (161) and imine (246), *via* the group's [2+3] palladium catalysed cycloaddition reaction (Scheme 86).



Scheme 86: Proposed route towards allylpyrrolidine (245).

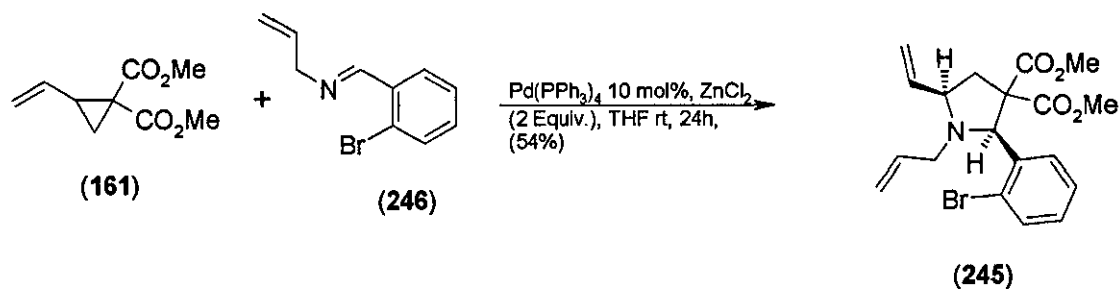
We were not expecting this substrate to undergo the full cascade reaction, as without the methyl group present on the allyl moiety, there would be nothing stopping dehydropalladation occurring after the initial Heck cyclisation. What we were more interested in was seeing if we could actually get the Heck step to work, and more importantly, to see which was the desired reaction pathway: *6-exo trig* or *7-endo trig*.

The first step was to prepare the required imine (246), using the same procedure as previously outlined. This was again achieved in high yields (Scheme 87).



Scheme 87: Synthesis of allyl-[1-(2-bromophenyl)-methylidene]-amine (246).

The imine was used immediately in order to reduce hydrolysis back to the amine and aldehyde and maximise the yield of the pyrrolidine (245) (Scheme 88).



Scheme 88: Synthesis of allylpyrrolidine (245).

We noticed a slight increase in yield, but again still found we recovered 20-30% of the furan by-product. Next we turned our attention to the Heck reaction (Table 11).

Pd (0) Source	Base	Equiv Base	Solvent	Temperature	Time	Yield
Pd(PPh ₃) ₄	NEt ₃	2	DMF	Microwave	1 h	Decomposition ^a
Pd(PPh ₃) ₄	NEt ₃	2	DMF	Microwave	10 min	SM ^a
Pd(PPh ₃) ₄	NEt ₃	2	DMF	Microwave	30 min	SM ^a
Pd(PPh ₃) ₄	NEt ₃	2	DMF	Microwave	45 min	SM ^a
Pd(PPh ₃) ₄	NEt ₃	-	-	Microwave	10 min	SM ^a
Pd(PPh ₃) ₄	NEt ₃	-	-	Microwave	30 min	SM ^a
Pd(PPh ₃) ₄	NEt ₃	2	DME	Microwave	10 min	SM ^a
Pd(PPh ₃) ₄	NEt ₃	2	DME	Microwave	30 min	SM ^a
Pd(PPh ₃) ₄	NEt ₃	2	DME	Microwave	1 h	Decomposition ^a
Pd(PPh ₃) ₄	NEt ₃	3	DME	Microwave	30 min	SM ^a
Pd(PPh ₃) ₄	NEt ₃	2	DME	Reflux	20 h	SM ^a
Pd(PPh ₃) ₄	NEt ₃	3	DME	Reflux	22 h	SM ^a
Pd(PPh ₃) ₄	NEt ₃	3	DME	Reflux	72 h	Decomposition ^a
Pd(OAc) ₂	NEt ₃	3	DME	Reflux	20 h	SM ^b
Pd(OAc) ₂	NEt ₃	3	DME	Reflux	72 h	Decomposition ^a
Pd(OAc) ₂	NEt ₃	3	DMF	Reflux	72 h	Decomposition ^b
Pd(PPh ₃) ₄	NEt ₃	3	DMF	Reflux	22 h	SM ^a

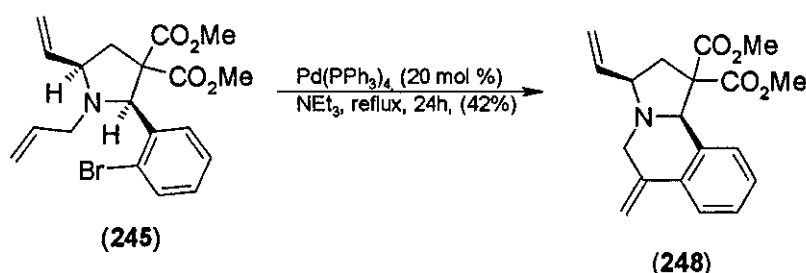
a: 20 mol % Pd(PPh₃)₄ used.

b: 10 mol % Pd(PPh₃)₄ used.

Table 11: Attempts at the Heck reaction.

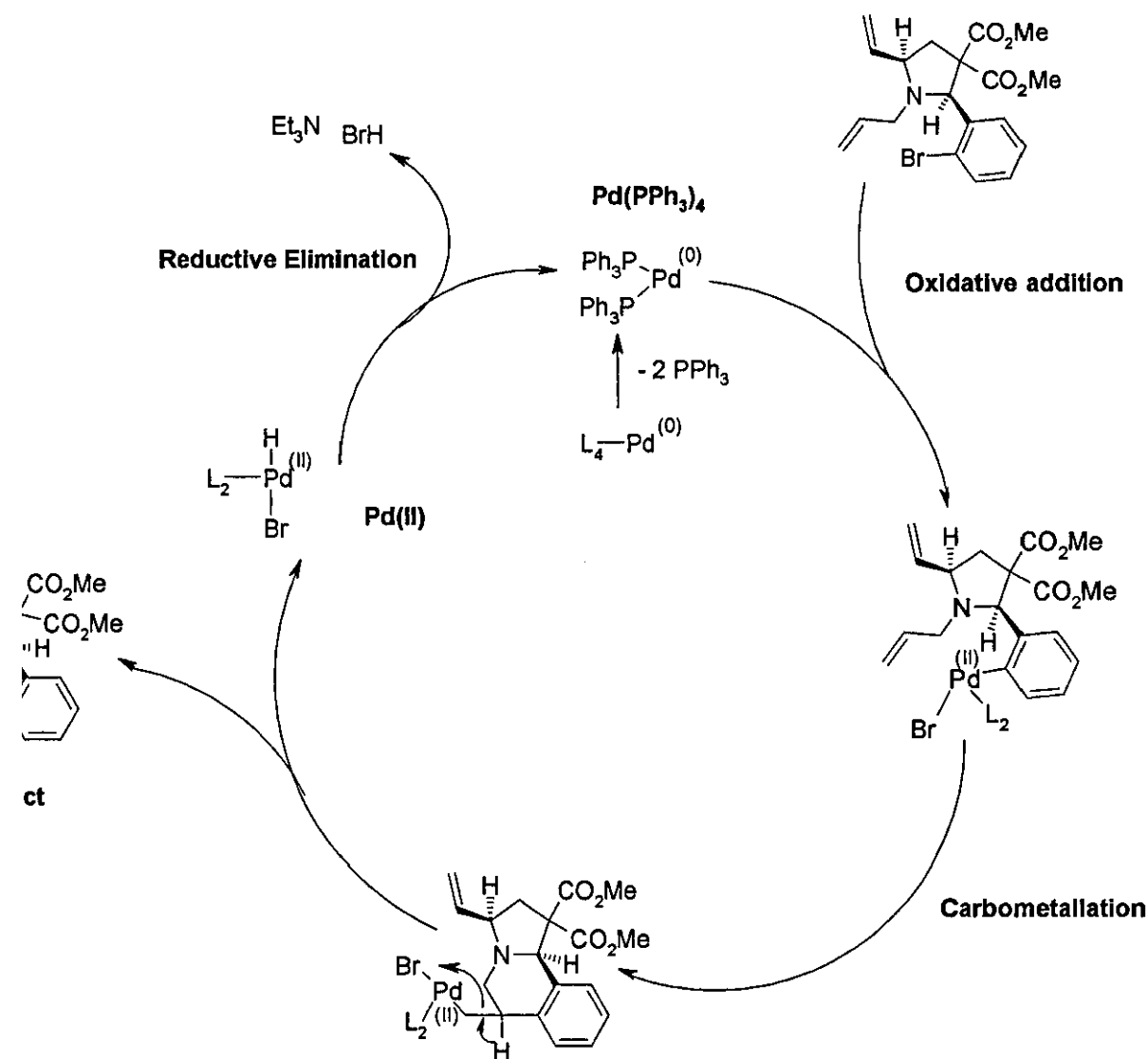
As with our previous attempts, the Heck reaction failed to work. We were unable to reproduce the interesting result we had achieved when trying the reaction in the microwave. Again various variables were looked at and altered, including the addition of silver carbonate (Ag_2CO_3), which had been reported from some quarters to enhance the Heck reaction.⁶⁶ We also investigated using $\text{Pd}(\text{OAc})_2$, and altering the ligand from triphenylphosphine (PPh_3), in an attempt to make the $\text{Pd}(0)$ source more reactive.⁶⁶ The reactions where the starting material had decomposed, we could not identify anything significant from the ^1H NMR data, and isolated a black gummy oil.

Having seemingly tried a large number of different variables, we decided to try the very first set of conditions used, in one final attempt to drive the Heck reaction forward. So $\text{Pd}(\text{PPh}_3)_4$ (20 mol %), was refluxed in neat triethylamine for 24 hours (Scheme 89).



Scheme 89: Synthesis of [4.3.0] bicyclic system (248).

Much to our delight we discovered that the Heck reaction was successful and had proceeded *via* a 6-*exo trig* pathway to yield the [4.3.0] bicyclic system (Scheme 90).



Scheme 90: Mechanism of Heck cyclisation.

We were pleased to find the reaction yielded a satisfactory 42% of our desired compound after purification by preparative HPLC. ¹H NMR data provided us with the evidence that we had successfully synthesised the [4.3.0] bicyclic system, with the characteristic *exo*-methylene hydrogens showing as two new singlets around 5-6 ppm (**Figure 11**).

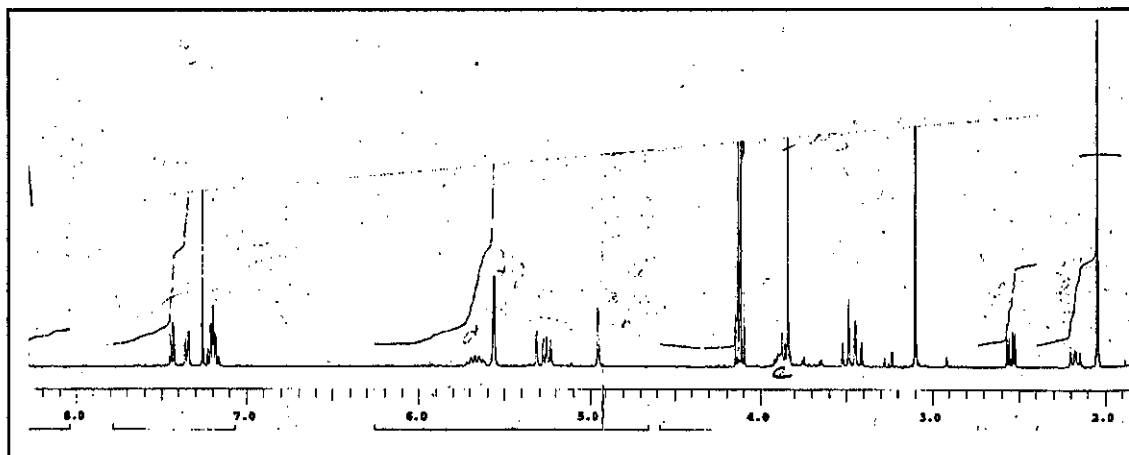
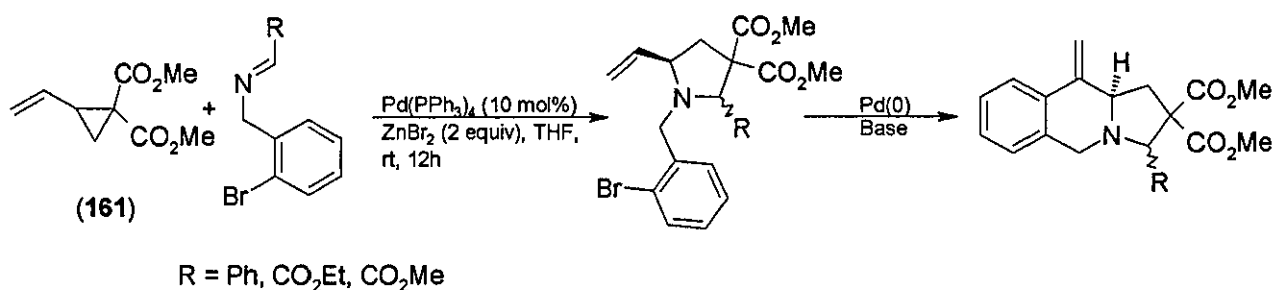


Figure 11: ^1H NMR of 6-methylene-3-vinyl-2,3,6,10b-tetrahydro-5H-pyrrolo[2,1a]isoquinoline-1,1-dicarboxylic acid dimethyl ester (**248**).

3.2 Applications of the Heck reaction towards functionalised polycyclic systems:

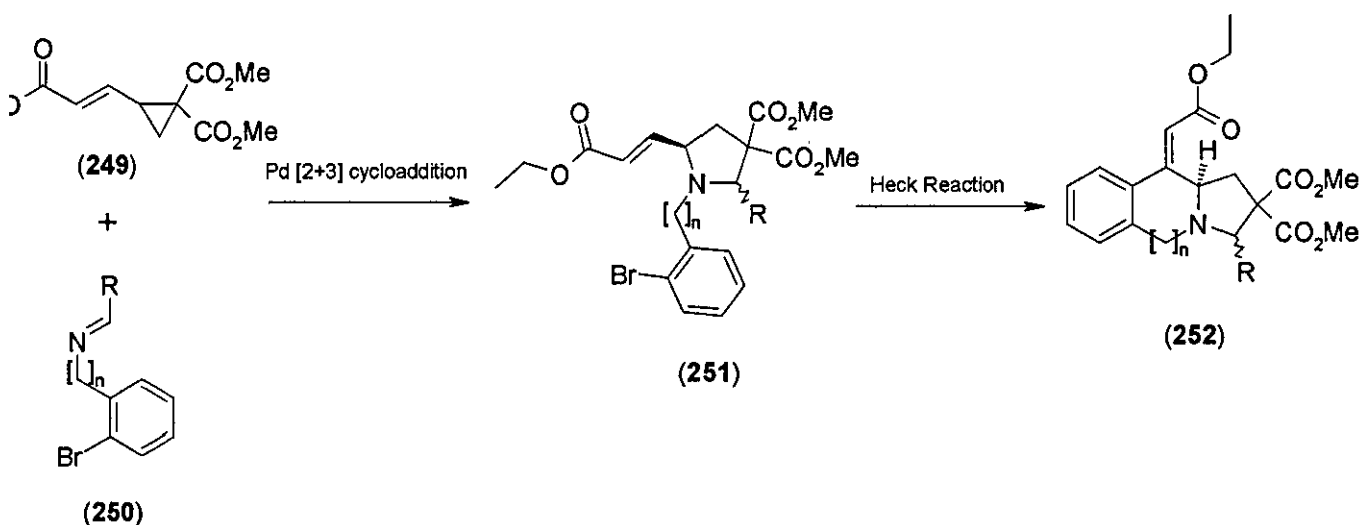
With the success of the Heck reaction, we decided to investigate the scope of using this alongside the [2+3] palladium catalysed cycloaddition chemistry developed within the group, towards synthesising a variety of functionalised polycycles. Some work had previously been done within the group around this area⁴² and we decided to investigate further, by looking at another cyclopropane derivative. Previous work concentrated on using vinylcyclopropane (**161**) as the building block, followed by subsequent [2+3] cycloaddition and Heck reactions to yield a variety of polycyclic systems (**Scheme 91**)⁴².



Scheme 91: Previous work looking at synthesising functionalised polycycles.⁴²

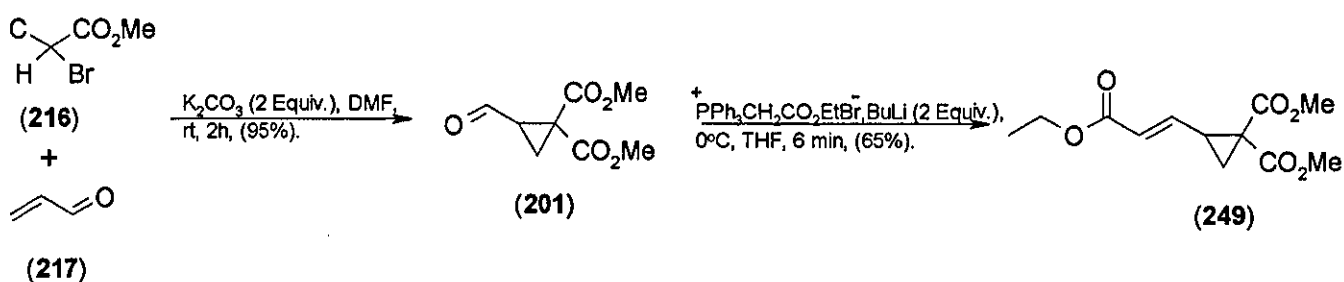
We decided to investigate the scope of this reaction further, by looking at an alternative cyclopropane derivative. We decided to look at an ethyl ester vinylcyclopropane

analogue (249), which we believed could be synthesised by utilising the Michael addition reaction of acrolein (217) and dimethyl bromomalonate (216) that we investigated earlier. A simple Wittig reaction of the subsequent aldehyde would construct the desired vinylcyclopropane derivative (249). Reactions between this vinylcyclopropane and a variety of functionalised imines (250), using the group's palladium catalysed [2+3] cycloaddition chemistry, would construct a wide range of functionalised pyrrolidines (251). We envisaged that these pyrrolidine structures would provide an ideal platform for us to investigate the synthesis of complex, highly functionalised polycycles *via* the Heck reaction (Scheme 92).



Scheme 92: Proposed synthesis of ethyl ester polycycle derivatives.

The route towards the desired cyclopropane would utilise chemistry we had previously looked at when trying to construct the allylvinylcyclopropane (213). We would use the cyclopropanation of acrolein (217) with dimethyl bromomalonate (216) to form the aldehyde (201). A Wittig reaction would then construct our desired cyclopropane analogue (249) (Scheme 93).



Scheme 93: Synthesis of 2-(2-ethoxycarbonyl-vinyl)-cyclopropane-1,1-dicarboxylic acid dimethyl ester (249).

Initial investigations into the Wittig reaction produced very poor yields. We were isolating between 9-20% of our desired product (249), with the rest of the material decomposing. With this in mind we decided to investigate the time factor of the reaction, hypothesising that the desired product (249) could be forming rapidly, but decomposing before we could isolate it. Initially we looked at a reaction time of 24 hours, but saw very poor yields of the desired product. When we began to decrease the time of reaction, we started to see an increase in yield, such that a reaction time of 2 hours now gave us a yield of 23%. This was still unacceptable so we decreased the reaction time further and found that just 10 minutes gave us our highest yield yet of 40%. Eventually a reaction time of 3 minutes gave us an acceptable optimum yield of 65% (Table 12).

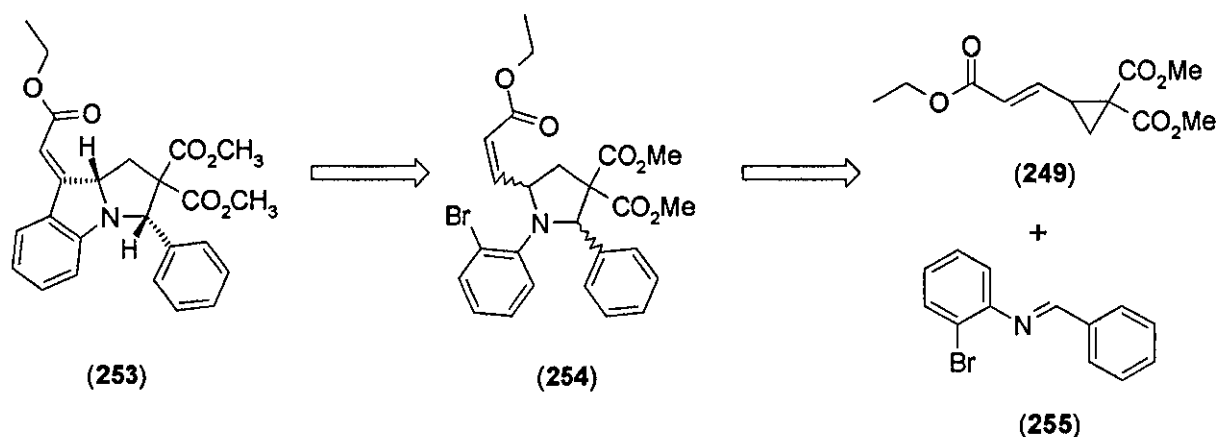
Equiv. Wittig Reagent	Base	Equiv Base	Temperature	Time	Solvent	Yield
2	BuLi	2	-70°C	24h	THF	9%
2	BuLi	2	-70°C	12h	THF	13%
2	BuLi	2	-70°C	2h	THF	20%
2	BuLi	2	0°C	12h	THF	16%
2	BuLi	2	0°C	2h	THF	23%
2	BuLi	2	0°C	10 min	THF	40%
2	BuLi	2	0°C	3 min	THF	65%

Table 12: Optimisation of Wittig reaction conditions.

With the route towards our building block optimised we focused our attention on the synthesis of the polycyclic systems.

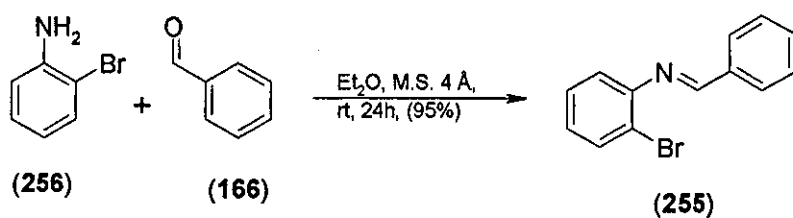
3.2.i Synthesis of 6-ethoxycarbonylmethylene-1-phenyl-8,8a-dihydro-1*H*-3a-aza-cyclopenta[α]indene-2,2-dicarboxylic acid dimethyl ester (**253**):

We decided to investigate the construction of the [3.3.0] fused polycycle (**253**). The *exo* methylene polycyclic system had previously been constructed within the group in high yields⁴² and we thought that this would provide an ideal starting place for our investigations into the ethyl ester derivatives. We believed that polycyclic system (**253**) could be constructed from a Heck cyclisation of pyrrolidine (**254**). This we believed could be constructed using the group's palladium catalysed [2+3] cycloaddition reaction of vinylcyclopropane (**249**) and imine (**255**), both easily prepared from simple building blocks (Scheme 94).



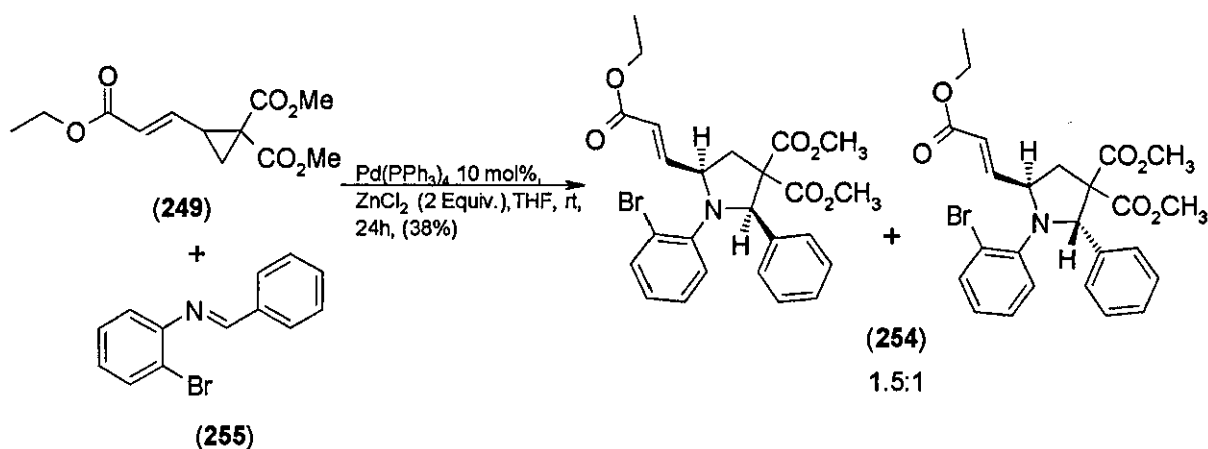
Scheme 94: Proposed synthesis of 6-ethoxycarbonylmethylene-2-phenyl-8,8a-dihydro-1*H*-3a-aza-cyclopenta[α]indene-2,2-dicarboxylic acid dimethyl ester (**253**).

The first step in the synthesis of this polycycle was to synthesise the appropriate imine. This was done in a simple one step reaction (Scheme 95).



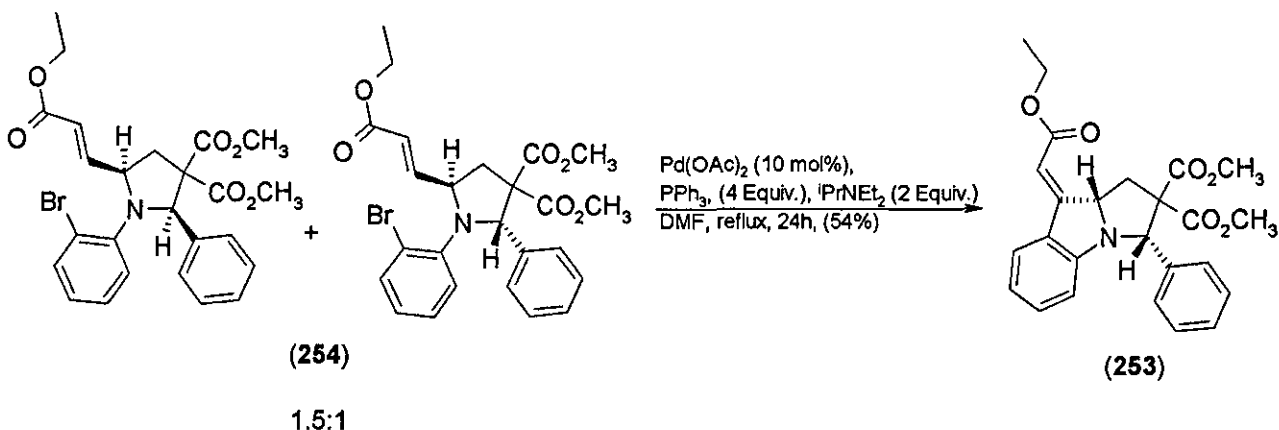
Scheme 95: Synthesis of benzylidene-(2-bromophenyl)-amine (255).

With the imine (255) in place it was time to use the [2+3] cycloaddition chemistry to construct the pyrrolidine required for the Heck reaction (Scheme 96).



Scheme 96: Synthesis of 1-(2-bromophenyl)-5-(2-ethoxycarbonylvinyl)-2-phenylpyrrolidine-3,3-dicarboxylic acid dimethyl ester (254).

The reaction yielded us our desired product in a mixture of isomers that we were unable to separate. We also recovered some of the tetrahydrofuran by-product. The *cis* isomer was the major product in a ratio of 1.5:1. At this stage we were not too concerned about trying to separate the isomers. We knew we could carry the diastereoisomers on to the Heck reaction and that both isomers would react to form our polycyclic compound. So the next step was to try the Heck reaction (Scheme 97).



Scheme 97: Synthesis of 6-ethoxycarbonylmethylene-1-phenyl-8,8a-dihydro-1*H*-3a-azacyclopenta[α]indene-2,2-dicarboxylic acid dimethyl ester (**253**).

We were delighted to find that the Heck cyclisation was successful and yielded us our desired product in decent yields of 54%. We found that using $\text{Pd}(\text{OAc})_2$ as the Pd(0) source and Hünig's base, gave us the highest yield. We recovered some of the *trans* isomer back from the reaction, which would suggest that the *cis* isomer was a lot more reactive than the *trans* isomer. ^1H NMR data showed us that the reaction had proceeded via a 5-*exo trig* pathway, with the hydrogen of the *exo* double bond, clearly showing up as a weak doublet at about 6ppm (**Figure 12**).

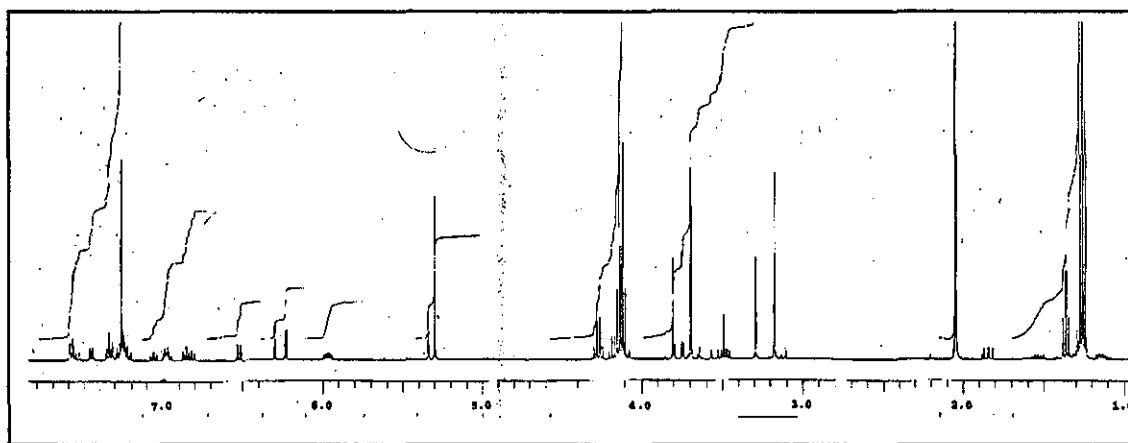


Figure 12: ^1H NMR of 6-ethoxycarbonylmethylene-1-phenyl-8,8a-dihydro-1*H*-3a-azacyclopenta[α]indene-2,2-dicarboxylic acid dimethyl ester (**253**).

The stereochemistry across the ring was assigned as *cis* by nOe experiments, which confirmed the 5-CH proton was on the same face as the 1-CH proton next to the phenyl substituent. This was to be expected due to the stereochemical preference of the Heck cyclisation and that the *cis* isomer was the most reactive (**Figure 13**).

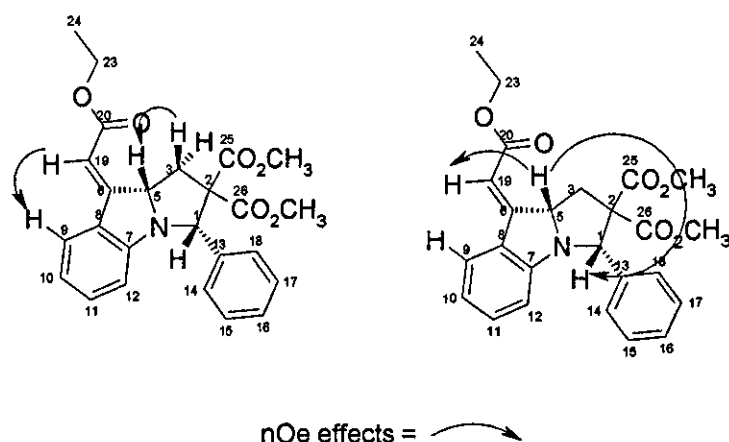
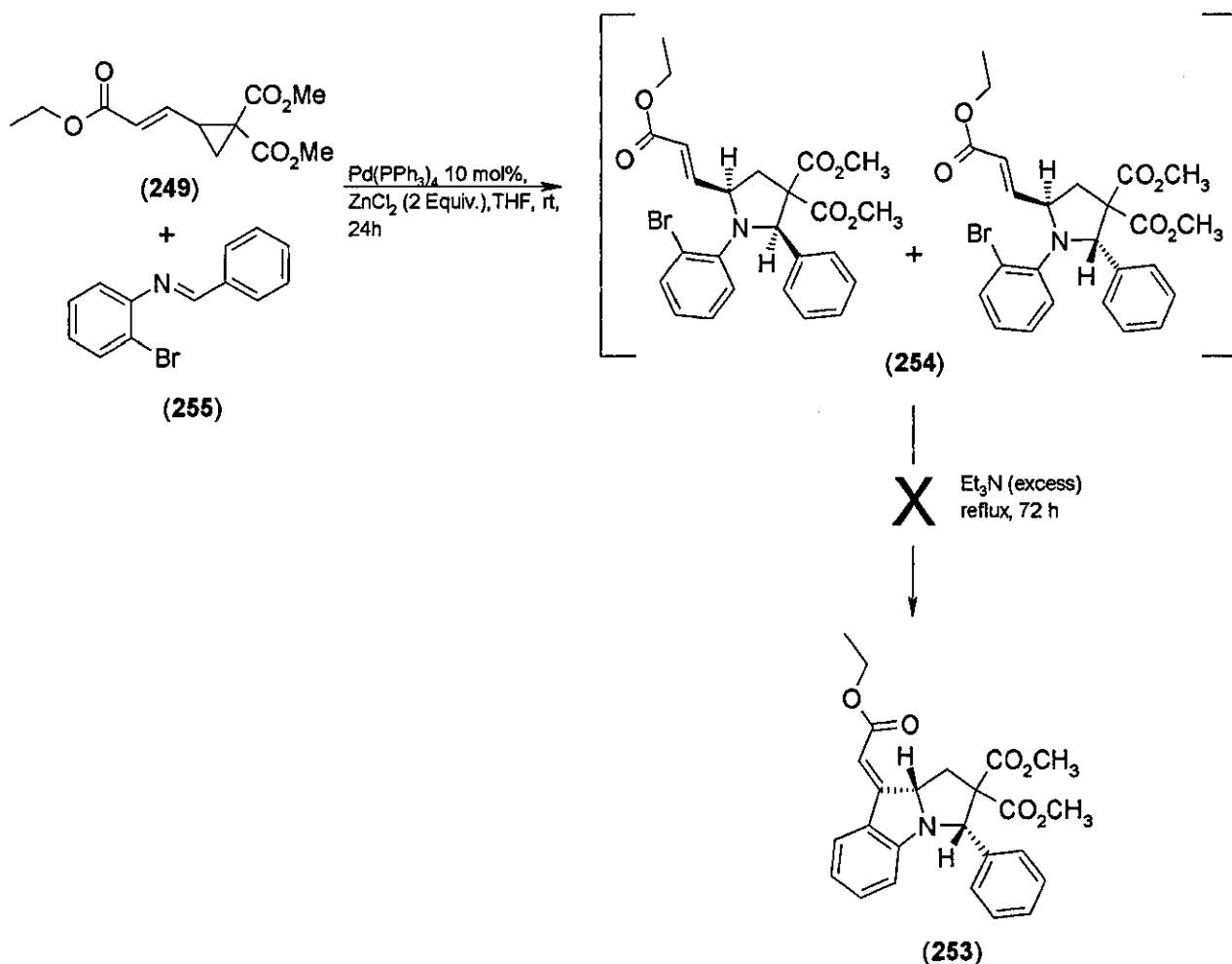


Figure 13: nOe Effects indicating the stereochemical outcome of 6-ethoxycarbonylmethylene-1-phenyl-8,8a-dihydro-1*H*-3a-aza-cyclopenta[α]indene-2,2-dicarboxylic acid dimethyl ester (**253**).

Now we had synthesised the bicyclic pyrrolidine (**253**) stepwise, we decided to investigate the possibility of doing this in a one-pot procedure. If this option was viable, it would be a powerful method of synthesising complex polycyclic systems, in one step, from simple building blocks (**Scheme 98**).

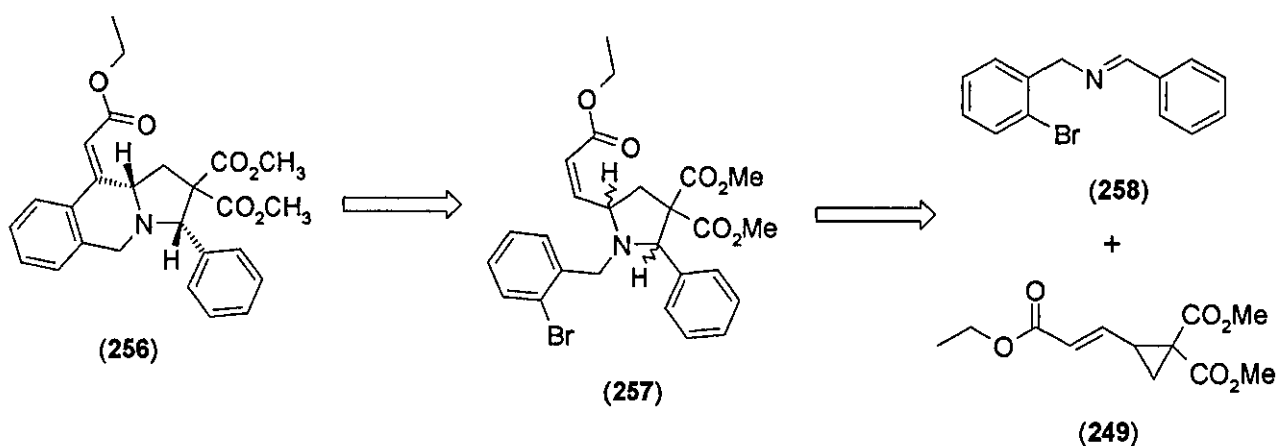


Scheme 98: One-pot intramolecular Heck cyclisation with 2-bromobenzyl substituted imines.

Unfortunately we were not able to recover any of the bicyclic pyrrolidine from the reaction. Crude ^1H NMR data showed no characteristic peaks that the bicyclic pyrrolidine had been formed, or that there was any starting material still present. The main challenge we faced within the one-pot procedure, was the conditions we used to successfully construct the polycyclic system *via* the Heck reaction in the step wise synthesis, could not be used here, as the [2+3] cycloaddition reaction, was reliant upon on $\text{Pd}(\text{PPh}_3)_4$ being used to form the pyrrolidine in the first place. We had already discovered that using $\text{Pd}(\text{PPh}_3)_4$ in these Heck reactions, did not produce great yields, and we suspected that this might have been the reason for the observed no reaction.

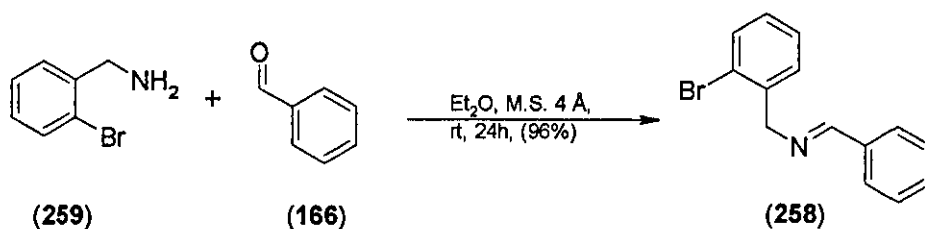
3.2.ii Synthesis of 6-ethoxycarbonylmethylene-2-phenyl-1,5,10,10a-tetrahydro-pyrrolo[1,2-*b*]isoquinoline-3,3-dicarboxylic acid dimethyl ester.

Having successfully synthesised the [3.3.0] bicyclic pyrrolidine, we decided to try and construct the [4.3.0] bicyclic pyrrolidine (**256**). We envisaged that pyrrolidine (**257**) would provide the perfect platform for us to investigate the Heck cyclisation on. We believed we could synthesise pyrrolidine (**257**) again utilising the group's palladium catalysed cycloaddition reaction of imine (**258**) with vinylcyclopropane (**249**) (Scheme 99).



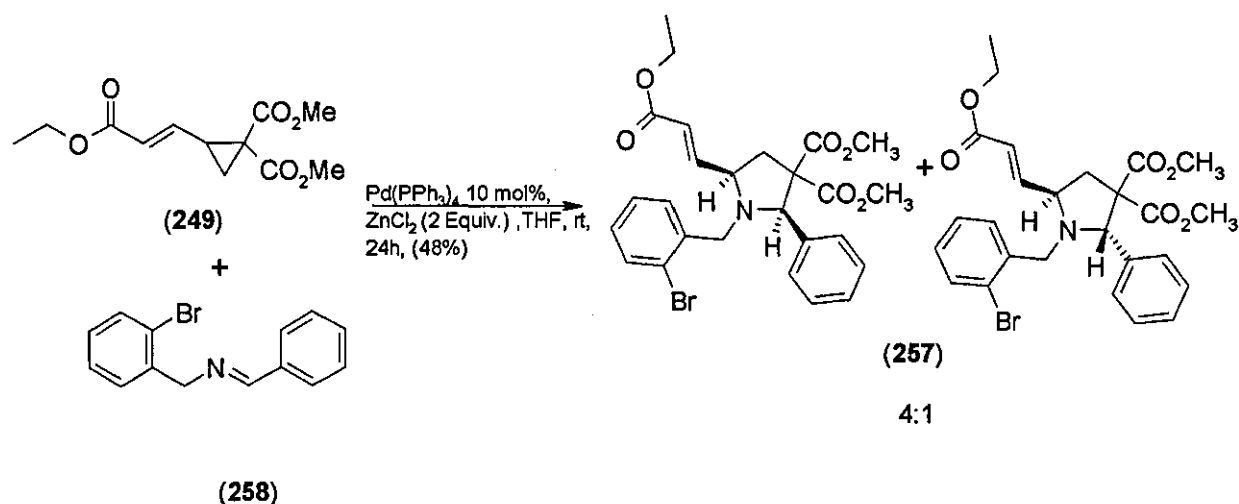
Scheme 99: Proposed synthesis of 6-ethoxycarbonylmethylene-2-phenyl-1,5,10,10a-tetrahydro-pyrrolo[1,2-*b*]isoquinoline-3,3-dicarboxylic acid dimethyl ester (**256**)

As with the synthesis of the [3.3.0] polycycle, the first step was to synthesise the required imine to use in the [2+3] cycloaddition reaction (Scheme 100).



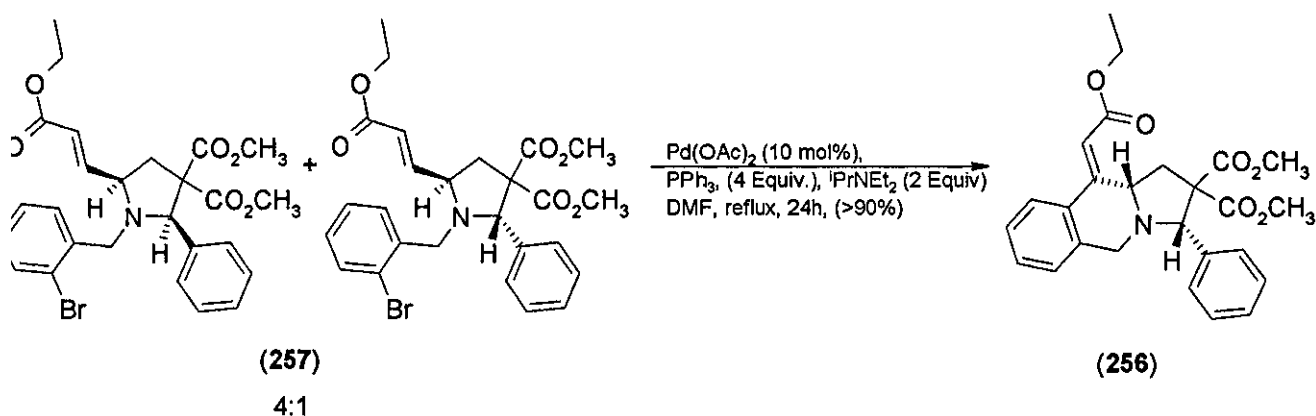
Scheme 100: Synthesis of benzylidene-(2-bromobenzyl)-amine (**258**).

With the imine in place, we again looked at synthesising the pyrrolidine required to try the Heck reaction, using the group's [2+3] cycloaddition methodology (**Scheme 101**).



Scheme 101: Synthesis of 1-(2-bromobenzyl)-5-(2-ethoxycarbonylvinyl)-2-phenylpyrrolidine-3,3-dicarboxylic acid dimethyl ester (**257**).

The reaction yielded the desired product in a 48% yield. A mixture of diastereoisomers was isolated, this time in a slightly better ratio of 4:1 in favour of the *cis* isomer. Again this did not overly concern us, because we had already shown that by reacting a mixture of isomers did not hinder the Heck cyclisation. The final stage was to try the Heck reaction using our preferred conditions of Hünig's base, Pd(OAc)_2 , PPh_3 in DMF (**Scheme 102**).



Scheme 102: Synthesis of 10-ethoxycarbonylmethylene-3-phenyl-1,5,10,10a-tetrahydropyrrolo[1,2-*b*]isoquinoline-2,2-dicarboxylic acid dimethyl ester (**256**).

We were delighted to find that the Heck cyclisation proceeded in excellent yields of >90% to give the [4.3.0] bicyclic pyrrolidine (**256**). The yield was representative of the better diastereomeric ratio we saw towards the more reactive *cis* isomer in the [2+3] cycloaddition reaction. From ^1H NMR data, we saw the hydrogen of the *exo* double bond again appearing as a weak doublet at around 6.5 ppm (Figure 14).

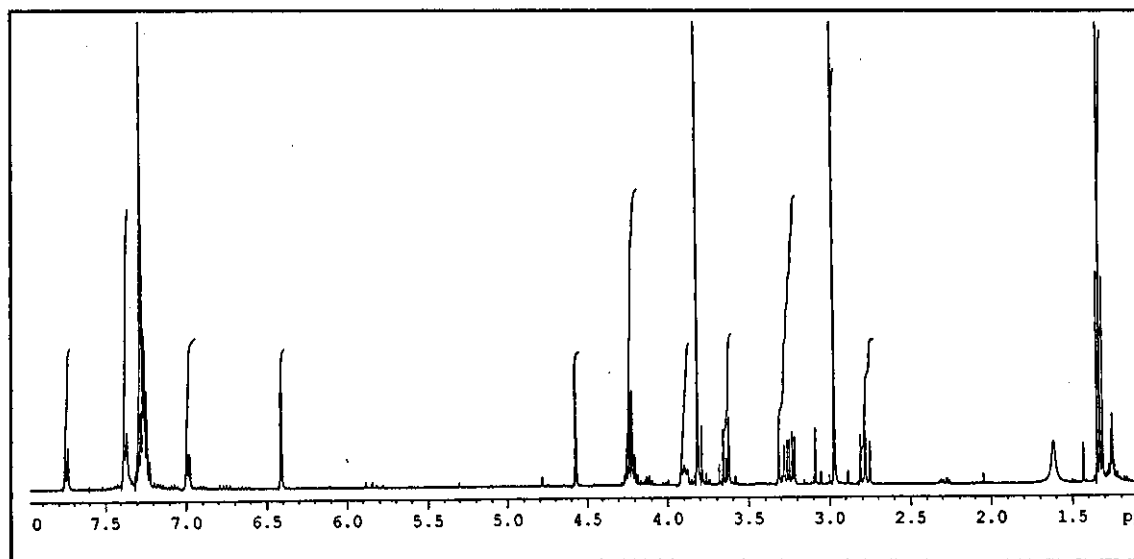


Figure 14: ^1H NMR of 6-ethoxycarbonylmethylene-2-phenyl-1,5,10,10a-tetrahydro-pyrrolo[1,2-*b*]isoquinoline-3,3-dicarboxylic acid dimethyl ester (**256**).

Again nOe experiments confirmed the stereochemistry across the ring as *cis* with 5-CH hydrogen being on the same face as 2-CH hydrogen. As with the [3.3.0] bicyclic system, again we saw a weak interaction of the *exo* double bond 20-CH hydrogen with the 5-CH hydrogen, explaining why we saw a doublet in the ^1H NMR data (Figure 15).

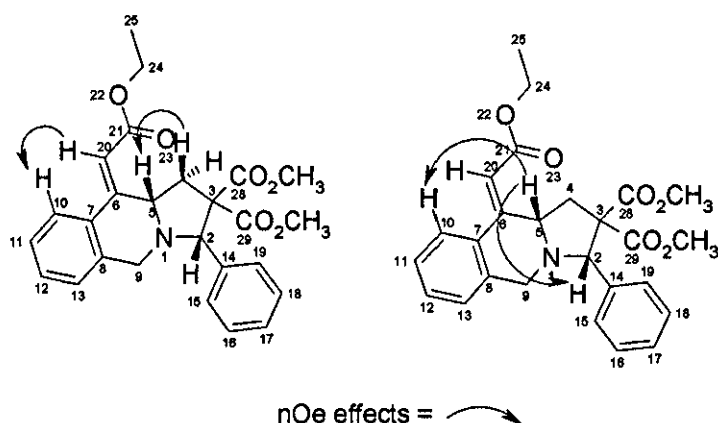
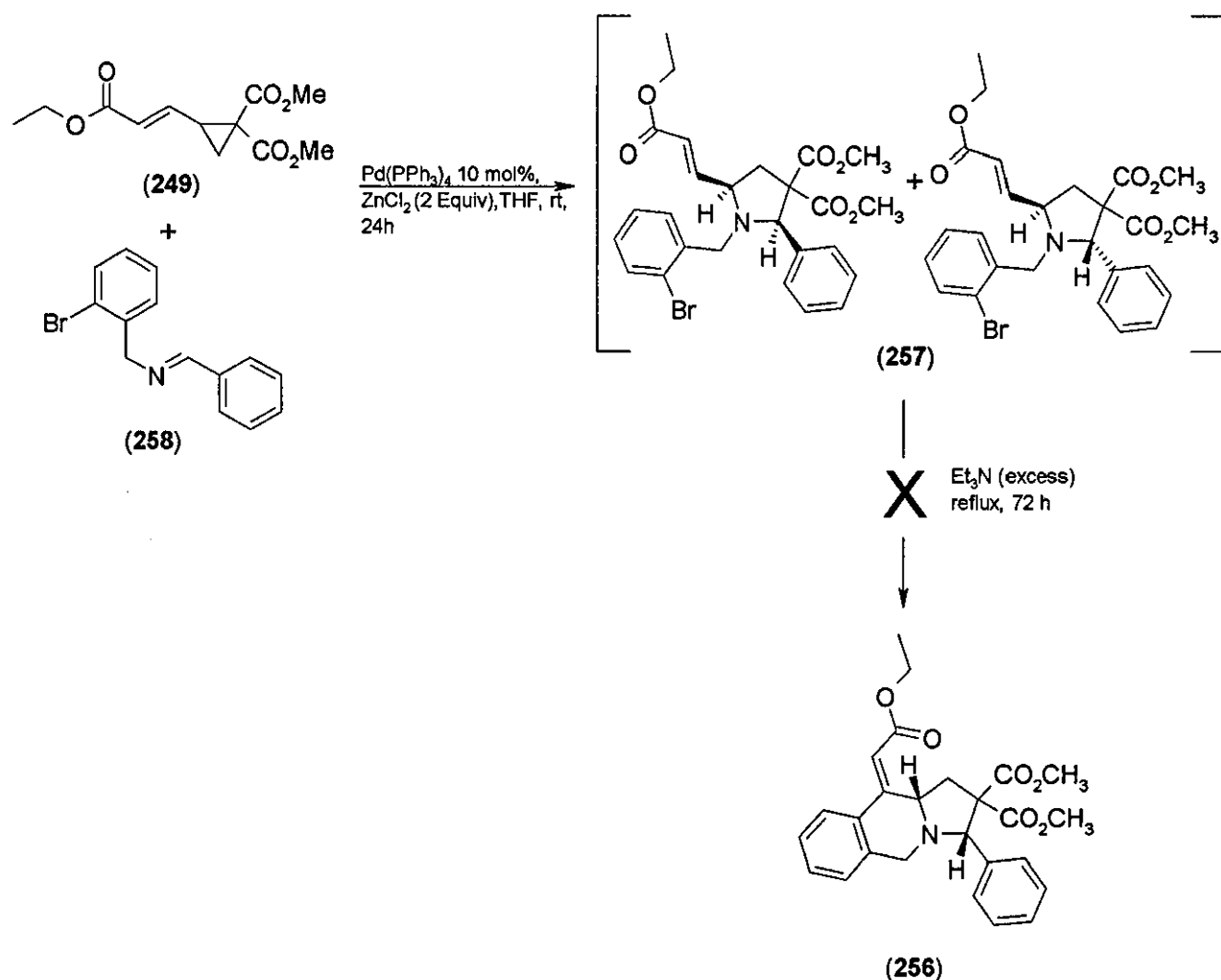


Figure 15: nOe Effects indicating the stereochemical outcome of 6-ethoxycarbonylmethylene-2-phenyl-1,5,10,10a-tetrahydro-pyrrolo[1,2-*b*]isoquinoline-3,3-dicarboxylic acid dimethyl ester (**256**).

Once again with the polycycle successfully isolated stepwise, we looked at the possibility of forming it in a one pot procedure (**Scheme 103**).

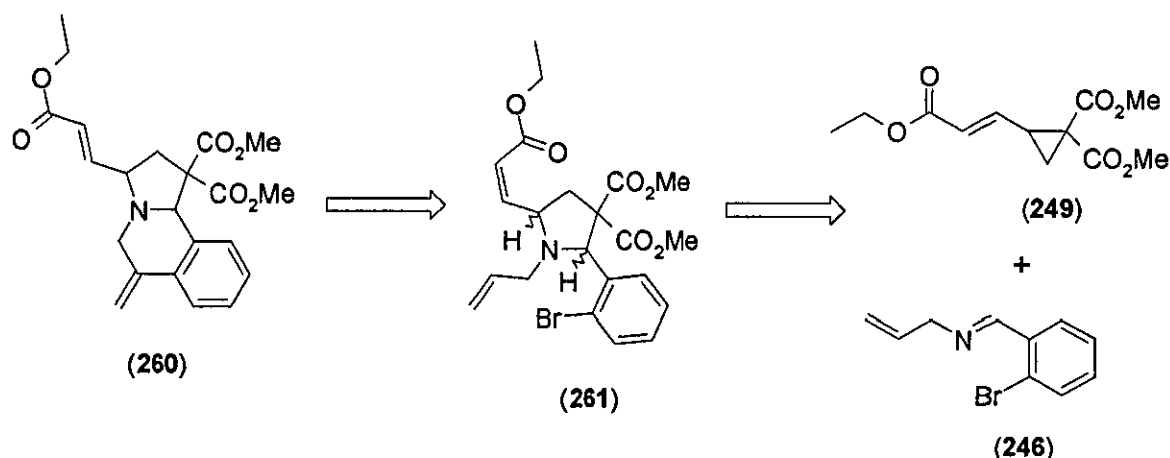


Scheme 103: One-pot intramolecular Heck cyclisation with 2-bromobenzyl substituted imines.

As with the previous attempt at this “one-pot” procedure we failed to get the bicyclic pyrrolidine (259). The crude ^1H NMR data gave a very complex mixture, with no characteristic signals showing evidence that either product or the pyrrolidine were present. Obviously it was a surprising result that we had failed to at least isolate some of the pyrrolidine, as these were the same conditions we had used previously to facilitate the cycloaddition. At this stage though, we were not too concerned about the one pot procedure, but more focused on synthesising a variety of polycyclic substrates, to show the powerful scope of using the [2+3] palladium catalysed cycloaddition reaction in conjunction with the Heck cyclisation.

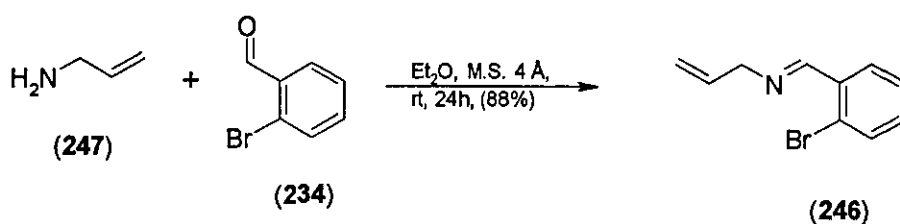
3.2.iii Synthesis of 3-(2-ethoxycarbonylvinyl)-6-methylene-2,3,6,10b-tetrahydro-5H-pyrrolo [2,1- α]isoquinoline-1,1-dicarboxylic acid dimethyl ester.

With the [3.3.0] and [4.3.0] bicyclic pyrrolidines successfully synthesised, we decided to look at another azepine derivative. We chose to look at azepine (260). We had already synthesised the vinyl analogue (248) and decided to investigate if the ethyl ester derivative could be constructed. We believed it could be synthesised by a Heck cyclisation of pyrrolidine (261), which we would construct *via* the group's [2+3] cycloaddition chemistry methodology, starting from vinylcyclopropane (249) and imine (246) (Scheme 104).



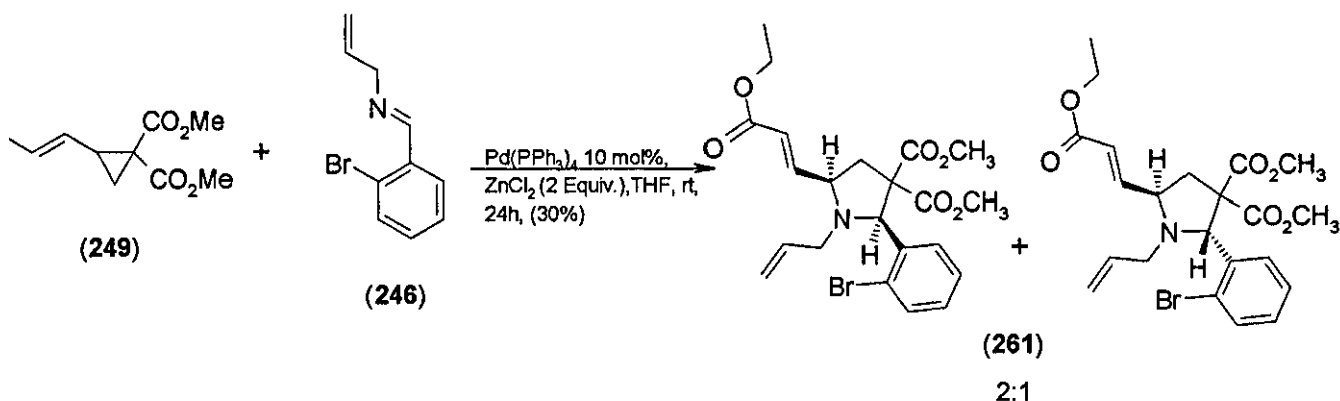
Scheme 104: Proposed synthesis of 3-(2-ethoxycarbonylvinyl)-6-methylene-2,3,6,10b-tetrahydro-5H-pyrrolo [2,1- α]isoquinoline-1,1-dicarboxylic acid dimethyl ester (260).

The first stage was to isolate the imine required for the [2+3] cycloaddition reaction, which was again achieved in high yields (Scheme 105).



Scheme 105: Synthesis of bromobenzyl substituted imine (246).

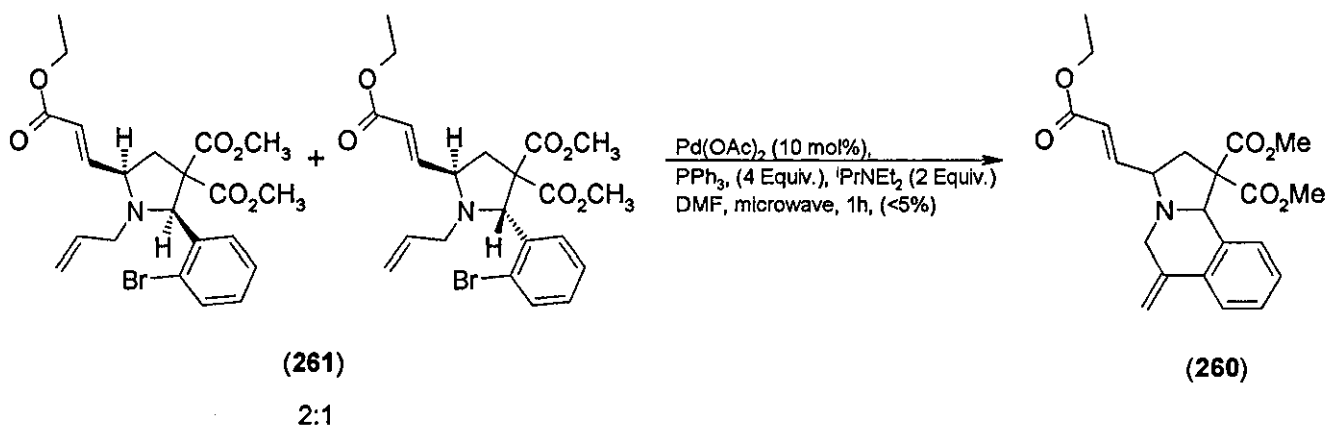
With the imine synthesised, we reacted this with the ethyl ester cyclopropane derivative (249) using the [2+3] palladium catalysed cycloaddition conditions to form our desired pyrrolidine (261) (Scheme 106).



Scheme 106: Synthesis of 1-allyl-2-(2-bromophenyl)-5-(2-ethoxycarbonylvinyl)-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (261).

We managed to isolate our desired pyrrolidine in a 2:1 ratio of diastereoisomers, favouring the *cis* isomer, but in a rather disappointing yield of 30%. The low yield could be attributed to the formation of the tetrahydrofuran by-product, which we isolated in 60% yields, formed by the reaction with the bromobenzaldehyde, which was described earlier.

Undeterred by the low yield of the pyrrolidine, we subjected it to the Heck reaction (Scheme 107).



Scheme 107: Attempted Heck cyclisation of 1-allyl-2-(2-bromophenyl)-5-(2-ethoxycarbonylvinyl)-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (261).

The Heck reaction on this substrate proved to be quite problematic. The conditions which were successful in previous reactions only yielded the starting material. Eventually we found that subjecting the reaction to one hour in the microwave gave us a very minimal amount of the [4.3.0] bicyclic Heck product, in a 5% yield. Due to the harsh conditions required to drive the reaction, we found that the majority of the starting material decomposed, which would explain the low yield. The table below summarises our attempts at this particular reaction (Table 13).

Pd (0) Source	Base	Equiv Base	Solvent	Temperature	Time	Yield
Pd(OAc) ₂	^t PrNEt ₂	2	DMF	100°C	24 h	SM
Pd(OAc) ₂	^t PrNEt ₂	2	DMF	100°C	48 h	SM
Pd(OAc) ₂	^t PrNEt ₂	2	DMF	100°C	72 h	SM
Pd(OAc) ₂	^t PrNEt ₂	2	DMF	200°C	24 h	SM
Pd(OAc) ₂	^t PrNEt ₂	2	DMF	200°C	72 h	SM
Pd(PPh ₃) ₄	NEt ₃	2	-	100°C	24 h	SM
Pd(PPh ₃) ₄	NEt ₃	2	-	100°C	72 h	SM
Pd(PPh ₃) ₄	NEt ₃	2	DMF	100°C	24 h	SM
Pd(PPh ₃) ₄	NEt ₃	2	DMF	100°C	72 h	SM
Pd(PPh ₃) ₄	NEt ₃	2	DMF	Microwave	30 min	SM
Pd(PPh ₃) ₄	NEt ₃	2	DMF	Microwave	1 h	Decomposition
Pd(OAc) ₂	^t PrNEt ₂	2	DMF	Microwave	30 min	SM
Pd(OAc) ₂	^t PrNEt ₂	2	DMF	Microwave	1 h	<5%

Table 13: Attempts at the Heck reaction.

3.2.iv. Synthesis of “bridged” furan and pyrrolidine polycycles:

Having successfully synthesised the bicyclic pyrrolidine and azepine type compounds, we thought about trying to synthesise other ring systems, for example the furan and pyrrolidine below (Figure 16).

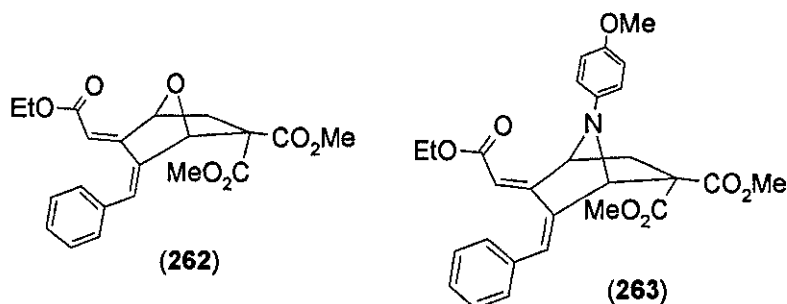
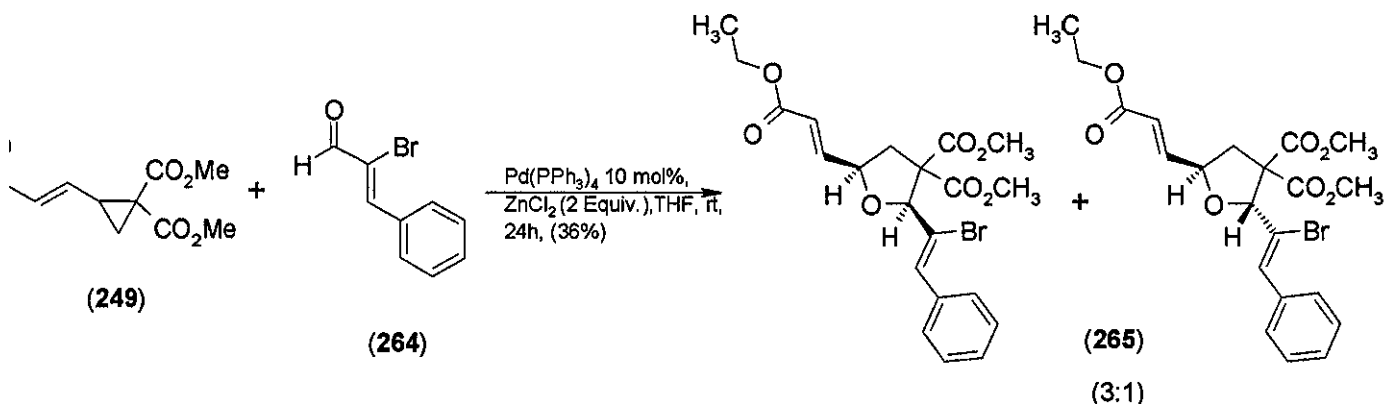


Figure 16: New Heck products.

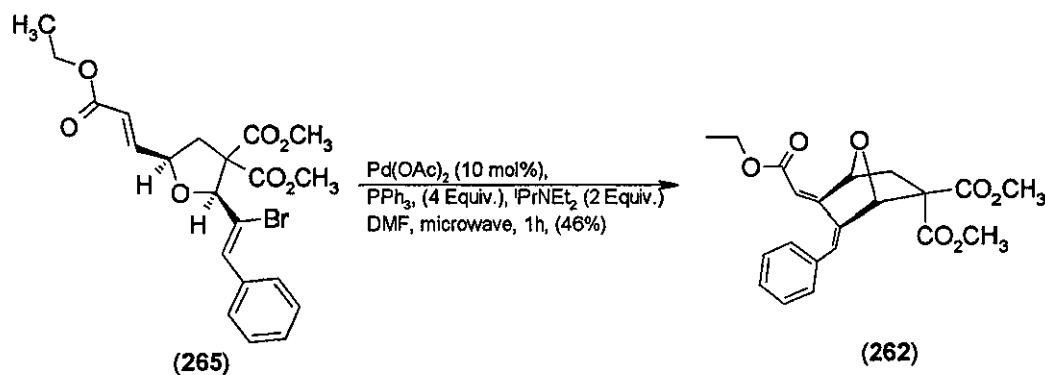
First we looked at the tetrahydrofuran derivative (262), which we envisaged could be synthesised from α -bromocinnamaldehyde (264) and the ethyl ester vinylcyclopropane (249) (Scheme 108).



Scheme 108: Palladium catalysed [2+3] cycloaddition with α -bromocinnamaldehyde.

We were pleased to isolate the tetrahydrofuran derivative in average yields of 36%, though we were confident that this could be optimised further. Again we saw a mixture of diastereoisomers, with the *cis* isomer being the major product, which was determined

from nOe experiments. We were able to separate the isomers using flash chromatography, so we subjected the *cis* isomer only to the Heck conditions (Scheme 109).



Scheme 109: Heck cyclisation of 2-(1-bromo-2-phenylvinyl)-5-(2-ethoxycarbonylvinyl)-dihydrofuran-3,3-dicarboxylic acid dimethyl ester (265).

We were delighted to find that we isolated the Heck product in a decent yield of 46%. From ¹H NMR data we saw the characteristic singlets at 5.9 and 6.7 ppm, corresponding to the alkene hydrogens adjacent to the phenyl and ethyl ester moiety respectively (Figure 17).

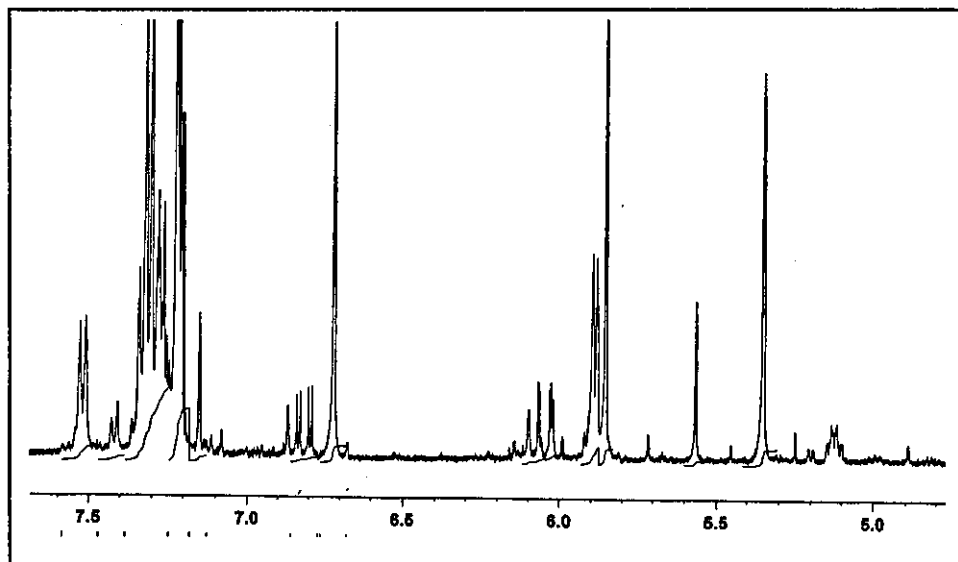
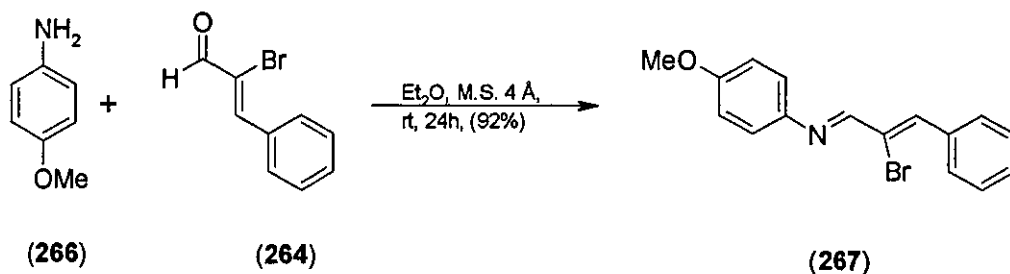


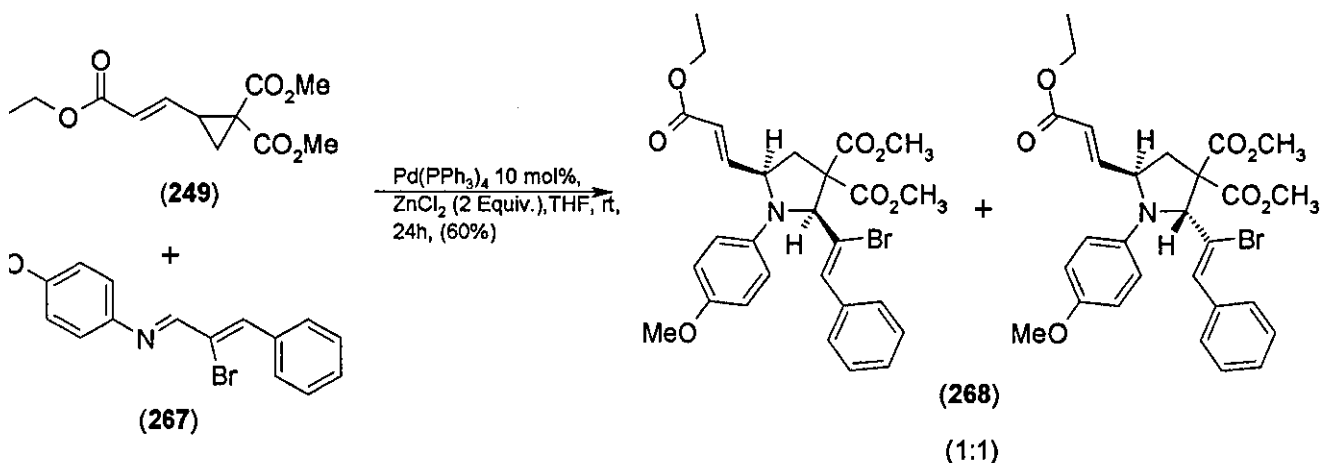
Figure 17: ¹H NMR of 6-benzylidene-1-ethoxycarbonylmethylene-7-oxabicyclo[2.2.1]heptane-6,6-dicarboxylic acid dimethyl ester (262).

Our focus now turned towards the pyrrolidine derivative (**263**) and our first step was to construct the imine required to take forward onto the cycloaddition reaction (Scheme 110).



Scheme 110: Synthesis of (2-bromo-3-phenylallylidene)-(4-methoxyphenyl)-amine (**267**).

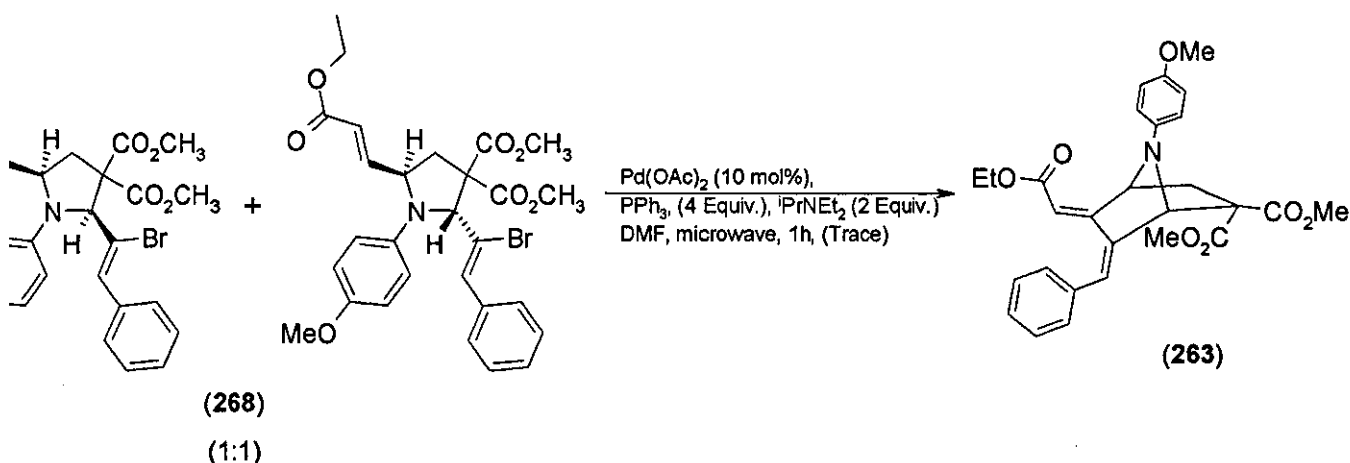
With the imine to hand, we set about trying to synthesise the pyrrolidine required to try the Heck reaction on (Scheme 111).



Scheme 111: Synthesis of 2-(1-bromo-2-phenylvinyl)-5-(2-ethoxycarbonylvinyl)-1-(4-methoxyphenyl)-pyrrolidine-3,3 dicarboxylic acid dimethyl ester (**268**).

The ^1H NMR data was extremely complex, but we had isolated our desired pyrrolidine, in a 1:1 mixture of diastereoisomers. We were unable to separate the isomers, so we decided to try the Heck cyclisation on the inseparable mixture anyway. The Heck cyclisation would only work on the *cis* isomer, so we expected to obtain starting material back,

which would correspond to the *trans* isomer, aswell as the cyclised product (Scheme 112).



Scheme 112: Heck cyclisation of 2-(1-bromo-2-phenylvinyl)-5-(2-ethoxycarbonylvinyl)-1-(4-methoxyphenyl)-pyrrolidine-3,3 dicarboxylic acid dimethyl ester (**268**).

After several attempts, only a trace amount of the Heck product was obtained, which we were unable to isolate after purification. The crude ^1H NMR data provided us with evidence that we had formed the cyclised product, with the hydrogens adjacent to the ethyl ester and phenyl group, showing up as singlets at around 6.5 ppm and 5.5 ppm respectively. We found that the conditions required to drive the reaction needed to be extremely harsh, with one hour heating in the microwave required to gain even the smallest amount of product. In some cases we recovered starting material from the reaction. When the reaction conditions were more severe, we observed complete degradation of the substrate, with ^1H NMR data providing us with no evidence that starting material or any other substance of note was present. The table below summarises our attempts (Table 14).

Pd (0) Source	Base	Equiv Base	Solvent	Temperature	Time	Yield
Pd(OAc) ₂	ⁱ PrNEt ₂	2	DMF	100°C	24 h	SM
Pd(OAc) ₂	ⁱ PrNEt ₂	2	DMF	200°C	24 h	SM
Pd(OAc) ₂	ⁱ PrNEt ₂	2	DMF	200°C	72 h	Decomposition
Pd(PPh ₃) ₄	NEt ₃	2	-	100°C	72 h	Decomposition
Pd(PPh ₃) ₄	NEt ₃	2	DMF	100°C	72 h	Decomposition
Pd(PPh ₃) ₄	NEt ₃	2	DMF	Microwave	30 min	SM
Pd(PPh ₃) ₄	NEt ₃	2	DMF	Microwave	1 h	Decomposition
Pd(OAc) ₂	ⁱ PrNEt ₂	2	DMF	Microwave	30 min	SM
Pd(OAc) ₂	ⁱ PrNEt ₂	2	DMF	Microwave	1 h	Trace

Table 14: Attempts at the Heck cyclisation of 2-(1-bromo-2-phenylvinyl)-5-(2-ethoxycarbonylvinyl)-1-(4-methoxyphenyl)-pyrrolidine-3,3 dicarboxylic acid dimethyl ester (**268**).

The research into the tandem [2+3] cycloaddition and Heck reaction proved a useful investigation. We have shown a wide representative of highly functionalised, complex, polycyclic systems can be synthesised in just two steps from very simple building blocks. The applications of this type of chemistry would be invaluable in natural product synthesis, with the ability to construct complex heterocycles, in decent yields and with the ability in most cases to direct the stereochemical outcome, proving a very useful tool. An area that we can still develop is the one pot cycloaddition/intramolecular Heck cyclisation. We were unsuccessful in our initial attempts, but we are confident that with time spent on optimising reaction conditions, we can get this one pot procedure to work. This would prove to be an enormous step forward, with the ability to go from simple cyclopropane derivatives and imine/aldehyde trapping agents, to a highly functionalised bicyclic or polycyclic system in just one step, proving to be very advantageous in complex total syntheses. The table below summarises the pyrrolidine/tetrahydrofuran precursors and the subsequent Heck cyclisation products (**Table 15**).

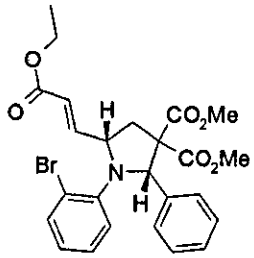
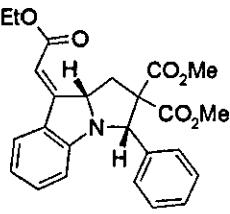
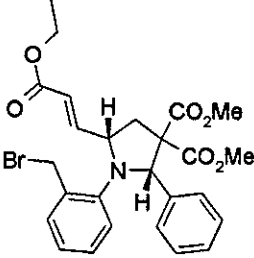
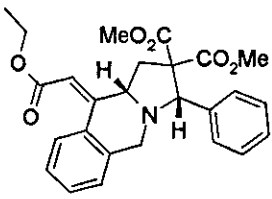
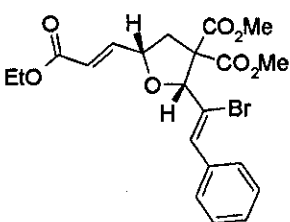
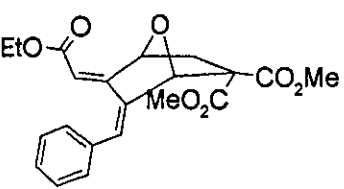
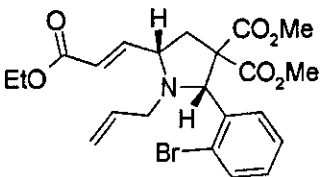
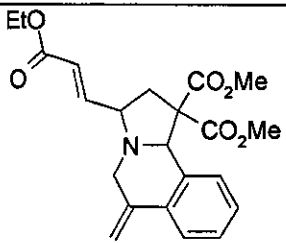
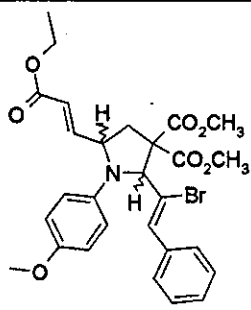
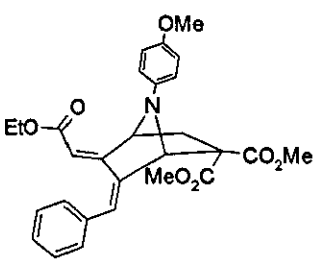
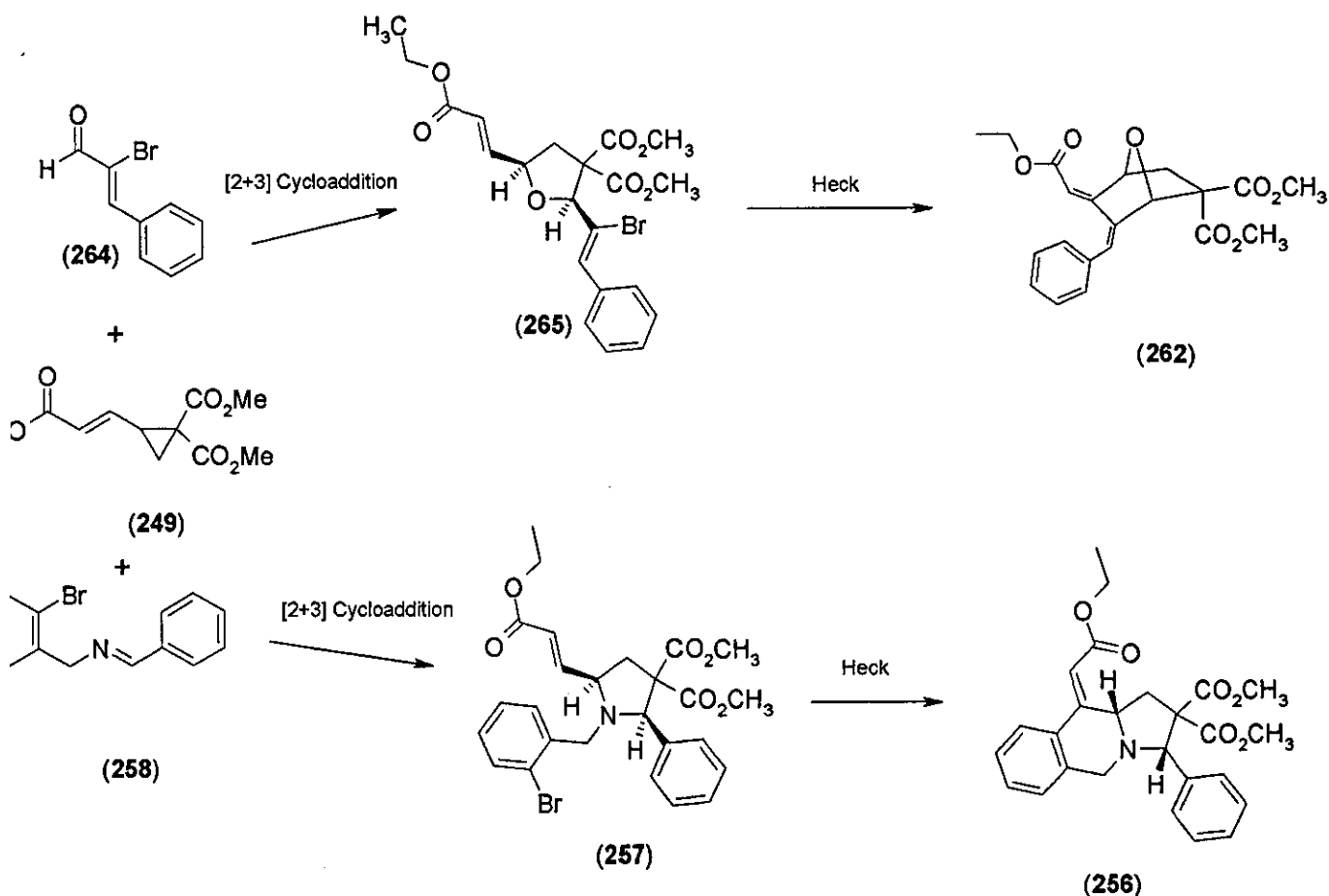
Cycloaddition Product	Yield	Heck Product	Yield
	55%		52%
	40%		56%
	36%		35%
	42%		<5%
	60%		Trace

Table 15: Examples of functionalised polycycles.

3.3 Conclusion:

Though our attempts to successfully show examples of the cascade reaction working effectively failed, we have managed to show the scope of the group's [2+3] palladium catalysed cycloaddition reaction when used in conjunction with the Heck reaction, to yield a variety of highly functionalised and in some cases, sterically demanding polycyclic systems. The ability to construct these types of compounds, using very simple building blocks, and in only two steps, would provide a very useful synthetic pathway in the total synthesis of natural product targets (**Scheme 113**).



Scheme 113: Preparation of functionalised polycycles.

Chapter 4 - Applications towards natural product synthesis:

4.1: Investigations into the synthesis of the [5.3.0] azepine core of the stemoamide group of *Stemona* alkaloids:

After the success of our investigations into the Heck reaction, we decided to investigate the second part of our project, which was applying this tandem [2+3] cycloaddition/Heck chemistry towards natural product targets. We decided to concentrate on the stemoamide group of the *Stemona* alkaloids, whose members all contain the characteristic [5.3.0] azepine core (Figure 18).

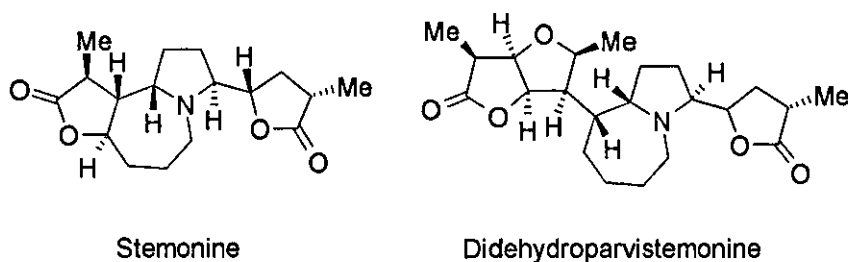
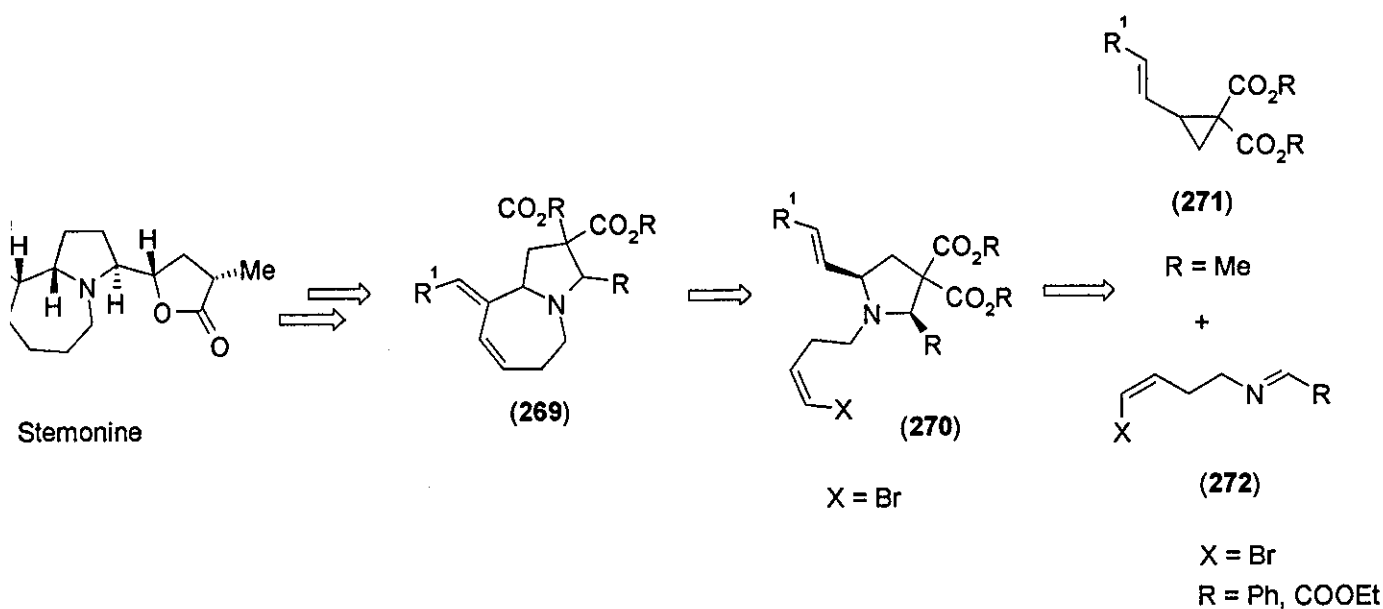


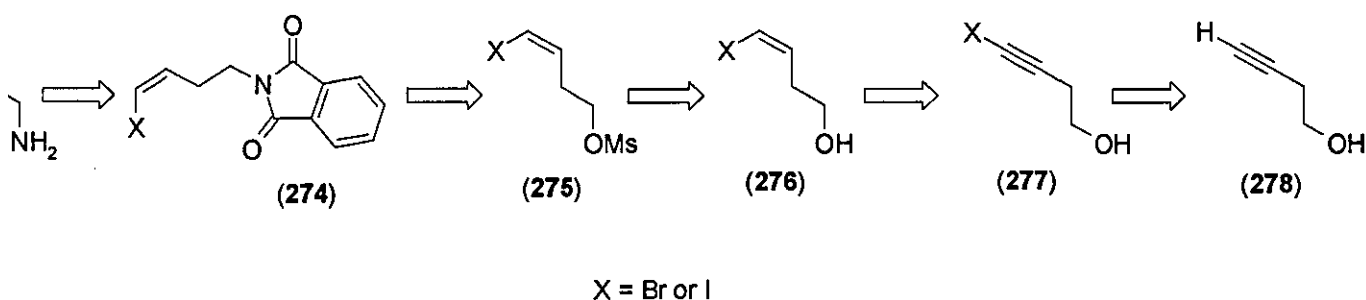
Figure 18: Two members of the stemoamide group of *Stemona* alkaloids.

In particular we thought that stemonine would make a viable target to aim for. We envisaged the palladium catalysed [2+3] cycloaddition of vinylcyclopropane (**271**) and a suitable imine trapping agent (**272**), would allow us to construct pyrrolidine (**270**) which could undergo an intramolecular Heck cyclisation, to form the [5.3.0]-bicyclic azepine core (**269**). This would leave us with the key D, C rings in place, and plenty of scope for further manipulation towards our natural product target (Scheme 114).



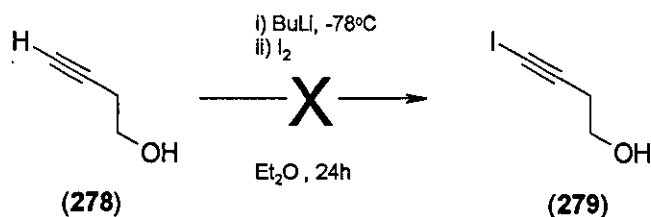
Scheme 114: Retrosynthesis of route towards [5.3.0] azepine core.

Our first target was to synthesise the imine we required for the cycloaddition step. This was not going to be as straight forward as with previous reactions, because the amine we required was not commercially available. We thought by taking commercially available 3-butyne-1-ol (**278**), we could form the corresponding halide (**277**) and reduce the acetylene to the *cis* alkene (**276**). Mesylation of the alcohol to (**275**), followed by displacement with a phthalamide group (**274**), would provide us with the protected primary amine (**274**) (Scheme 115).⁶⁸



Scheme 115: Proposed synthesis of primary amine (**273**).

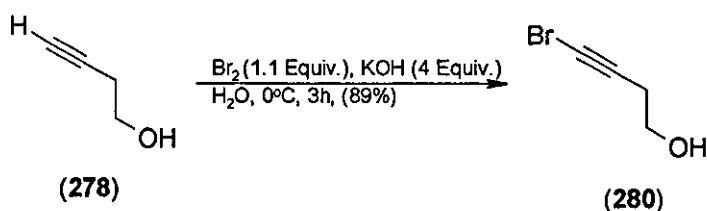
The first stage in the synthesis was to form the vinyl halide from commercially available 3-butyne-1-ol (**278**). The literature gave us a procedure in which the iodo derivative was formed using the exact same substrate.⁶⁸ We decided to use the exact same procedure to yield the iodo-alcohol derivative (**Scheme 116**).



Scheme 116: Attempted iodination of 3-butyne-1-ol.⁶⁸

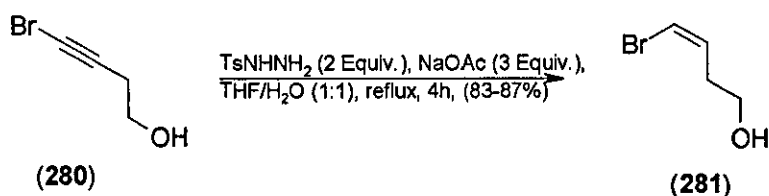
Unfortunately we failed to yield any of the desired product. Crude ¹H NMR data suggested that there was complete decomposition of starting material and no sign that the iodine analogue had been synthesised.

We decided to look at trying to construct the bromo derivative⁶⁹ due to our failed attempts at isolating the iodo compound. Again we followed the literature procedure to yield our desired target (**Scheme 117**).⁶⁹



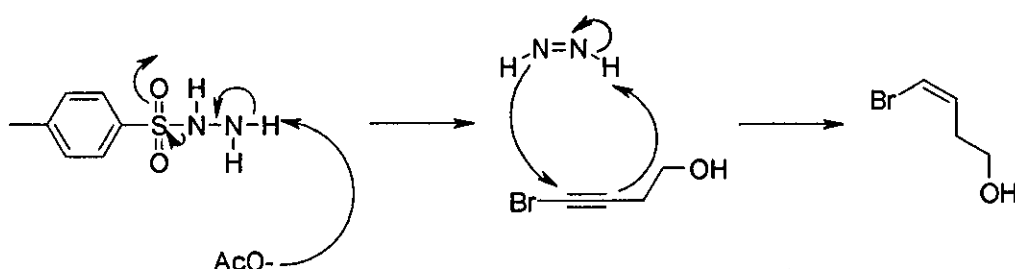
Scheme 117: Bromination of 3-butyne-1-ol (**278**).⁶⁹

The reaction worked in excellent yields of 89% and after extraction with diethyl ether and drying over Na₂SO₄, there was no need for purification. The next step was to reduce the acetylene to the *cis* alkene, again this procedure was available to us in the literature (**Scheme 118**).⁶⁹



Scheme 118: Selective reduction of acetylene (280).

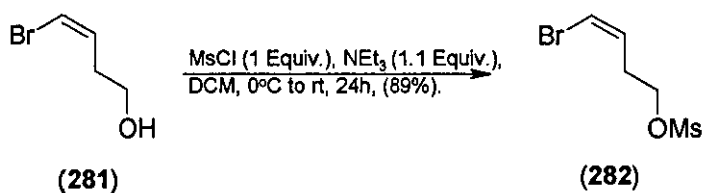
The diimide reduction proceeded smoothly and the *cis* alkene was isolated in excellent yields of 83-87% (**Scheme 119**).



Scheme 119: Mechanism of diimide reduction.

The advantage we found with this reaction was that it could be done on large scales. We had found with other reactions that increasing the scale often had an adverse affect on the yield, but were delighted to find we could use a 10 g scale and saw no reduction in the yield.

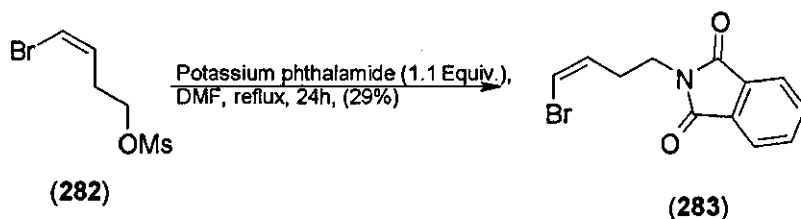
With the *cis* alkene to hand, the next stage was to mesylate the alcohol⁷⁰, so that we would have a suitable leaving group to try the displacement reaction with potassium phthalamide (**Scheme 120**).



Scheme 120: Mesylation of bromo-alcohol (281).

As expected the mesylation reaction proceeded smoothly and we got excellent yields of 89% of the mesylated product. Other bases, such as pyridine, were briefly investigated to see if the yield could be increased, but we found no significant change in the yield obtained.

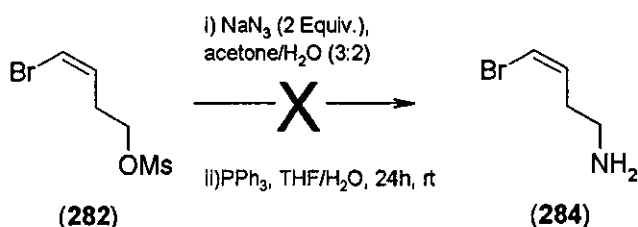
We were now just two steps away from synthesising our target amine, and the next step was crucial in the synthesis. We needed to displace the mesylate with a phthalamide group, which would enable us to follow a literature procedure in converting the phthalamide to the desired primary amine.⁷¹ The displacement of the mesylate group with phthalamide was a literature procedure (Scheme 121).⁷²



Scheme 121: Displacement of mesylate with potassium phthalamide.⁷²

Though we isolated the phthalamide product, the yield was poor at 29% and the work-up proved to be problematic, with the reaction mixture often turning to a very gelatinous substance that made handling very difficult. At this stage we decided to look at an alternative route towards the amine that would hopefully provide us with higher yields and also be easier to handle.

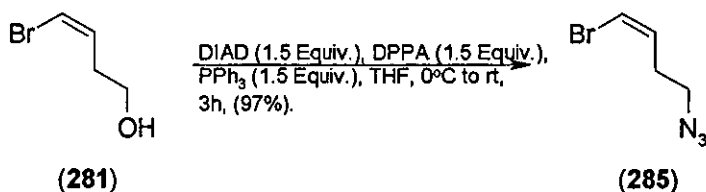
Our initial thought was to convert the mesylate group to an azide instead of the phthalamide, then reduce the azide to the amine. So we took some of our mesylated compound (**282**) and reacted this with sodium azide in acetone/water to form the azide and then triphenylphosphine in THF/water to try and synthesise the amine (Scheme 122).



Scheme 122: Attempted synthesis of amine (**285**).

Unfortunately we did not synthesise the amine. Nothing of any real significance was recovered from the reaction and it looked like complete degradation of the starting material had occurred.

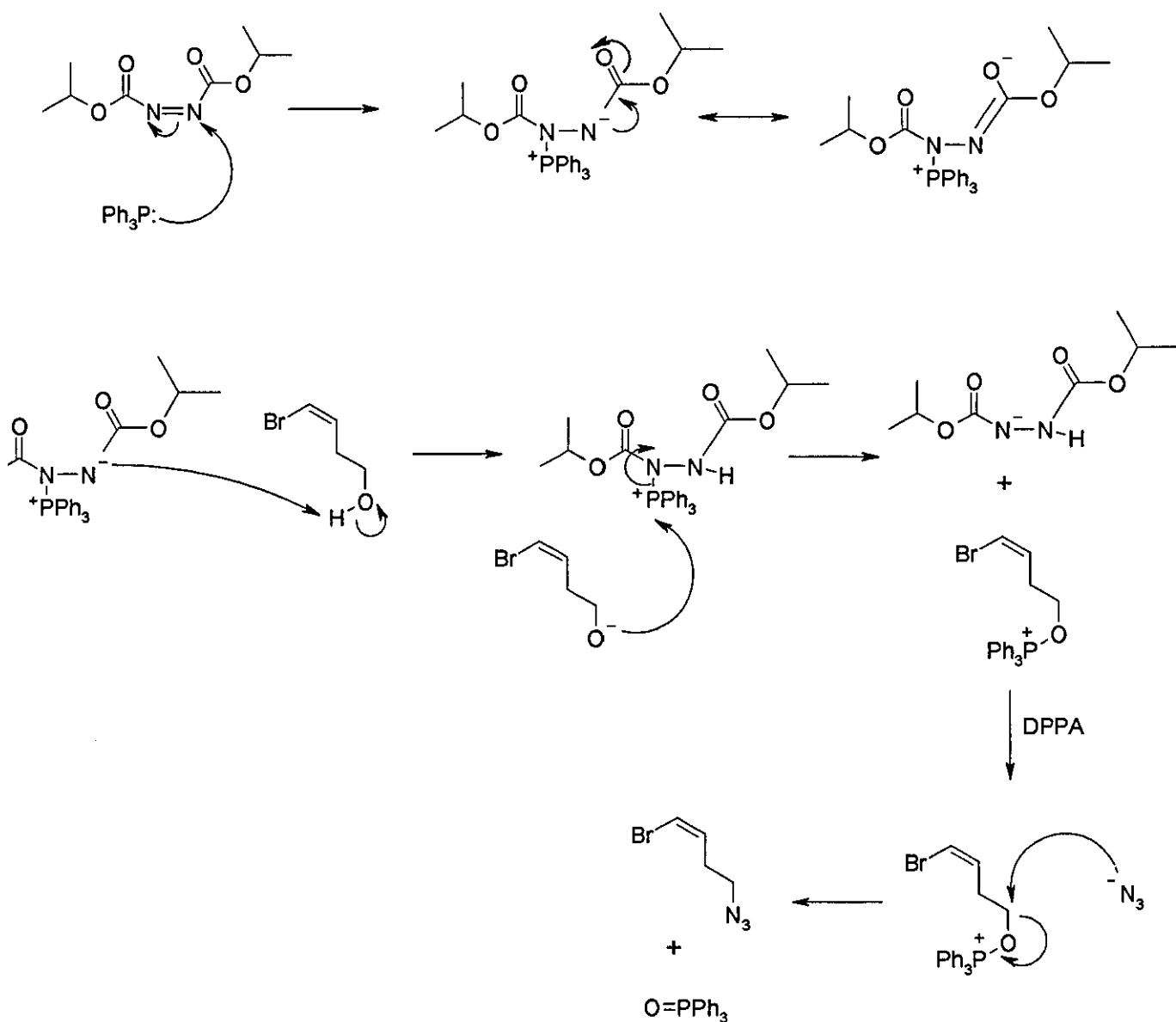
Though our initial attempt to construct the amine had failed, we were still keen to explore the potential of this methodology towards our amine target. We decided to look at the viability of using the Mitsunobu reaction in synthesising our azide^{73,74}, then use the Staudinger reaction to reduce the azide to the primary amine. So we took bromo-alcohol (**281**) and subjected it to the Mitsunobu reaction (Scheme 123).^{73,74}



Scheme 123: Synthesis of azide (**285**).

The azide was afforded in good yields of 97% (Scheme 124).

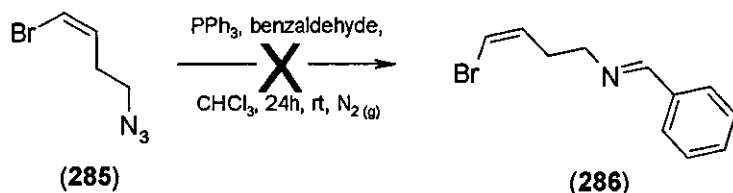
Activation of the DIAD:



Scheme 124: Mechanism of the Mitsunobu reaction.

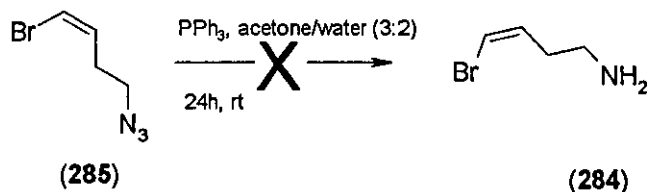
There were challenges when it came to purification of the azide. It was almost impossible to isolate the azide pure due to the fact that the diisopropylazodicarboxylate (DIAD) in particular co-eluted in every solvent system we tried. At this stage we were not too concerned and believed we could purify the amine with more success as the polarities of the DIAD and amine would be significantly different.

With the azide to hand, we now started thinking about constructing the amine. Initially we hypothesised about using an aza-Wittig type reaction, which would take us directly to our required imine. Research into the literature proved that this was an option for us. Marcus M. Sa *et al.* had used aza-Wittig type reactions to construct a variety of imines, all starting from an azide precursor.⁷⁵ Naturally we were keen to explore this further and decided to try the conditions on our azide substrate (Scheme 125).



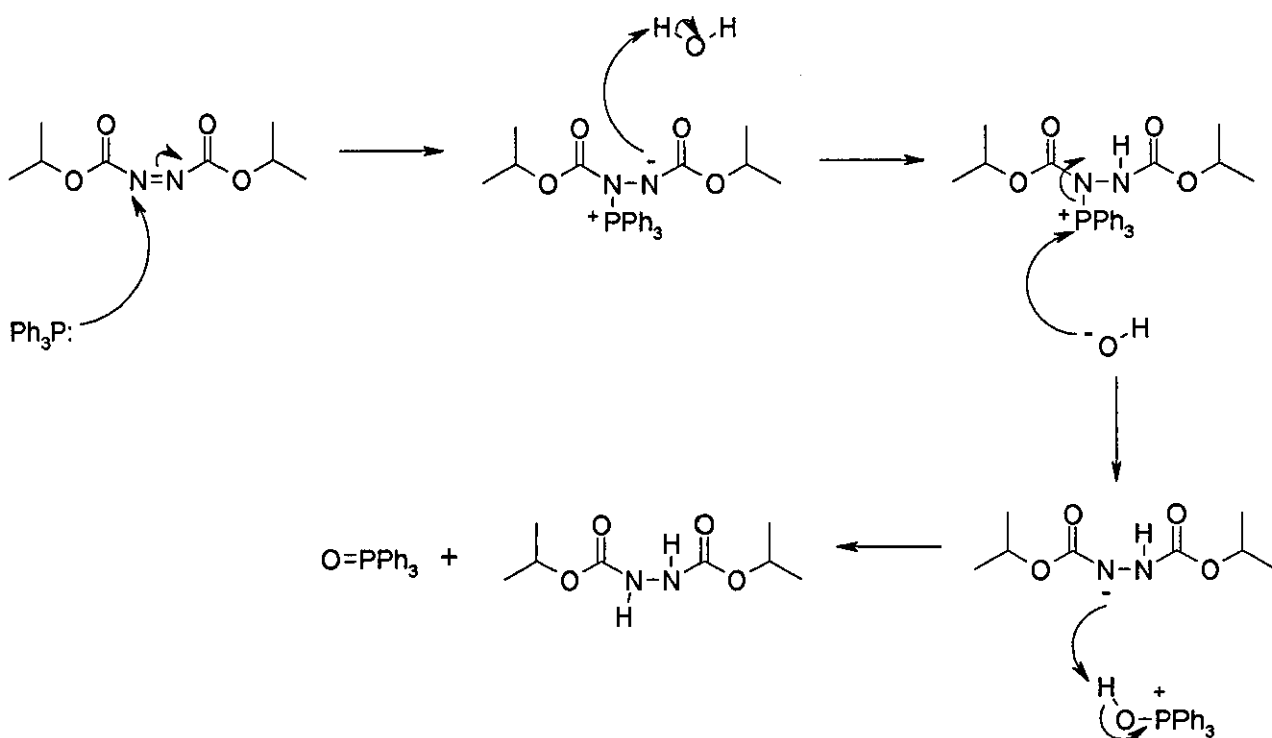
Scheme 125: Attempted aza-Wittig reaction.⁷⁵

Unfortunately we isolated none of the imine (286), only benzaldehyde was recovered from the reaction. We briefly looked at changing the solvent system and investigated using DCM and THF as alternatives. But these did not have an affect on the reaction outcome. Though we were slightly disappointed that the aza-Wittig reaction had failed, we were still keen to synthesise the amine, so we tried the Staudinger reaction again on the azide to try and yield us the primary amine (Scheme 126).



Scheme 126: Attempted Staudinger reaction of azide (285).

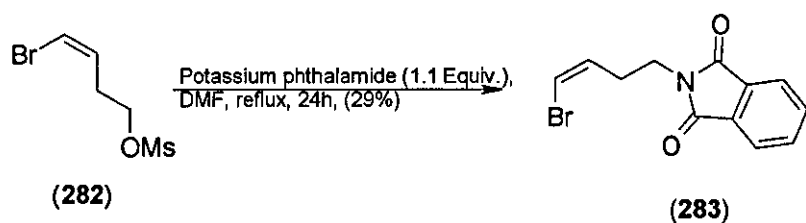
Again we failed to yield the amine. Interestingly we found that from the ¹H NMR data, there were significant signal shifts in those corresponding to the DIAD product we had carried through from the Mitsunobu reaction. This led us to believe that the DIAD by-product was in fact being reduced rather than the azide. This would explain the reason why we were seeing no sign of the amine (Scheme 127).



Scheme 127: Mechanism of DIAD being reduced by excess PPh_3 , instead of the azide compound (285)

Though we had potentially uncovered the reason why the reaction had failed, it did not help us in actually constructing the amine we required. With the fact that it was the DIAD causing the problems and we had already found we could not separate the azide cleanly from it, we decided to go back to the original phthalamide route.

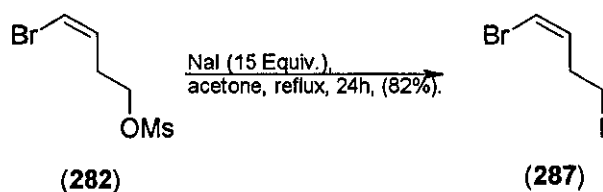
When we first looked at this procedure we managed to isolate the desired phthalamide product, but in very low yields of 29%, so we decided to look at how we could increase this yield significantly. The obvious place to start, was to look at using different solvent systems (Table 16).



Solvent	Yield	Temperature
DMF	29%	Reflux
Acetone	15%	Reflux
DME	33%	Reflux
2-butanone	37%	Reflux
DCM	8%	Reflux

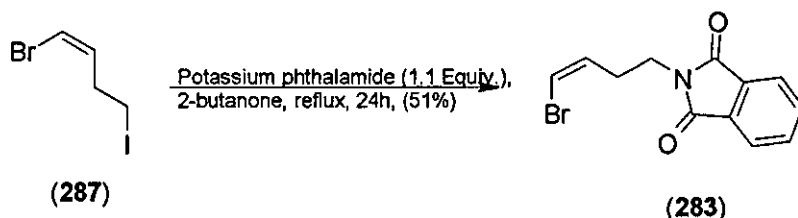
Table 16.

From our investigations we found that by using 2-butanone, a lower boiling point solvent, we managed to increase the yield to 37%. This still was not satisfactory, so we decided to look at changing the group we were displacing. We thought initially that the mesylate would prove to be a suitable leaving group, but with the low yields we were obtaining, we decided to look at an alternative. Replacing the mesylate with iodine, would provide an excellent alternative for us to investigate. The mesylate could easily be converted into an iodine by use of the Finkelstein type reaction.⁷⁶ This would then allow us to try the displacement reaction again with potassium phthalimide and hopefully see an increase in the yield (Scheme 128).



Scheme 128: Finkelstein reaction.⁷⁶

The Finkelstein worked in excellent yields of 82% and even more pleasing was that no purification was required after work-up. The next stage was to re-try the reaction with potassium phthalamide (**Table 17**).

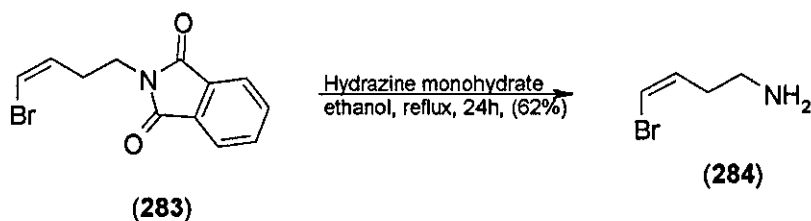


Solvent	Yield	Temperature
DMF	35%	Reflux
Acetone	10%	Reflux
DME	27%	Reflux
2-butanone	51%	Reflux
DCM	No Reaction	Reflux

Table 17.

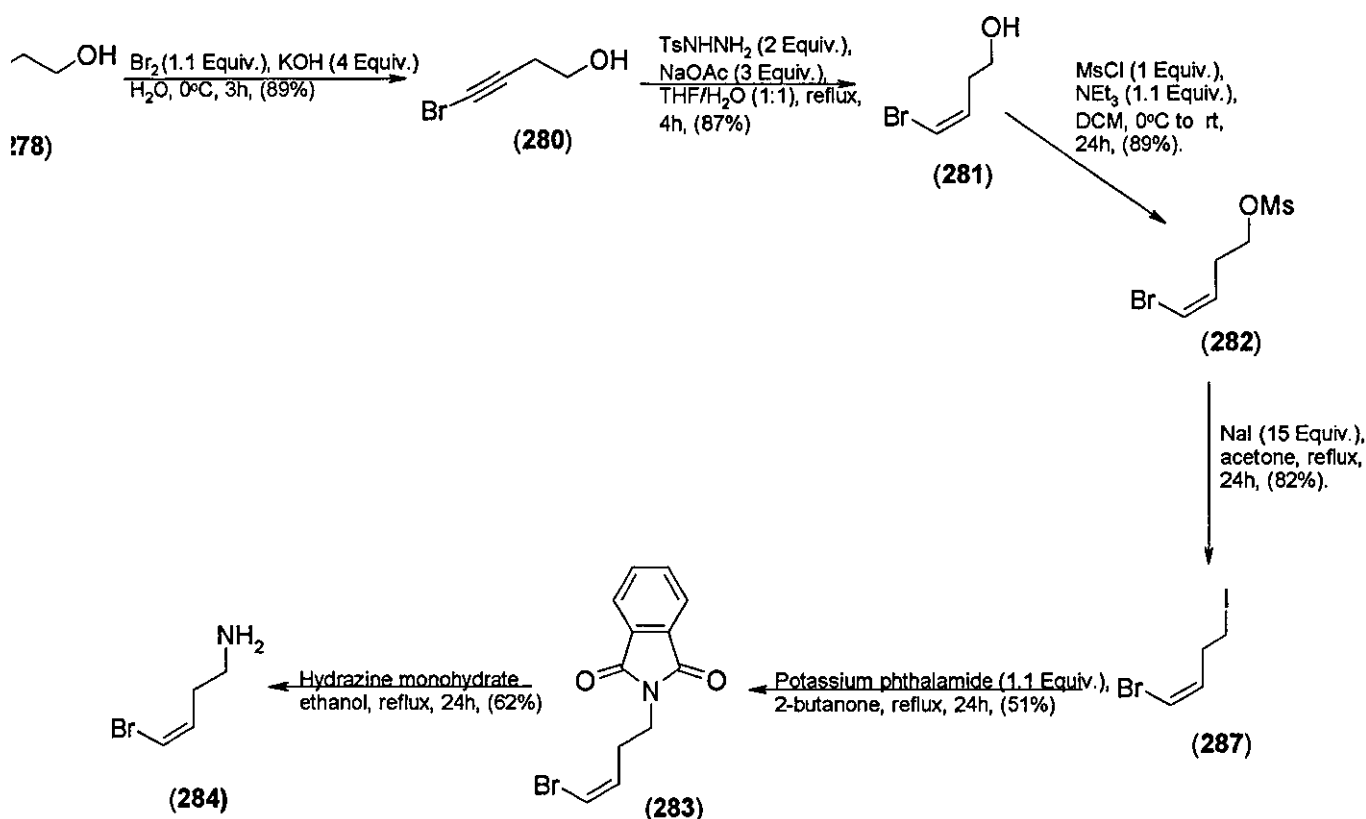
We found that the reaction proceeded in an increased yield of 51% when 2-butanone was used as the solvent. Purification was a simple task as well, with flash chromatography easily separating out the desired phthalamide product and unreacted starting material was recovered that could be recycled into producing more of the phthalamide.

The final step of the Gabriel synthesis was to de-protect the amine. Again after research into the literature we found a suitable procedure for us to test on our substrate (**Scheme 129**).⁷⁷



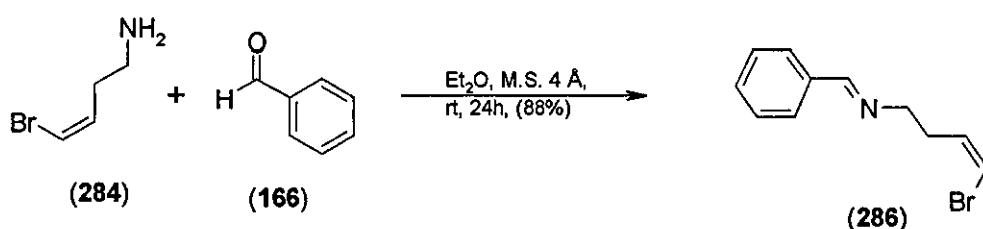
Scheme 129: Final stage of the Gabriel synthesis to form amine (284).

We finally achieved our initial target of the amine in an overall yield of 18 % in six steps. We were pleased with this outcome, particularly as all of the steps within the synthesis could be done on large scales, which gave us a good amount of the amine material to work with. The scheme below summarises the total synthesis of the primary amine (284) (Scheme 130).



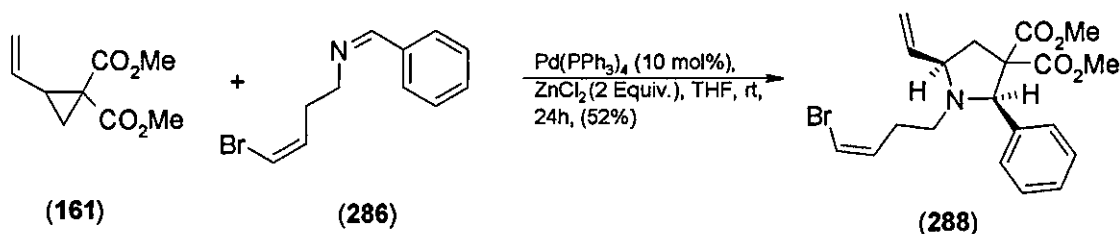
Scheme 130: Total synthesis of amine (285) in six steps from 3-butyn-1-ol (278).

Now we had successfully synthesised the amine we could turn our attention back to constructing the [5.3.0] bicyclic azepine core. The next stage in this approach was to use the freshly prepared amine and form the imine we required for the [2+3] cycloaddition step. Imine (**286**) was chosen as an initial target because we felt the presence of the phenyl group would make the imine more robust (**Scheme 131**).



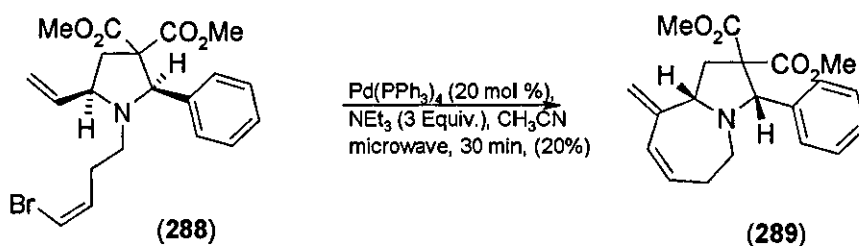
Scheme 131: Synthesis of imine (**286**).

We isolated the benzyl imine derivative in decent yields of 88%. With the imine to hand we attempted to construct the pyrrolidine required to carry out the Heck cyclisation investigations on (**Scheme 132**).



Scheme 132: [2+3] cycloaddition to form pyrrolidine (**288**).

The [2+3] palladium catalysed cycloaddition proceeded smoothly and yielded us our desired pyrrolidine in a 52% yield exclusive to the *cis* isomer. The tetrahydrofuran by-product was isolated in yields of about 35%. The final step was to try the Heck cyclisation (**Table 18**).

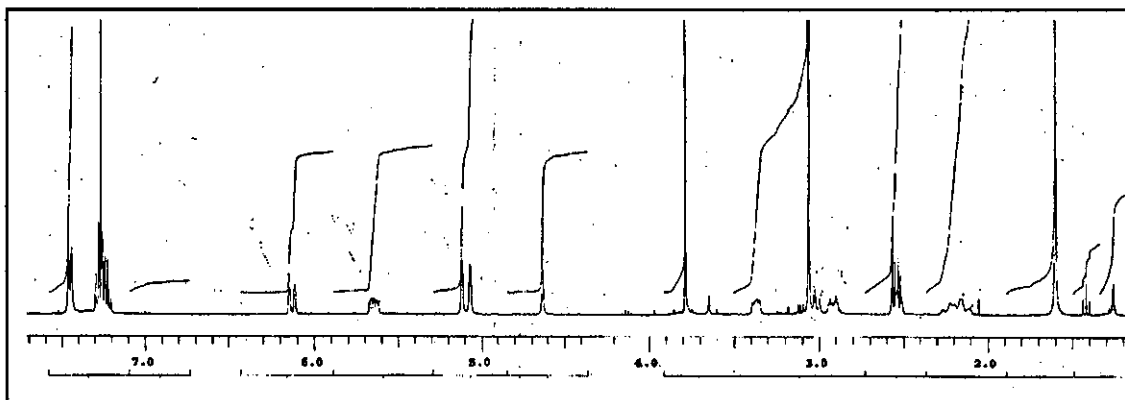


Pd (0) Source	Base	Equiv Base	Solvent	Temperature	Time	Yield
$\text{Pd(PPh}_3)_4$	NEt_3	3	-	100°C	24h	5%
Pd(OAc)_2	$^i\text{PrNEt}_2$	2	DMF	100°C	24 h	15%
$\text{Pd(PPh}_3)_4$	NEt_3	3	CH_3CN	Microwave	15 min	27% ^a

a: 5 mol% $\text{Pd(PPh}_3)_4$

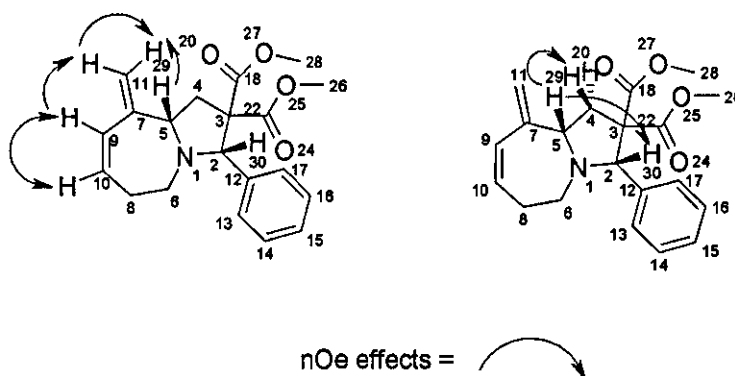
Table 18.

We were delighted to find that the Heck cyclisation was successful and the product we isolated was consistent with that of the Heck reaction proceeding *via* a 7-*exo trig* pathway. This meant we had accessed the [5.3.0] azepine core in just two steps from simple building blocks. Initial reactions were carried out in the microwave using a catalyst loading of 20 mol% $\text{Pd(PPh}_3)_4$, but we found that this could be reduced to as little as 5 mol% and the reaction time reduced to just 15 minutes in the microwave. We also proved that the Heck cyclisation was capable of working using Pd(OAc)_2 and heated for 24 hours, albeit in a slightly less yield. From ^1H NMR data, we could see clearly the formation of an *exo* methylene group, with the 2 hydrogens of the methylene moiety appearing as 2 singlets around 5 ppm, a characteristic splitting pattern for an *exo* methylene group (Scheme 133).



Scheme 133: ^1H NMR of 7-methylene-2-phenyl-5,6,9,9a-tetrahydro-1H-pyrrolo[1,2-a]azepine-3,3-dicarboxylic acid diethyl ester (**289**).

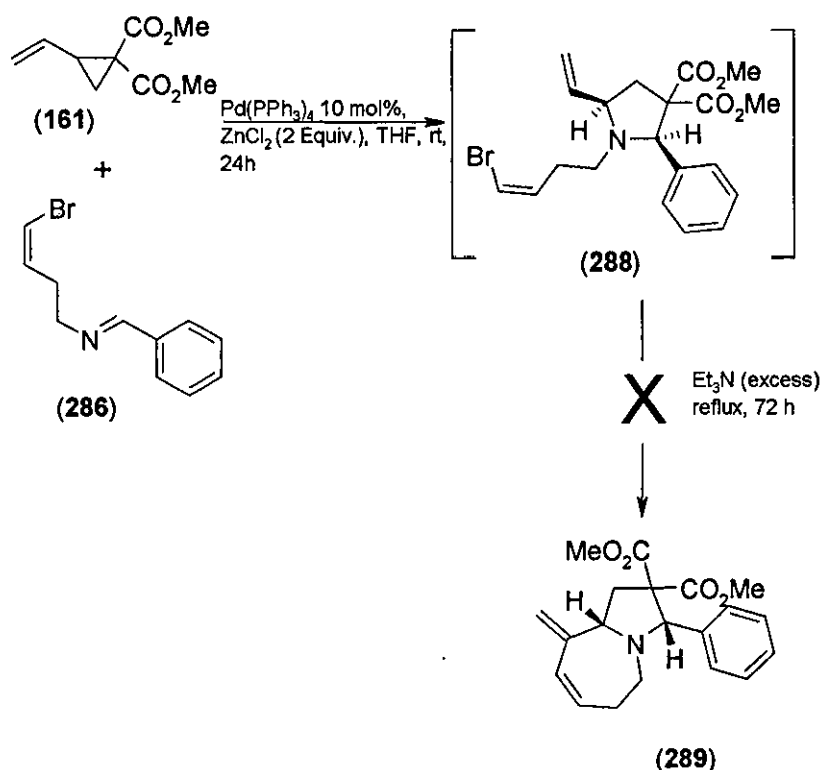
The stereochemistry across the ring was assigned as *cis* by nOe experiments. We could clearly see an interaction between the 5-CH hydrogen and the 2-CH hydrogen which showed they were both on the same face (**Scheme 134**).



Scheme 134: nOe effects showing the stereochemical outcome of 7-methylene-2-phenyl-5,6,9,9a-tetrahydro-1H-pyrrolo[1,2-a]azepine-3,3-dicarboxylic acid diethyl ester (**289**).

The scope of this reaction was investigated further and we looked into the possibility of doing this reaction in a one-pot procedure. If successful, this would provide an extremely quick and efficient route into the [5.3.0] bicyclic core of the stemoamide group of

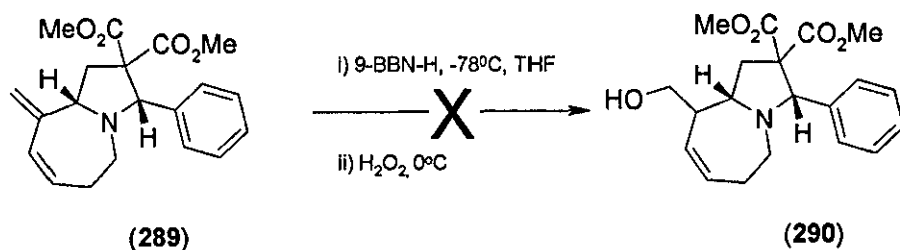
Stemona alkaloids, with plenty of flexibility for further manipulation towards a natural product target (Scheme 135).



Scheme 135: One-pot intramolecular Heck cyclisation with alkylbromine substituted imines.

Unfortunately we did not isolate any of the Heck product, but we did recover some of the cycloaddition product back (15-20%), which proved that at least the first stage of the reaction was working, and gave us hope that we would be able to get this one-pot procedure to work.

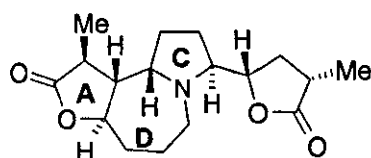
Due to the preference of the Heck cyclisation to react *via* the 7-*exo trig* pathway this left an *exo* double bond which would be ideal for further chemical manipulation, as it would be more reactive than the internal double bond. This would allow us to try a hydroboration to convert the alkene into an alcohol or an ozonolysis to form the aldehyde. This added chemical reactivity would be invaluable if we were looking to try and construct a natural product target from this azepine skeleton. We decided to investigate the reactivity of this *exo* double bond, to prove our theories were correct. So we decided to try a hydroboration reaction, to form the alcohol (Scheme 136).



Scheme 136: Attempted hydroboration of 7-methylene-2-phenyl-5,6,9a-tetrahydro-1H-pyrrolo[1,2-a]azepine-3,3-dicarboxylic acid diethyl ester (290).

Unfortunately we were unable to isolate any of the desired product. We tried the hydroboration reaction on a simple substrate, like styrene, and found we were able to isolate the alcohol product in decent yields of 60%. We were confident that we could apply the same success to the [5.3.0] azepine core substrate, but at this stage we were more concerned with adapting the methodology to leave us in a better position to construct a natural product target.

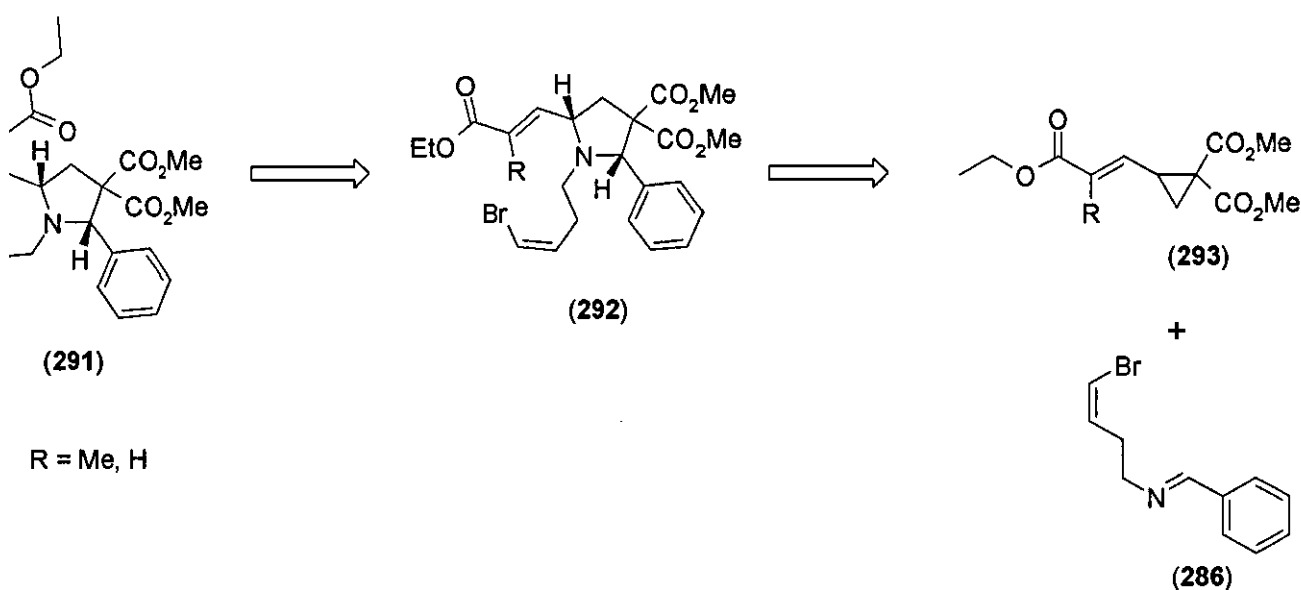
With the success of constructing the azepine skeleton, we decided to investigate the possibility of synthesising stemonine. With the core D, C rings of the structure already completed, it was the construction of the lactone A ring which we targeted next (Figure 19).



Stemonine

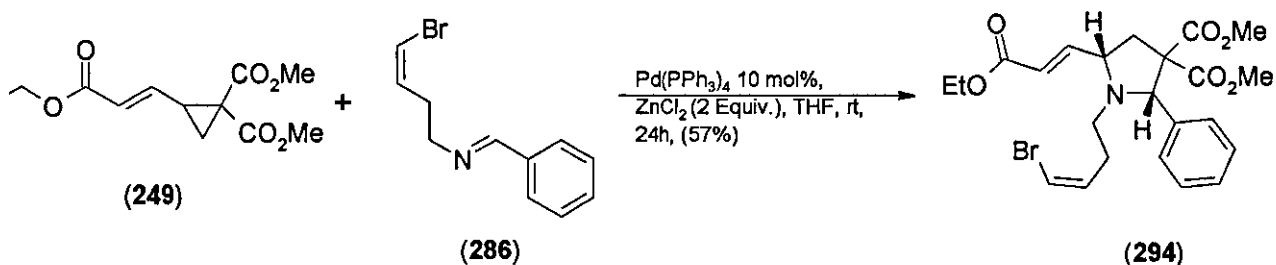
Figure 19.

We felt that we could manipulate our previous methodology in synthesising the [5.3.0] bicyclic skeleton, to leave us in an ideal position to form the lactone ring in later steps. Though with azepine skeleton (289) we could construct the lactone ring by manipulating the *exo* double bond, we felt we could reduce the number of steps required to do this, by incorporating the correct number of carbons right from the start. We envisaged using the ethyl ester cyclopropane derivative (293) and reacting this with the imine (286) to give us the ethyl ester pyrrolidine structure (292). Finally a Heck cyclisation would yield us the [5.3.0] bicyclic structure (291). Now we would have an ethyl ester group, which we could easily manipulate to perform an iodolactonisation reaction and construct the lactone ring. More importantly, if this route was successful, it would also allow us the opportunity to incorporate the methyl group of the lactone ring at the Wittig stage. (Scheme 137).



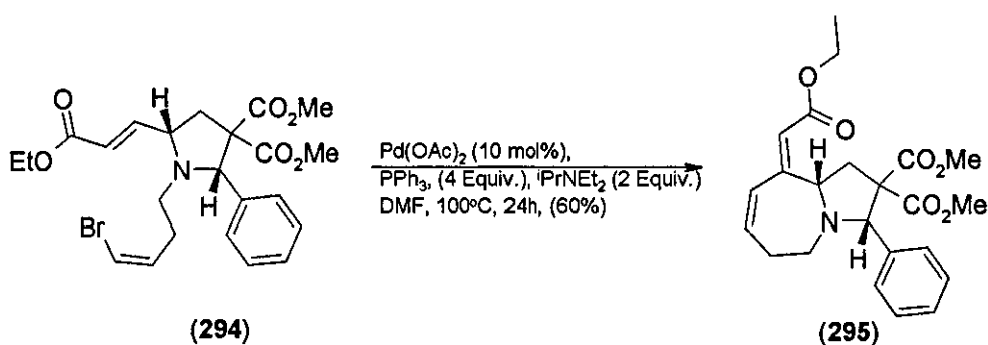
Scheme 137: Proposed synthesis of ethyl ester bicyclic derivative.

Firstly we needed to construct the cyclopropane we required, which we did using the previous methodology of cyclopropanating acrolein (214), followed by a Wittig reaction as described earlier. We then took our pre-prepared imine (286), synthesised using the same methodology as described previously and constructed the pyrrolidine structure (294) using the group's [2+3] palladium catalysed cycloaddition reaction (Scheme 138).



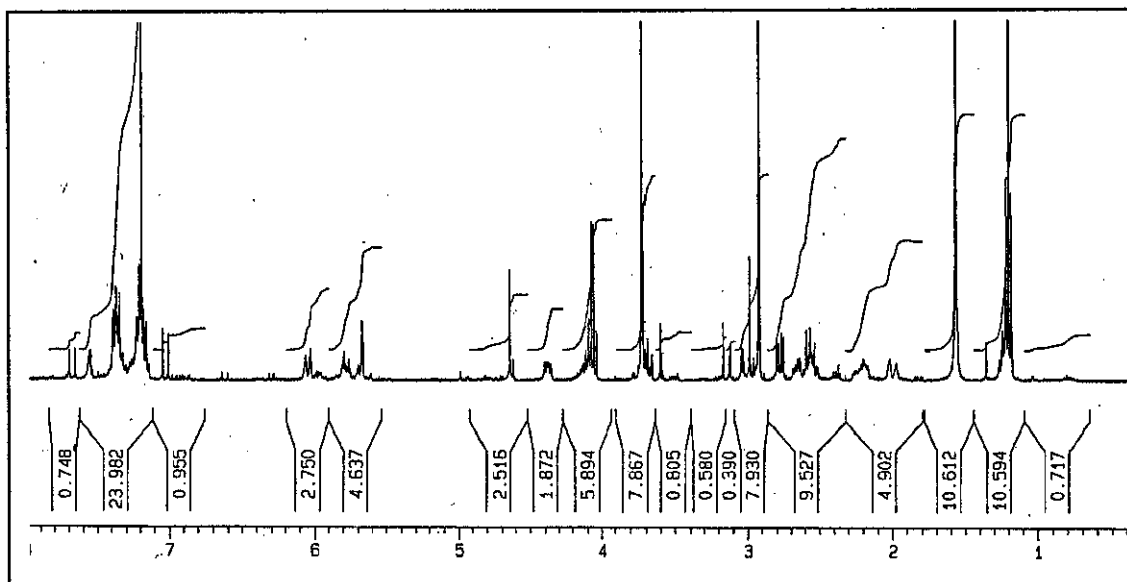
Scheme 138: Synthesis of pyrrolidine scaffold (295).

The reaction worked well with the pyrrolidine being isolated in a 57% yield. We also saw complete stereoselectivity towards the *cis* isomer. Again we isolated approximately 40% of the tetrahydrofuran by-product. The final stage was to try the Heck cyclisation on the ethyl ester pyrrolidine derivative (Scheme 139).



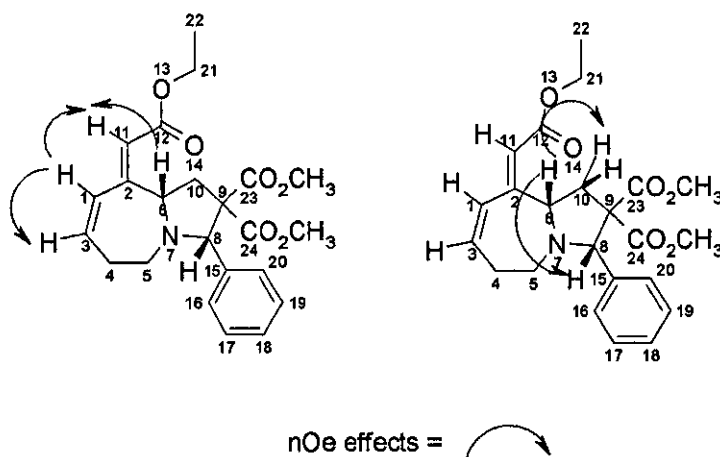
Scheme 139: Heck cyclisation of pyrrolidine (294).

The Heck cyclisation worked in excellent yields of 60%. Interestingly with this particular cyclisation we found that the optimum conditions were in fact Pd(OAc)_2 , heating in DMF at 100°C. From ^1H NMR data, we were able to identify the characteristic peak of the hydrogen of the *exo* alkene moiety appearing as a singlet at around 5.6 ppm, pointing towards the reaction proceeding *via* a 7-*exo* *trig* pathway (Scheme 140).



Scheme 140: ^1H NMR of 2-ethoxycarbonylmethylene-8-phenyl-5,6,9,9a-tetrahydro-1*H*-pyrrolo[1,2- α]azepine-9,9-dicarboxylic acid dimethyl ester (**295**).

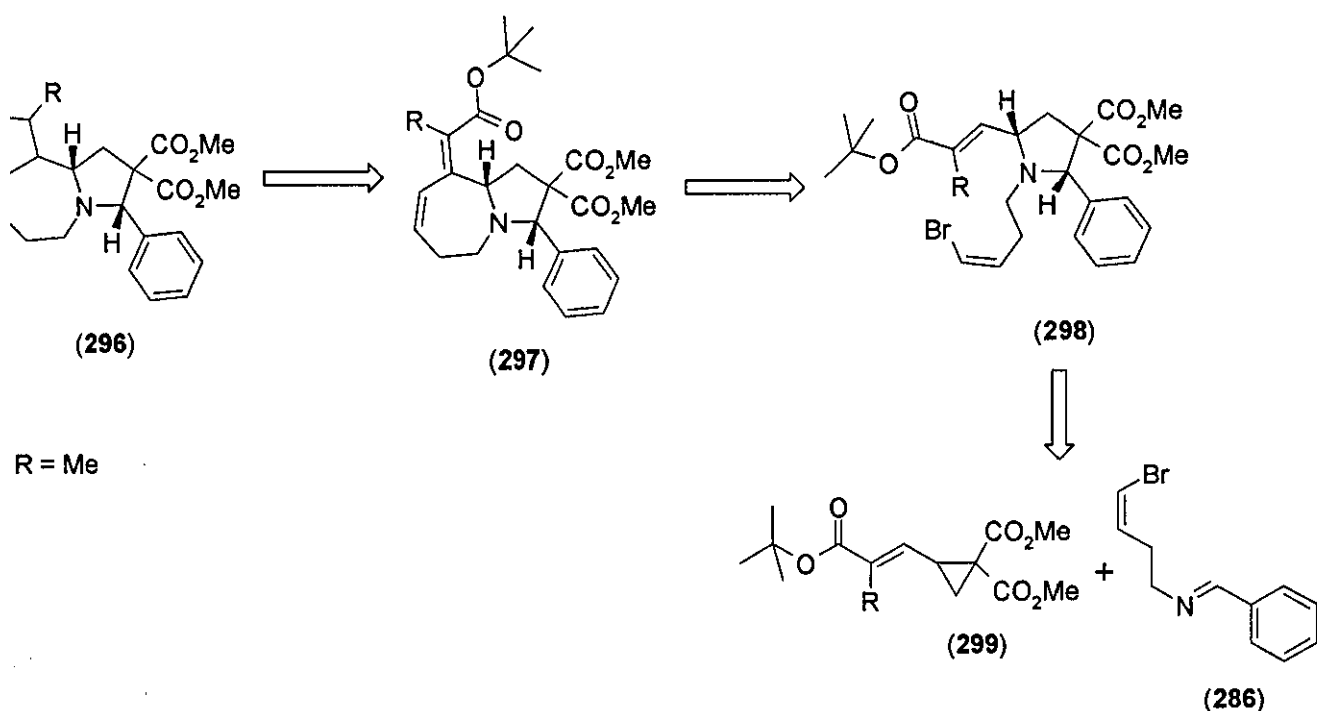
The stereochemistry across the ring was again *cis*, determined from nOe experiments, which indicated that the 6-CH hydrogen was on the same face as the 8-CH hydrogen (**Scheme 141**).



Scheme 141: nOe Effect showing the stereochemical outcome of 2-ethoxycarbonylmethylene-8-phenyl-5,6,9,9a-tetrahydro-1*H*-pyrrolo[1,2- α]azepine-9,9-dicarboxylic acid dimethyl ester (**295**).

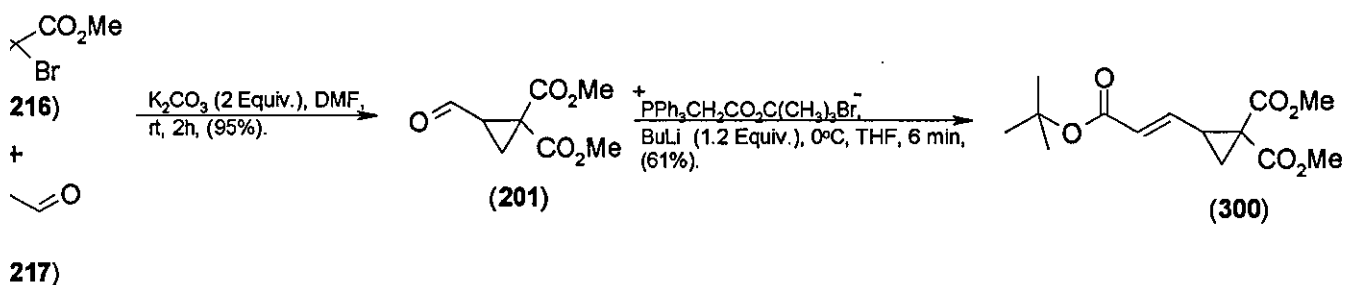
We observed decreased yields when the same reaction was tried in the microwave. This was an important step towards constructing the lactone ring of stemonine. We now proved that we could isolate an alternative [5.3.0] bicyclic azepine derivative, with the potential to go on and construct the lactone ring.

The success with the previous Heck cyclisation, lead us to propose an alternative route towards the lactone ring “A” of stemonine. We believed that if we could isolate the *tert*-butoxy analogue, this would put us in an even stronger position to perform the iodolactonisation to construct the lactone ring. The route towards this new target would follow a similar path like our previous methods. We envisaged bicyclic structure (297) could be constructed from a Heck cyclisation of pyrrolidine (298). We believed that a [2+3] cycloaddition reaction between cyclopropane (299) and imine (286) would construct the desired pyrrolidine (298). If the Heck cyclisation followed a 7-*exo-trig* reaction pathway, like previous attempts had done, this would enable us to look into constructing the tricyclic system (296). Either a straight iodolactonisation reaction could be carried out on (297), depending on the geometry of the *tert*-butoxy group on the alkene, or a selective reduction of the *exo* double bond, followed by an iodolactonisation, would construct the lactone ring and leave us very close to a natural product target. We could even look at incorporating the methyl group of the lactone ring, at the beginning of the synthesis, by using an appropriate Wittig reagent and constructing the required cyclopropane derivative. This showed the huge potential of the [2+3] cycloaddition chemistry when used in tandem with the Heck reaction. We could easily construct highly functionalised bicyclic systems in just two steps from simple building blocks, a major advantage in natural product synthesis, something we were looking to highlight in our strategy towards stemonine (Scheme 142).



Scheme 142: Proposed route to *tert*-butoxy bicyclic derivative.

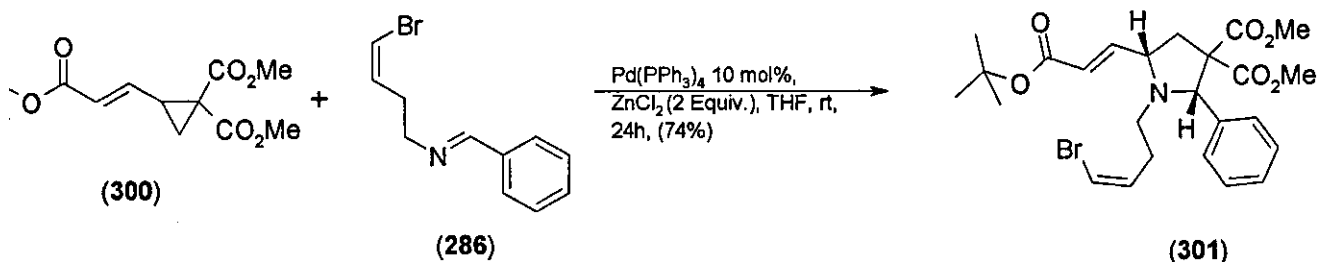
The *tert*-butoxy cyclopropane (**300**) analogue was prepared using the same methodology as described previously. Cyclopropanation of acrolein (**214**) using dimethyl bromomalonate (**216**) and then a Wittig reaction of the resulting aldehyde (**201**) gave us the desired cyclopropane derivative in decent yields of 61% (**Scheme 143**).



Scheme 143: Synthesis of 2-(2-*tert*-butoxycarbonylvinyl)-cyclopropane-1,1-dicarboxylic acid dimethyl ester (**300**).

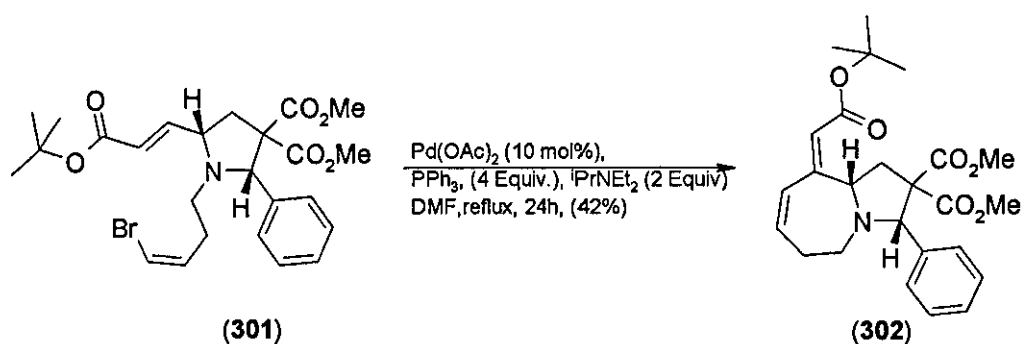
The next step was to try and construct the pyrrolidine we required for the Heck cyclisation. Again this utilised the group's [2+3] palladium catalysed cycloaddition reaction. The imine (**286**) was prepared in the same way as described previously and

reacted with the cyclopropane (**300**), in the same manner as previous cycloaddition reactions (**Scheme 144**).



Scheme 144: Preparation of pyrrolidine (**302**) via the [2+3] cycloaddition reaction.

The reaction proceeded smoothly, and purification was a simple matter done by flash chromatography, to yield the desired pyrrolidine in a 74% yield, stereospecific to the *cis* isomer. Crucially we isolated <10% of the tetrahydrofuran by-product, a factor in why we saw such a dramatic increase in the yield, to the previous cycloaddition reactions. We were delighted with this particular result because the cycloaddition afforded the *cis* isomer exclusively, which left us in an ideal position for the subsequent Heck reaction (**Scheme 145**).

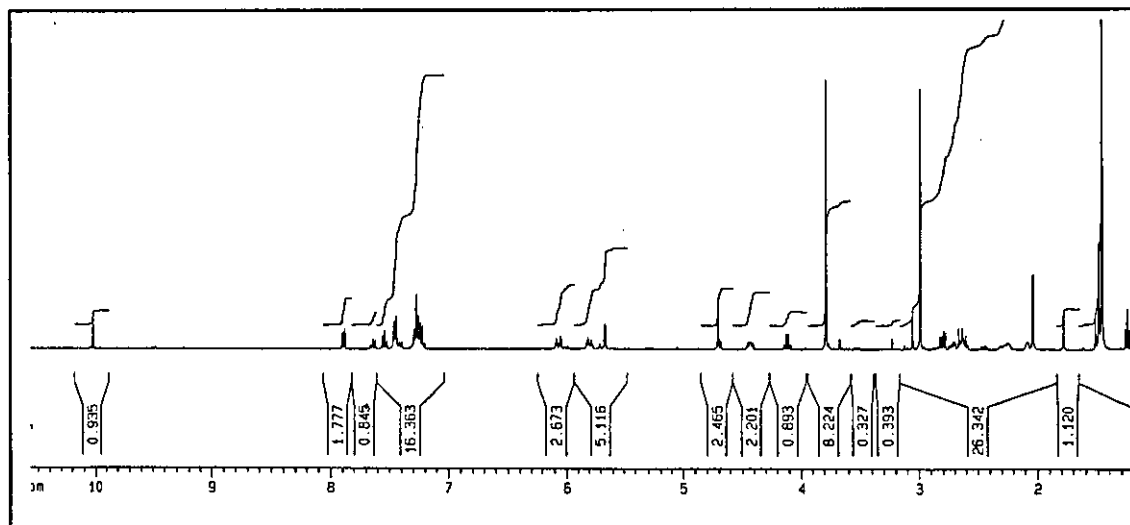


Pd (0) Source	Base	Equiv Base	Solvent	Temperature	Time	Yield
Pd(PPh ₃) ₄	NEt ₃	3	-	100°C	24h	15%
Pd(OAc) ₂	ⁱ PrNEt ₂	2	DMF	100°C	24 h	42%
Pd(PPh ₃) ₄	NEt ₃	3	CH ₃ CN	Microwave	30 min	17%

Scheme 145: Heck cyclisation of pyrrolidine (**302**).

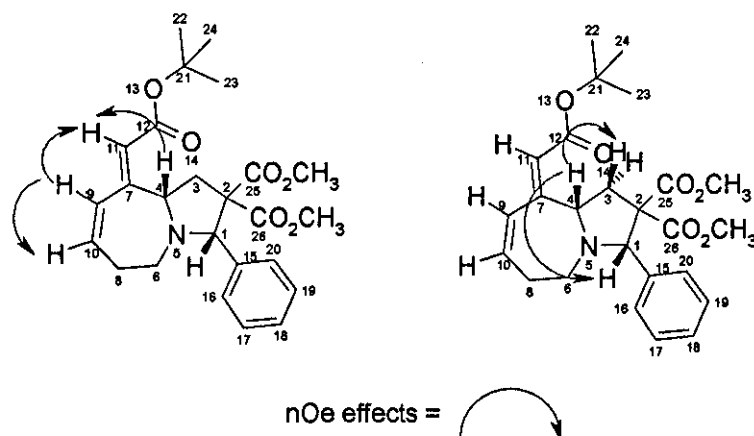
The Heck cyclisation proved to be successful once again. The use of Pd(OAc)₂, Hünig's base and heating at 100°C in DMF for 24 hours, gave the highest yield. The reaction was

tried using $\text{Pd}(\text{PPh}_3)_4$ in both the microwave and under reflux and though using these conditions we isolated the Heck product, the yields were dramatically reduced. From ^1H NMR data, we were confident that the reaction had proceeded *via* a 7-*exo trig* pathway, as we could clearly identify the hydrogen of the *exo* alkene moiety, appearing as a singlet at around 5.5 ppm (**Scheme 146**).



Scheme 146: ^1H NMR of 7-*tert*-butoxycarbonylmethylene-1-phenyl-5,6,9,9a-tetrahydro-1*H*-pyrrolo[1,2*a*]azepine-2,2-dicarboxylic acid dimethyl ester (**302**).

The stereochemistry across the ring was also assigned as *cis*, by using nOe experiments. Again this followed the pattern of previous successful Heck cyclisations, with the *cis* stereochemistry being the preferred geometry for the cyclisation to adopt due to the *cis* stereochemical nature of the pyrrolodine (**Scheme 147**).



Scheme 147: nOe Effects showing stereochemical outcome of 7-*tert*-butoxycarbonylmethylene-1-phenyl-5,6,9,9a-tetrahydro-1*H*-pyrrolo[1,2*a*]azepine-2,2-dicarboxylic acid dimethyl ester (**302**).

With the success of the Heck cyclisation, it was crucial for us to discover the geometry of the *tert*-butoxy group across the *exo* double bond. If the geometry was correct, this would enable us to perform the iodolactonisation reaction without having to selectively reduce the *exo* double bond first. If not, we would be required to selectively reduce the *exo* double bond and then perform an iodolactonisation reaction to construct the lactone ring. The only way we could conclusively prove the geometry of the *tert*-butoxy group across the *exo* double bond was by X-ray crystallography. We were delighted to find that we were able to grow a suitable crystal that would allow us to get an X-ray structure to determine which route we would need to take towards constructing the lactone ring (Figure 20).

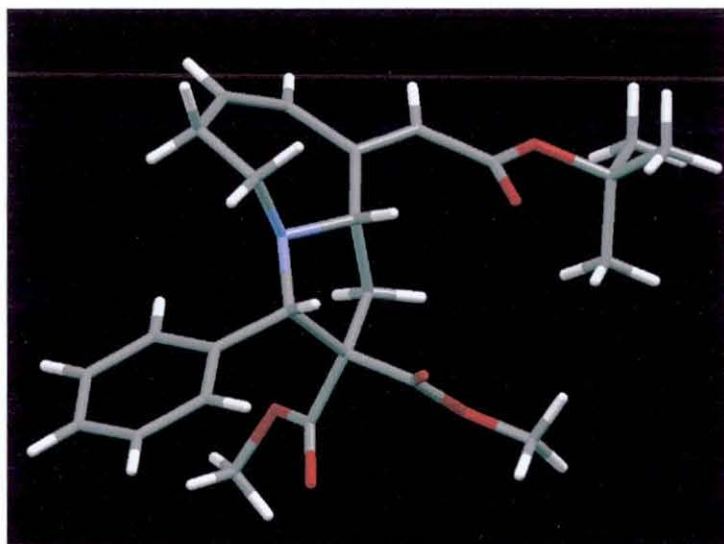
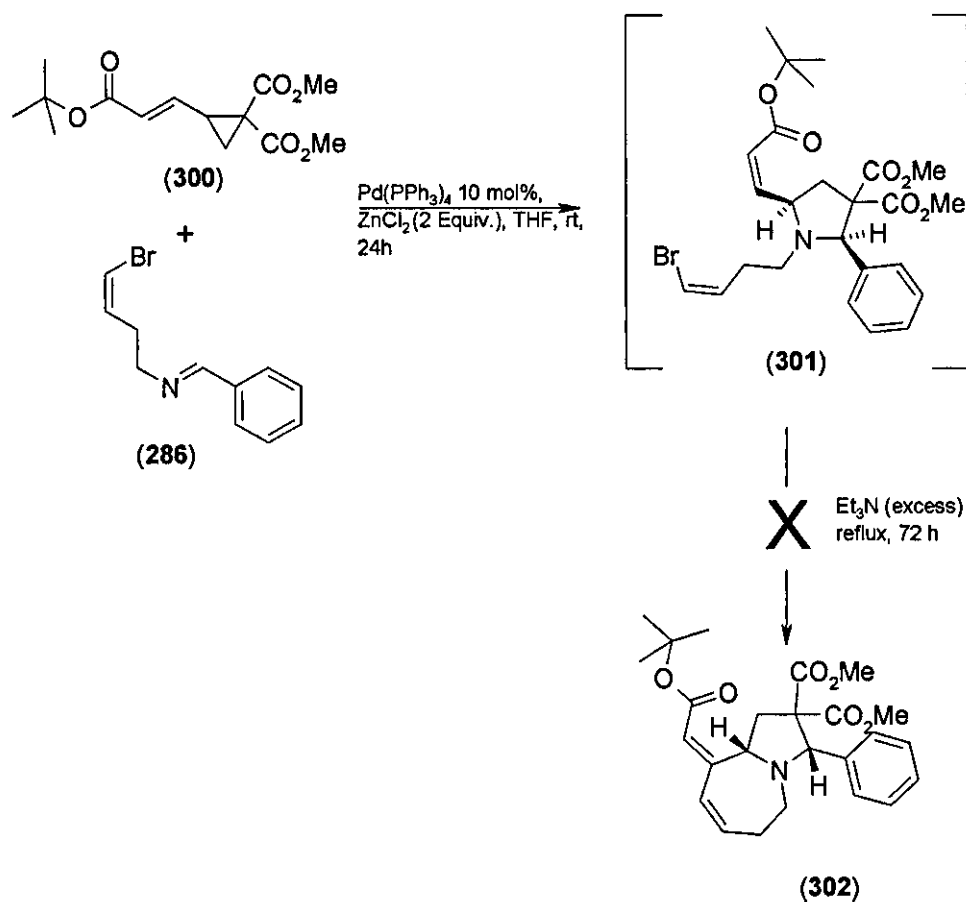


Figure 20: X-ray crystal structure of [5.3.0] bicyclic azepine (**303**). Obtained by Dr Mark Elsegood, Loughborough University.

The X-ray crystal structure of our [5.3.0] bicyclic system, clearly showed the *tert*-butoxy group in the wrong geometry for us to try the iodolactonisation directly. We can see that the *tert*-butoxy group is directed away from the 7 membered ring and is orientated more towards the 5 membered pyrrolidine ring. If we were to try the iodolactonisation directly, we would require the geometry to be such that the *tert*-butoxy group was orientated in the opposite manner, i.e. we would see it orientated over the seven membered ring and be in the correct geometry to successfully do an S_N2 attack on the iodine, to form the lactone ring.

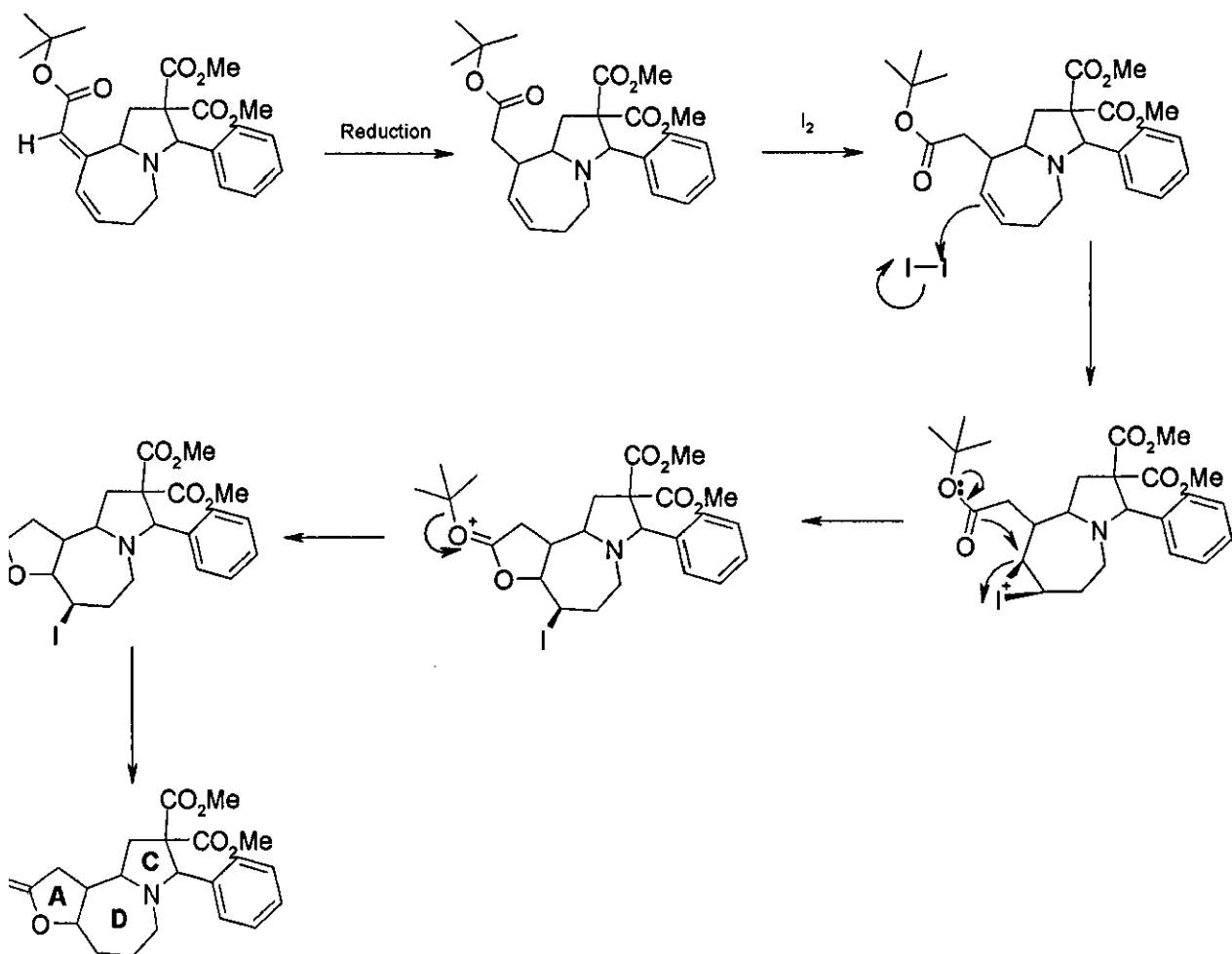
Before looking at the synthesis of the lactone ring we thought about the viability of applying this substrate to the one-pot procedure. The high yields of the cycloaddition reaction and the favourable formation of the *cis* isomer would leave us in an ideal position for the Heck cyclisation to occur successfully, particularly as we had shown the Heck cyclisation to be successful under alternative reaction conditions, albeit in a slightly less yield (**Scheme 148**).



Scheme 148: One-pot intramolecular Heck cyclisation.

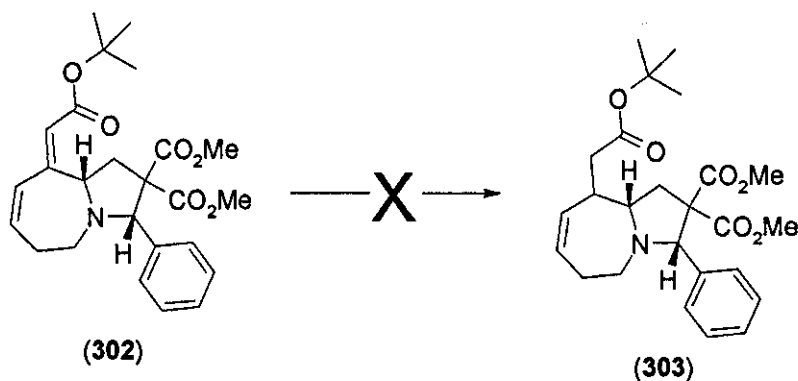
The one pot procedure again proved to be unsuccessful. We did managed to recover some of the cycloaddition product (301) (25-30%), which gave us hope that with alterations to the reaction conditions, we may be able to drive the Heck cyclisation to completion, which would prove to be a very powerful route towards our natural product target.

With the [5.3.0] azepine skeleton to hand, we turned our attention towards constructing the lactone ring. From the X-ray crystallography data the geometry across the *exo* double bond was such that we could not do the iodolactonisation directly. We would have to selectively reduce the *exo* double bond and then perform the iodolactonisation to construct the lactone ring (**Scheme 149**).



Scheme 149: Iodolactonisation mechanism to construct lactone ring.

Though it was somewhat disappointing not to be able to try the iodolactonisation directly, we now knew what was required and set about trying to selectively reduce the *exo* double bond. Research into the literature provided us with several method of selectively reducing alkene double bonds (**Scheme 150**).^{6,78,79,80,81,82}

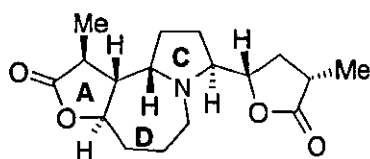


Reducing Agent	Solvent	Time	Yield
Red-Al	THF	1 h	SM
Red-Al	THF	24 h	SM
Red-Al	THF	48 h	SM
NaBH ₄	Ethanol	5 h	SM
NaBH ₄	Ethanol	24 h	SM
Diphenylsilane	CHCl ₃	3 h	SM
Diphenylsilane	CHCl ₃	24 h	?

Scheme 150: Attempted selective reduction of *exo* double bond.^{6,78,79,80,81,82}

We found with most of our attempts that we recovered starting material. Interestingly neither the *exo* or the internal double bond had been affected during the course of the reaction. Only the reaction with diphenylsilane provided us with any sort of interesting result. From crude ¹H NMR data, we could see something had happened. The characteristic singlet corresponding to the hydrogen on the *exo* alkene had gone, and we saw new multiplet signals around 2-3 ppm, where we might expect to see signals corresponding to the resulting CH₂ formed from the reduction. Unfortunately we were unable to isolate any of the material after purification, due to the small scale the reaction was done on.

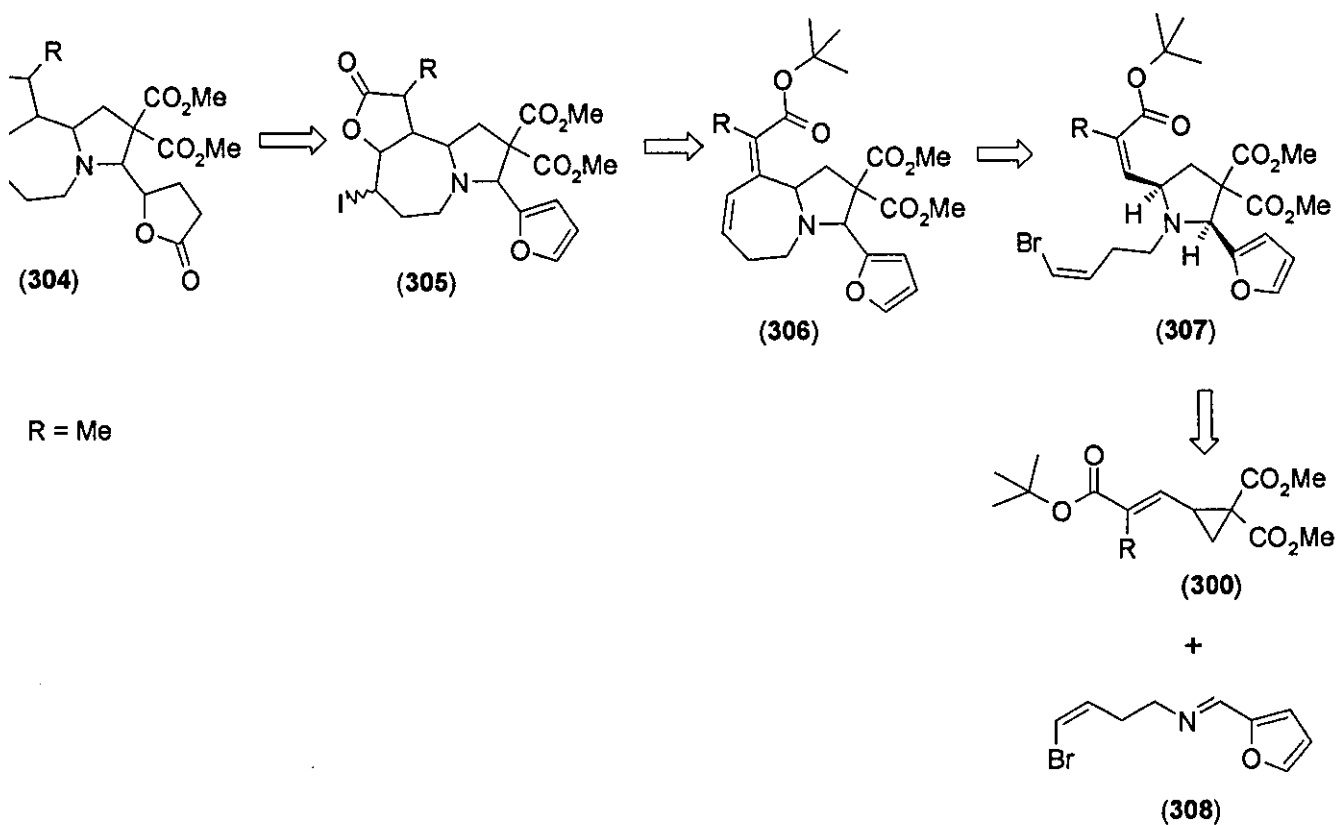
Alongside our investigations into the selective reduction of the *exo* double bond, we were also looking at how to incorporate the second lactone ring of stemonine (Figure 21).



Stemonine

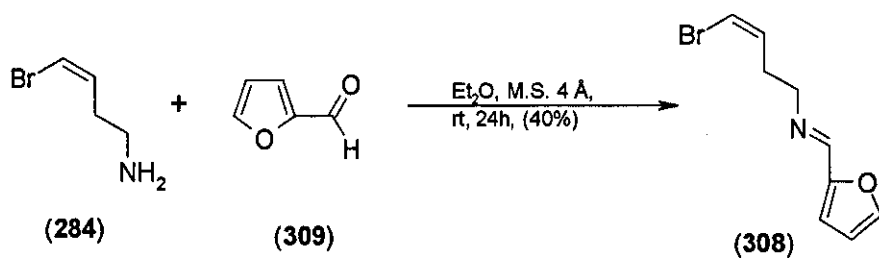
Figure 21.

We envisaged that pyrrolodine (**307**) would provide the ideal platform for us to try the Heck cyclisation to give us bicyclic system (**306**). This pyrrolidine could be constructed by a [2+3] cycloaddition reaction between imine (**308**) and cyclopropane (**300**). Again selective reduction of the exo double bond, followed by iodolactonisation would construct the lactone ring and give us (**305**). Now with the furan group in place of the benzyl group, we could oxidise this to the second lactone ring and give us structure (**304**). As before, we also have the option of incorporating the methyl group of the lactone ring at an early stage in the synthesis, by using an appropriate Wittig reagent (**Scheme 151**).



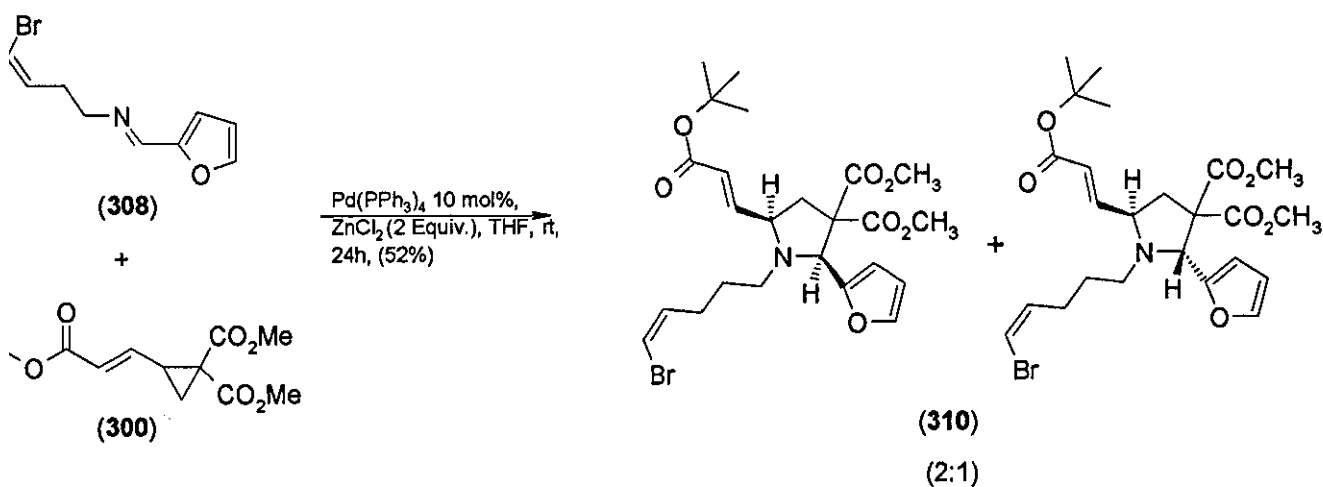
Scheme 151: Proposed synthesis of azepine structure (306).

We constructed the imine we required by reacting our pre-prepared amine (284) and 2-furaldehyde (308) (Scheme 152).



Scheme 152: Preparation of (4-bromobut-3-enyl)-furan-2-ylmethyleamine (309).

Subsequent [2+3] cycloaddition reaction yielded the desired pyrrolidine in a 52% yield, with a diastomeric ratio of 2:1, in favour of the *cis* isomer (Scheme 154).



Scheme 154: Formation of 1-(4-bromobut-3-enyl)-5-(2-*tert*-butoxycarbonylvinyl)-2-furan-2-ylpyrrolidine-3,3-dicarboxylic acid dimethyl ester (310).

The pyrrolidine (310) constructed now could undergo a Heck cyclisation to form the [5.3.0] bicyclic structure. Then formation of the lactone A ring could be achieved by selective reduction of the *exo* alkene followed by iodolactonisation. Then oxidation of the furan ring would provide the second lactone and the stemonine skeleton structure would be virtually completed. Obviously the main point to note is the *trans* stereochemistry across the pyrrolidine ring in stemonine, and the preference of the group's [2+3] cycloaddition reaction to form the *cis* isomer. Previous work within the group has shown that by altering the solvent that the cycloaddition reaction takes place in can affect the stereochemical outcome, and we can alter the reaction conditions to give us the *trans* isomer (Figure 22).^{38,39,42}

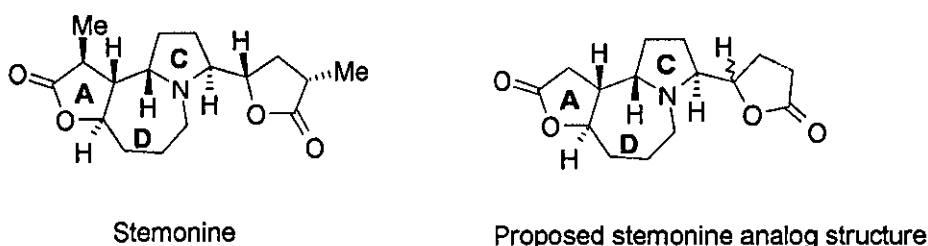
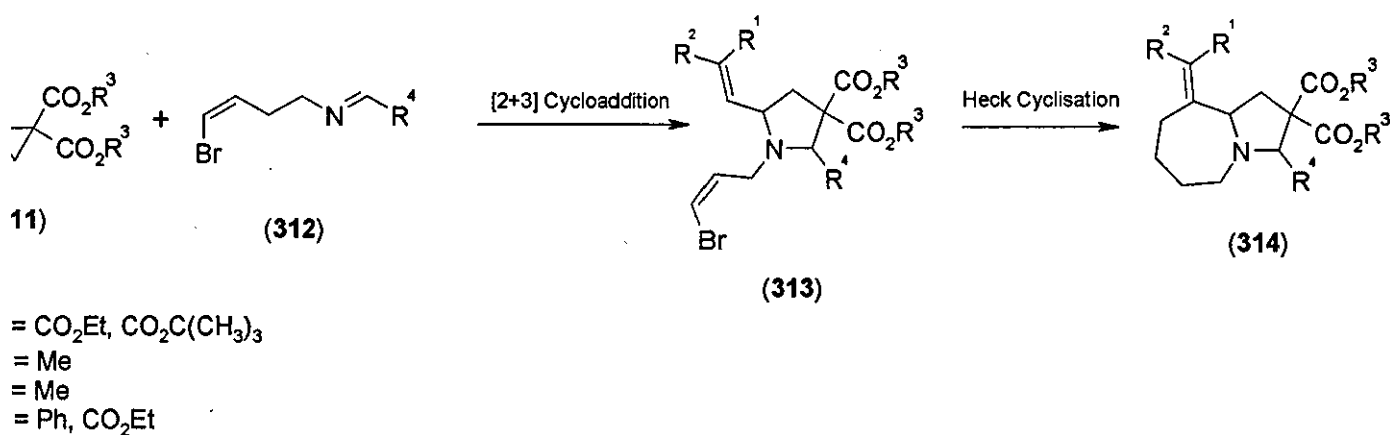


Figure 22: Proposed structural outcome after Heck cyclisation, iodolactonisation and oxidation steps.

Chapter 5 - Conclusion:

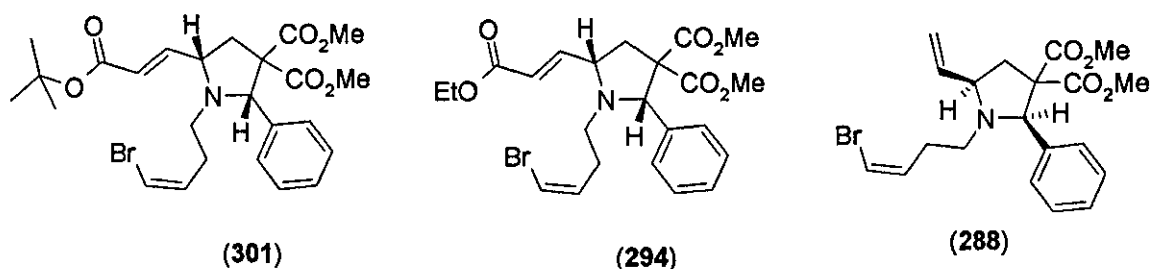
We have developed a clean and facile route into the [5.3.0] azepine core of the Stemoamide group of the *Stemona* alkaloids, starting from simple building blocks (Scheme 155).



Scheme 155: Synthesis of [5.3.0] azepine core from simple starting materials.

Our investigations into synthesising the natural product target, Stemonine, were unsuccessful, but we have shown the potential for this natural product target to be constructed using the methodology we have outlined in this report.

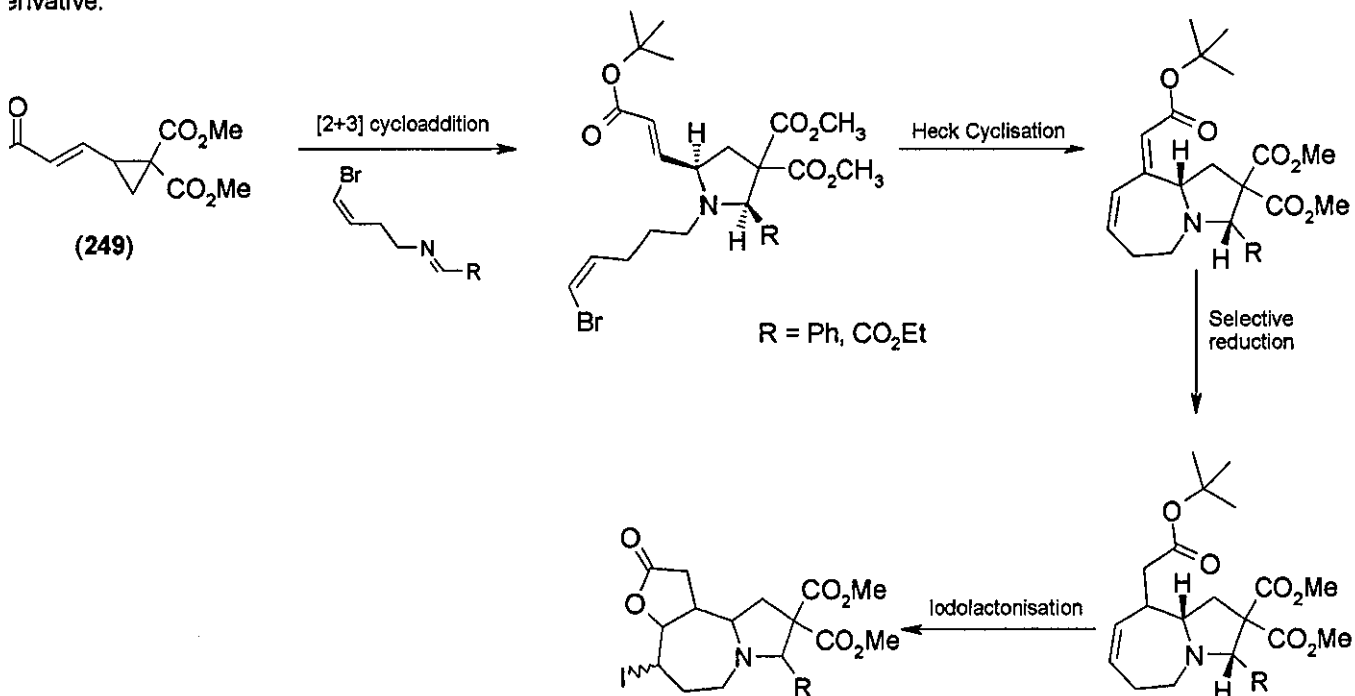
The construction of the lactone “A” ring was our initial target. We have shown the versatility of the [2+3] cycloaddition reaction, to construct a variety of pyrrolidine precursors which might have enabled us to construct the lactone ring after a Heck cyclisation (Scheme 156).



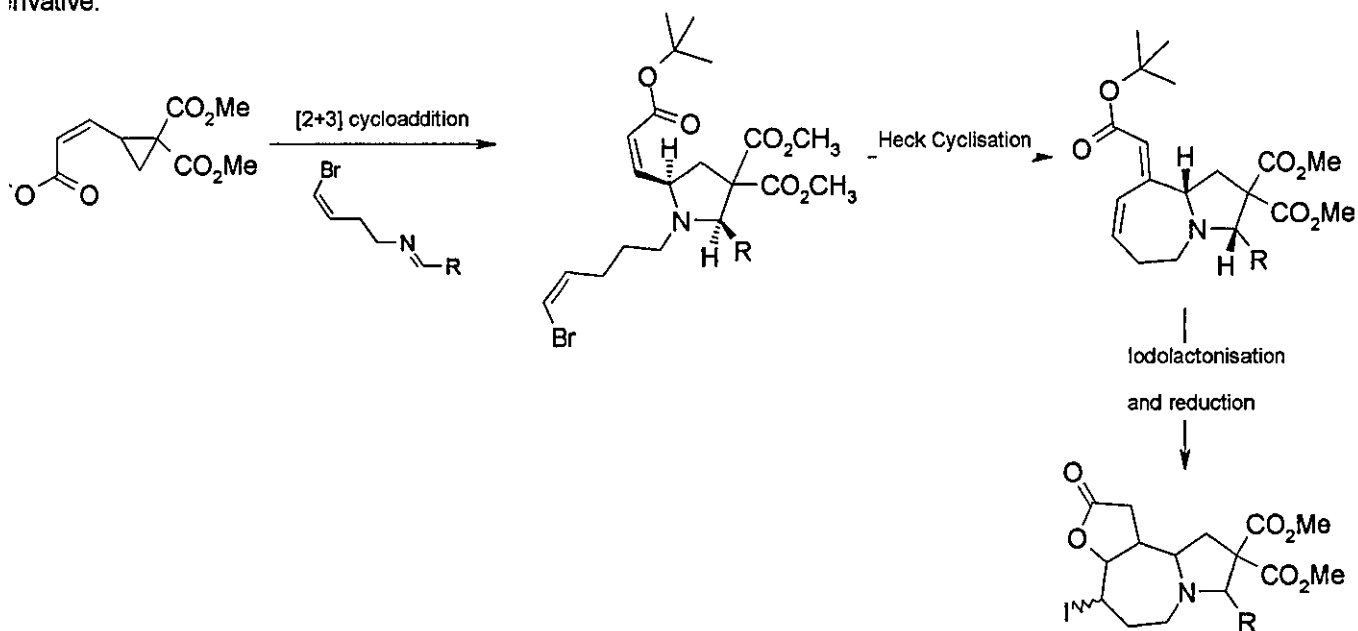
Scheme 156: Examples of pyrrolidine scaffolds.

We finally decided to use pyrrolidine (301) as the precursor for our Heck cyclisations. We successfully constructed a variety of [5.3.0] azepine structures, each following a 7-*exo trig* reaction pathway, to leave us ideally placed to construct the lactone ring *via* an iodolactonisation reaction. We discovered that the geometry of the *tert*-butoxy moiety across the *exo* double bond of these [5.3.0] bicyclic systems was such that we could not try the iodolactonisation directly, but would need to selectively reduce the *exo* double bond first. This selective reduction proved fruitless in our initial investigations, but future work could investigate the possibility of constructing the cyclopropane derivative at the start of the synthesis, with the opposite stereochemistry across the double bond to what we initially used. This would allow us to do the iodolactonisation directly, to construct the lactone ring and leave out the problematic selective reduction step. A simple hydrogenation would then cleanly afford us our desired lactone ring (**Scheme 157**).

derivative:

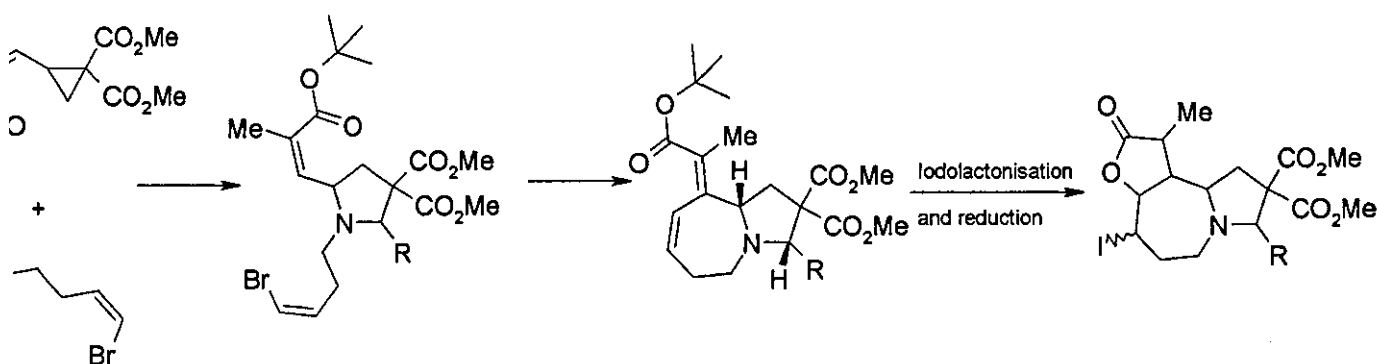


derivative:



Scheme 157: Alternative routes towards constructing the lactone ring, using the *trans* cyclopropane derivative.

This method could be adapted further to incorporate the methyl group of the lactone at the start of the synthesis instead of trying to add it at a later step. By using a suitable Wittig reagent, the methyl group could already be incorporated when the pyrrolidine scaffold was being constructed. This would further reduce the number of steps required in the total synthesis (**Scheme 158**).



Scheme 158: Proposed route towards synthesising lactone ring A.

By following this proposed route, we would have constructed the crucial A, D, C rings of the natural product stemonine. Again, by altering the solvent system in which we performed the [2+3] cycloaddition in, we could also drive the reaction towards favouring the *trans* isomer, which is crucial if we wanted to complete the total synthesis of stemonine (**Figure 23**).

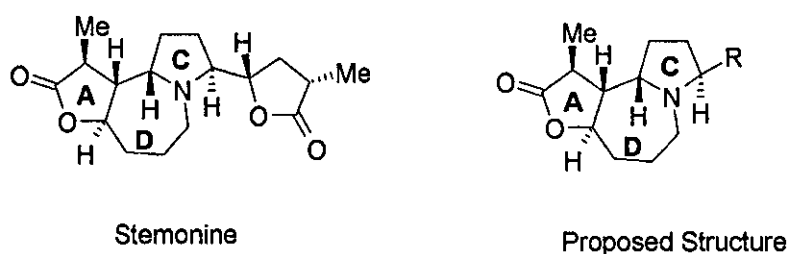
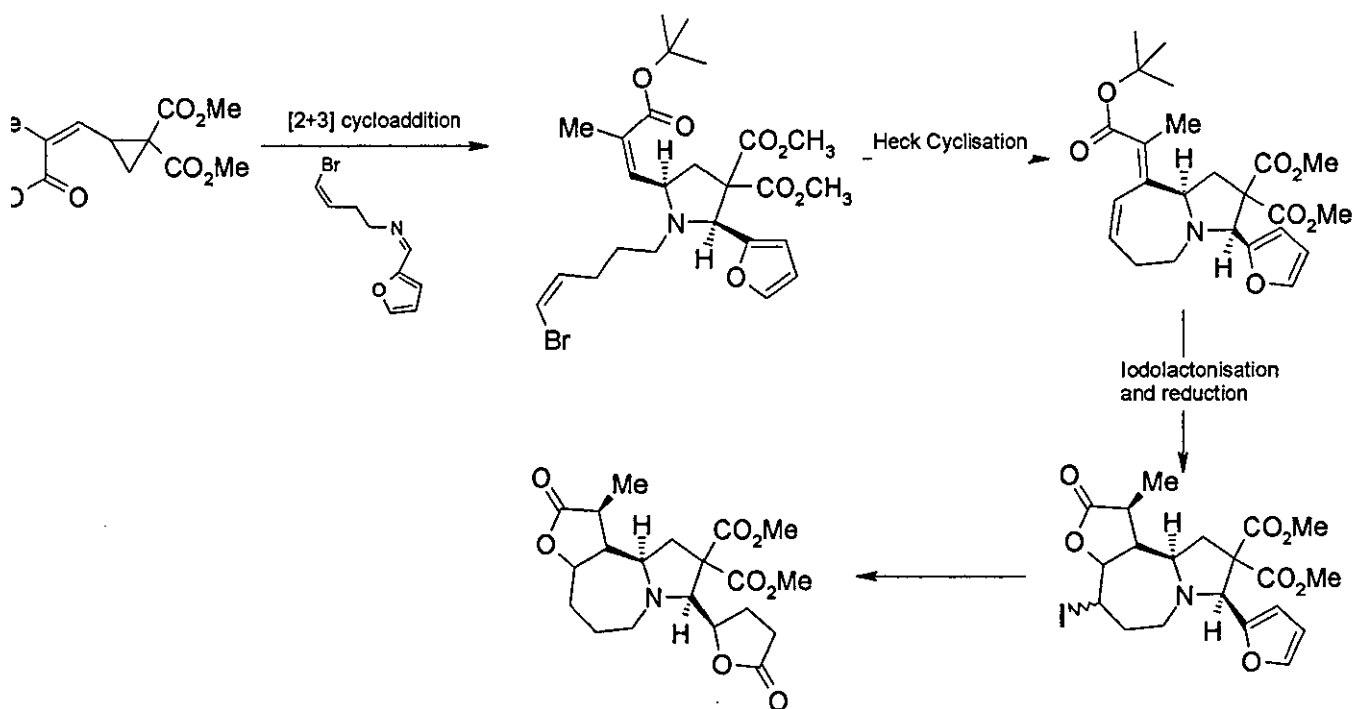


Figure 23: Structure after the successful iodolactonisation.

The final focus would be on constructing the second lactone ring. We have already shown the versatility of the [2+3] cycloaddition reaction, by varying the R group from benzene to a furan group, something which would enable us to manipulate further

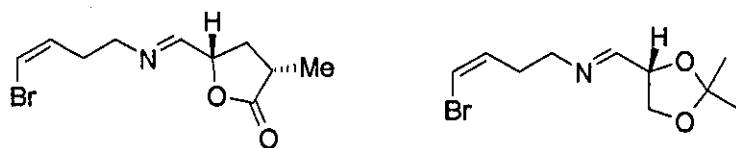
We believe that this methodology will provide an efficient route towards the total synthesis of stemonine and other members of the Stemoamide group. Investigations into this are currently on-going within the group.

towards achieving the lactone ring. We initially chose to construct the furan derivative, because this would allow us to attempt to oxidise the furan to the lactone (Scheme 159)



Scheme 159: Proposed synthesis of stemonine.

The use of the furan as a method of synthesising the second lactone ring is only one option that could be available. Due to the versatility of the [2+3] cycloaddition reaction, pyrrolidines all constructed from a variety of suitable imines could provide the platform for the synthesis of the second lactone ring (Scheme 160).



Scheme 160: Alternative imine precursors that could be used to construct a suitable pyrrolidine scaffold to set-up the formation of the second lactone ring.

Chapter 6 - Experimental:

General Information

6.1. Solvents and Reagents

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

6.2. 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 (254nm) as well as through staining with 1% vw/v potassium permanganate in aqueous alkaline solution followed by heat where appropriate. Flash chromatography was conducted using Merck Kieslgel (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.

6.3. 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.

6.4. ^1H NMR

Proton magnetic resonance spectra (^1H NMR) were recorded at 250 and 400 MHz using a Brücker AC-250 or Brücker DPX-400 spectrometer as solutions of deuterated CDCl_3 unless otherwise specified. Chemical shifts (δ_{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 envelope (env.). Assignment of individual proton signals was assisted by analysis of ^1H 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 ^1H NMR spectra.

6.5. ^{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. (δ_{C}) 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.

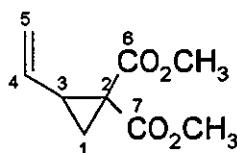
6.6. Mass Spectra

Mass spectra (high/low resolution) were recorded using a Fisons VG Quattro II SQ instrument, with modes of ionisation being indicated as electron impact (EI) and fast atom bombardment (FAB) and electron spray (ES) with only the molecular ion, molecular 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.

6.7 ^1H NMR Data

When isomers have been successfully separated by purification, they are reported separately in the experimental data. The isomers which have not been separated, shall be identified by H' corresponding to the *cis* isomer.

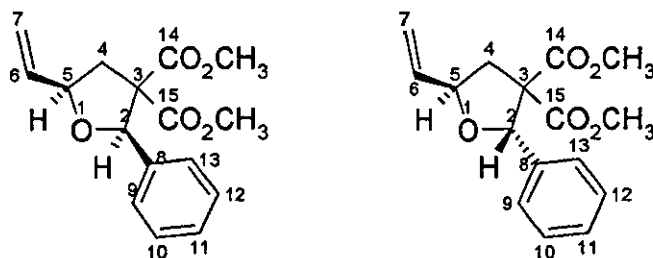
Preparation of 2-vinylcyclopropane-1,1-dicarboxylic acid dimethylester (161)



To a stirred solution of sodium methoxide prepared from sodium (2.30 g, 50.00 mmol) in methanol (40 ml), was added dropwise dimethylmalonate (11.78 ml, 51.50 mmol) followed by a solution of trans-1,4-dibromobut-2-ene (10.70 g, 25.00 mmol) in MeOH (40 ml). The mixture was refluxed for 2.5 h and then cooled to room temperature. The white precipitate was filtered off and the filtrate was concentrated *in vacuo* to give an oily residue. The residue was partitioned between Et₂O (30 ml) and distilled water (30 ml). The layers were separated and the organics were washed with H₂O (2 x 30 ml), dried (MgSO₄) and concentrated *in vacuo* to afford a pale yellow oil which was further purified by flash chromatography (petrol:EtOAc, 2:1) to give a colourless oil (4.61 g, 75%).

ν_{max} (neat)/cm⁻¹: 2954, 1731, 1438, 1330, 1274, 1210 and 1131; δ_{H} (CDCl₃, 400 MHz) 1.53 (1H, dd, *J* 5.0 & 7.5 Hz, CH₂=CHCHCHH), 1.66 (1H, dd, *J* 5.0 & 7.5 Hz, CH₂=CHCHCHH), 2.49-2.55 (1H, m, CH₂=CHCH), 3.67 (6H, s, 2 x OCH₃) 5.06-5.09 (1H, m, CHH=CHCH), 5.21-5.26 (1H, m, CHH=CHCH) and 5.32-5.41 (1H, m, CH₂=CHCH); δ_{C} (CDCl₃, 100 MHz) 20.65 (C1), 30.26 (C3), 35.74 (C2), 52.65 (OCH₃), 52.78 (OCH₃), 118.76 (C5), 132.96 (C4), 167.83 (CO) and 170.06 (CO); *m/z*: (EI) 184 (M⁺, 32%), 152 (100), 124 (89), 93 (56), 71 (71), 65 (60), 59 (88); HRMS Found (184.0733, C₉H₁₂O₄ requires 184.0735).

Preparation of 2-(R),5-(R)-2-phenyl-5-vinyldihydrofuran-3,3-dicarboxylic acid dimethylester (*cis:trans*; 2:1)

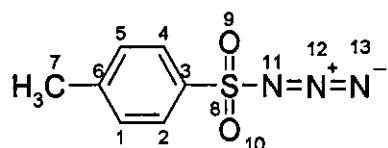


To a stirred solution of 2-vinylcyclopropane-1,1-dicarboxylic acid dimethylester (**162**) (0.18 g, 1.00 mmol) in anhydrous MeOH (5 ml) was added benzaldehyde (**166**) (0.11 g, 1.00 mmol) and ZnBr₂ (2 equiv) at room temperature. This mixture was left to stir for 10 min under nitrogen before a catalytic amount of tetrakis(triphenylphosphine)palladium(0) (0.12 g, 0.10 mmol) was added. The resulting mixture was allowed to stir at room temperature for 48 h. The solvent was removed *in vacuo* and the residue dissolved in EtOAc (20 ml). The palladium catalyst was filtered under suction through a plug of silica, and the organic layer was washed several times with distilled H₂O (2 x 30 ml). The organics were dried (MgSO₄) and concentrated *in vacuo* to give a yellow oil which was further purified by flash chromatography (petrol:EtOAc, 2:1) to give a colourless oil (0.14 g, 47%).

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$: 2950, 1731, 1433 and 1270; $\delta_{\text{H}}(\text{CDCl}_3, 400 \text{ MHz})$ 2.13 (1H, dd, J 7.0 & 13.0 Hz, CH₂=CHCHCHH), 2.43 (1H, dd, J 6.0 & 13.0 Hz, CH₂=CHCHCH'H), 2.70 (1H, dd, J 10.0 & 13.0 Hz, CH₂=CHCHCHH'), 2.96 (1H, dd, J 7.0 & 13.0 Hz, CH₂=CHCHCHH), 3.04 (3H, s, OCH'₃), 3.10 (3H, s, OCH₃), 3.70 (3H, s, OCH₃), 3.74 (3H, s, OCH'₃), 4.32-4.36 (1H, m, CH₂=CHCH'), 4.85-5.02 (1H, m, CH₂=CHCH), 5.09-5.13 (1H, m, CHH=CHCH), 5.21 (1H, dt, J 1.0 & 9.0 Hz, CH'H=CHCH), 5.26-5.30 (1H, m, CHH=CHCH), 5.34 (1H, dt, J 1.2 & 15.8 Hz, CHH'=CHCH), 5.62 (1H, s, CH₂=CHCHOCH'Ar), 5.72 (1H, s, CH₂=CHCHOCHAr), 5.80-5.88 (1H, m, CH₂=CHCH), 6.00-6.07 (1H, m, CH₂=CH'CH), 7.18-7.34 (5H, m, Ar-H') and 7.18-7.34

(5H, m, Ar-*H*); δ_c (CDCl₃, 100 MHz) 40.34 (C4'), 40.51 (C4), 52.21 (OCH₃'), 52.86 (OCH₃), 53.02 (OCH₃'), 66.18 (OCH₃), 77.02 (C3), 77.24 (C3'), 79.27 (C5'), 79.98 (C5), 83.49 (C2), 84.21 (C2'), 116.18 (C7), 117.78 (C7'), 126.50 (C9 & C13), 126.96 (C9' & C13'), 127.83 (C10' & C12'), 127.89 (C10 & C12), 128.02 (C11), 128.15 (C11'), 132.46 (C6), 136.44 (C6'), 137.75 (C8'), 138.115 (C8), 168.99 (C14'), 169.11 (C14), 170.35 (C15) and 171.23 (C15'); m/z : (EI) 290 (M⁺, 28%), 236 (84), 184 (69), 152 (84), 124 (57), 105 (100) and 77 (43); HRMS Found (290.1157, C₁₆H₁₈O₅ requires 290.1154).

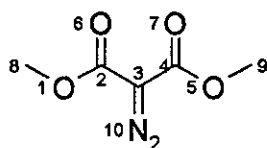
Preparation of tosyl-azide (183)⁴²



Tosyl chloride (7.00 g, 36.80 mmol) and sodium azide (5.00 g, 77.00 mmol) was dissolved in acetone (60 ml) and H₂O (40 ml). The reaction mixture was stirred under reflux at room temperature over 2h. Water (40 ml) was added and the organic layer extracted with DCM (2 x 100 ml) and dried over MgSO₄. Evaporation of the solvent under reduced pressure yielded the tosyl-azide as a colourless oil (5.92 g, 82%);

ν_{\max} (neat)/cm⁻¹: 2343, 2127, 1594, 1370, 1167 and 1085; δ_H (CDCl₃, 400 MHz) 2.49 (3H, s, CH₃Ar), 7.41 (2H, d, *J* 8.0 Hz, Ar-*H*) and 7.85 (2H, d, *J* 8.0 Hz, Ar-*H*).

Preparation of dimethyl diazomalonate (182)⁴³ Method A



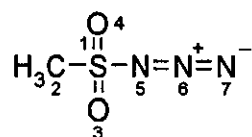
Tosyl azide (**183**) (2.39 g, 10.00 mmol), dimethyl malonate (**184**) (1.57 g, 10.00 mmol) and triethylamine (1.24 g, 0.01 mol) were allowed to stand in CH₃CN (100 ml) at room temperature for 22 h. The solvent was evaporated under reduced pressure to yield a white solid. The solid was triturated with Et₂O (150 ml) and the ether extract was washed with KOH (2.70 g, 48.13 mmol) in H₂O (100 ml). The aqueous layer was saturated with Na₂SO₃ and extracted with Et₂O (100 ml). The combined ethereal extractions were acidified with 6M HCl and dried with Na₂SO₄. Evaporation of the solvent under reduced pressure yielded the dimethyl diazomalonate as an orange oil (0.75 g, 47%).

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$: 2137, 1760, 1737, 1436, 1332 and 1275; $\delta_{\text{H}}(\text{CDCl}_3, 400 \text{ MHz})$ 3.70 (6H, s, 2 \times OCH₃).

Preparation of dimethyl diazomalonate (182)⁴⁴ Method B

Tosyl azide (**183**) (4.43 g, 20.00 mmol), dimethyl malonate (**184**) (3.01 g, 20.00 mmol) and triethylamine (2.38 g, 20.00 mmol) were allowed to stand in dry benzene (20 ml) at room temperature for 18h. The reaction mixture was filtered and the solid was washed with cold benzene. The combined extracts were concentrated *in vacuo* to afford dimethyl diazomalonate as an orange oil (1.54 g, 48%). Data as shown in Method A.

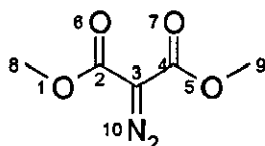
Preparation of mesyl azide (188)⁴⁵



A 250 ml, 3 necked round bottomed flask equipped with a rubber septum and nitrogen inlet adapter was charged with a solution of methanesulfonyl chloride (9.00 ml, 13.32 g, 116.00 mmol) in acetone (60 ml). Sodium azide (11.34 g, 174.00 mmol) was then added over 30 min via a powder addition funnel, and the resulting mixture was stirred an additional 1.5 h at 25°C. The reaction mixture was filtered through a sintered glass funnel, and the salts which were separated were washed with 3 x 20 ml portions of acetone. Rotary evaporation of the filtrate removed most of the solvent, and the residual liquid was further concentrated with stirring at 25°C under reduced pressure for 1.5 h. Methanesulfonyl azide (13.47 g, 99%) was obtained as a colourless oil.

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$: 2141, 1357, 1328, 1199 and 1166; δ_{H} (CDCl_3 , 400MHz) 3.62 (3H, s, CH_3)

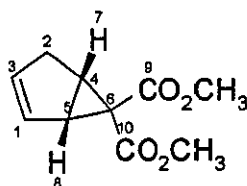
Preparation of dimethyl diazomalonate (182)⁴³ Method C



A flame dried, one necked round bottom flask equipped with a nitrogen inlet and septum was charged with dimethyl malonate (184) (10.00 g, 75.70 mmol), methanesulfonyl azide

(188) (10.07 g, 83.33 mmol) and CH_3CN (50 ml). To this solution was added triethylamine (15.32 g, 21.10 ml, 151.00 mmol). The reaction was monitored by TLC, but took approx. 3 h. The mixture was diluted with 10% NaOH (40 ml) and extracted with DCM (5×20 ml) The combined organic extracts were dried over MgSO_4 and concentrated *in vacuo* to yield dimethyl diazomalonate (9.59 g, 80%) as an orange oil. See data from Method A.

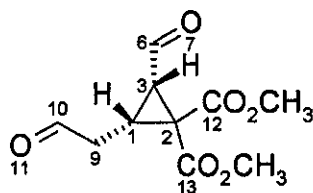
Preparation of 4-(S),5-(S)-dimethyl bicyclo [3.1.0] hex-2-ene-6, 6-dicarboxylate (177)⁴²



Dimethyl diazomalonate (182) (0.56 g, 3.54 mmol), 1,3-cyclopentadiene (176) (1.00 g, 15.10 mmol) and $\text{Rh}_2(\text{OAc})_4$ (0.07g, 0.10 mmol) were stirred under reflux for 3 h in DCM (10 ml). The reaction mixture was allowed to cool to room temperature to yield a viscous brown oil. The oil was purified by flash chromatography (SiO_2 , hexane:EtOAc 2:1) and reduced *in vacuo* to give the desired product as a colourless oil (0.29 g, 10%).

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$: 1731, 1434, 1317, 1158 and 1085; δ_{H} (CDCl_3 , 400 MHz) 2.36-2.40 (1H, m, $\text{CH}_2\text{CHC}(\text{CO}_2\text{CH}_3)_2$), 2.63-2.69 (2H, m, $\text{CH}_2\text{CHC}(\text{CO}_2\text{CH}_3)_2$), 2.75-2.77 (1H, m, $\text{CH}=\text{CHCHC}(\text{CO}_2\text{CH}_3)_2$), 3.57 (3H, s, OCH_3), 3.66 (3H, s, OCH_3), 5.54-5.57 (1H, m, $\text{CH}=\text{CHCH}$) and 5.72-5.74 (1H, m, $\text{CH}=\text{CHCH}$); δ_{C} (CDCl_3 , 100 MHz) 31.65 (C4), 34.39 (C2), 37.63 (C6), 39.40 (C5), 52.21 (OCH_3), 52.66 (OCH_3), 129.51 (C1), 132.21 (C3), 166.55 (C9) and 170.36 (C10); m/z : (EI) 196 (M^+ , 36%) 164 (100), 136 (27), 105 (38) and 77 (31); HRMS Found (196.0737 $\text{C}_{10}\text{H}_{12}\text{O}_4$ requires 196.0735).

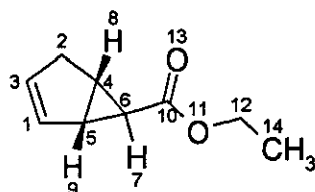
Preparation of 1-(R),3-(R)-2-formyl-3-(2-oxoethyl)-cyclopropane-1,1-dicarboxylic acid dimethyl ester (178)



Dimethyl bicyclo [3.1.0] hex-2-ene-6,6-dicarboxylate (176) (0.10 g, 0.50 mmol) in DCM (20 ml) was treated with ozone with stirring. Once the mixture had turned blue, the reaction was quenched with PPh_3 (0.13g, 0.50 mmol). The mixture was reduced *in vacuo* to give a colourless oil, which was further purified by flash chromatography (SiO_2 , 100% Et_2O), to give the di-aldehyde as a colourless oil (65 mg, 57%).

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$: 1736, 1731, 1434, 1317, 1158, 1085, 722 and 670; δ_{H} (CDCl_3 , 400 MHz) 2.31 (1H, m, $\text{CHOCH}_2\text{CHC}(\text{CO}_2\text{CH}_3)_2$), 2.84 (1H, dd, J 8.0 & 19.0 Hz, $\text{CHOCHHCHC}(\text{CO}_2\text{CH}_3)_2$), 2.98 (1H, dd, J 2.0 & 9.0 Hz, $\text{CHOCHC}(\text{CO}_2\text{CH}_3)_2$), 3.12 (1H, dd, J 7.0 & 19.0 Hz, $\text{CHOCHHCHC}(\text{CO}_2\text{CH}_3)_2$), 3.68 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 9.69 (1H, d, J 2.0 Hz, $\text{CHOCH}_2\text{CHC}(\text{CO}_2\text{CH}_3)_2$) and 9.71 (1H, s, $\text{CHOCHC}(\text{CO}_2\text{CH}_3)_2$); δ_{C} (CDCl_3 , 100 MHz) 27.46 (C1), 29.71 (C3), 35.81 (C2), 37.91 (C9), 52.94 (OCH_3), 53.56 (OCH_3), 165.24 (C12), 168.61 (C13), 196.20 (C6) and 198.20 (C10); m/z : (EI) 228 (M^+ , 37%), 134 (100), 98 (52) and 64 (44); HRMS Found (228.2014 $\text{C}_{10}\text{H}_{12}\text{O}_6$ requires 228.2016).

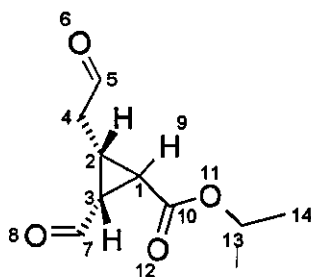
Preparation of 4-(S),5-(S)-bicyclo [3.1.0] hex-2-ene-6-carboxylic acid methyl ester (197)



To a flame dried round bottom flask was added 1,3-cyclopentadiene (176) (6.00 g, 91.00 mmol) and $\text{Rh}_2(\text{OAc})_4$ (0.05 g, 0.12 mmol). This mixture was left to stir for 20 min, before ethyl diazoacetate (192) (0.31 g, 1.72 ml, 16.40 mmol) was added dropwise through a syringe over a period of 1 h. The mixture was then left to stir for a further 1 h at room temperature. The compound was purified *via* flash chromatography (hexane:EtOAc, 5:1) and the solvent reduced *in vacuo* to give the desired product as a colourless oil (1.80 g, 72%).

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$: 3059, 2979, 2904, 1718, 1399 and 1350; δ_{H} (CDCl_3 , 400MHz) 0.89-0.91 (1H, m, $\text{CH}=\text{CHCH}$), 1.19 (3H, t, J , 7.2, Hz, $\text{CO}_2\text{CH}_3\text{CH}_2$), 2.12-2.15 (1H, m, CHCH_2CH), 2.34-2.40 (1H, m, CHCHHCHCH), 2.34-2.40 (1H, m, CHCH_2CHCH), 2.59-2.80 (1H, m, CHCHHCHCH), 4.05 (2H, q, J 7.2 Hz $\text{CO}_2\text{CH}_3\text{CH}_2$), 5.45-5.48 (1H, m, $\text{CH}=\text{CHCH}$) and 5.83-5.87 (1H, m, $\text{CH}=\text{CHCHCH}$); δ_{C} (CDCl_3 , 100 MHz) 14.29 (C14), 26.08 (C4), 30.39 (C5), 34.38 (C6), 36.16 (C2), 60.32 (C12), 130.38 (C3), 132.08 (C1) and 173.44 (C10); m/z : (EI) 152 (M^+ , 18%), 94 (100), 79 (53), 77 (47), 66 (54) and 65 (35) HRMS Found (152.0834 $\text{C}_9\text{H}_{12}\text{O}_2$ requires 152.0837).

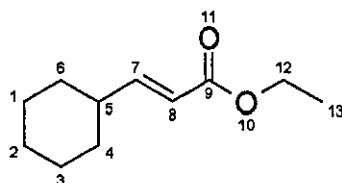
**Preparation of 2-(S),3-(S)-2-formyl-3-(2-oxoethyl)-
cyclopropanecarboxylic acid ethyl ester (198)**



Bicyclo [3.1.0] hex-2-ene-6-carboxylic acid methyl ester (197) (0.20 g, 1.30 mmol) in DCM (10 ml) was treated with ozone with stirring. Once the mixture had turned blue, PPh_3 (0.42g, 1.60 mmol) was added. The organics were reduced *in vacuo* to give a colourless oil, which was further purified by flash chromatography (SiO_2 , 100% Et_2O) to give the di-aldehyde as a colourless oil (0.10 g, 42%).

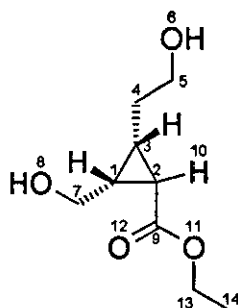
$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$: 722, 1075, 1158, 1333, 1454, 1733 (CO) and 1735 (CO); δ_{H} (CDCl_3 , 400 MHz) 1.21 (3H, t, J 7.2 Hz, CH_3CH_2), 2.11-2.15 (1H, m, $\text{CHOCH}_2\text{CHCH}$), 2.23 (1H, dd, J 4.7 & 6.1 Hz, CHOCHCH), 2.65 (1H, dd, J 8.1 & 19.0 Hz, CHOCHHCHCH), 2.73-2.77 (1H, m, $\text{CHOCH}_2\text{CHCH}$), 2.85-2.91 (1H, m, CHOCHHCHCH), 4.07-4.13 (2H, m, CH_3CH_2), 9.64 (1H, s, CHOCHCH) and 9.76 (1H, dd, J 0.6 & 1.9 Hz, $\text{CHOCH}_2\text{CHCH}$); δ_{C} (CDCl_3 , 100 MHz) 14.14 (C14), 24.29 (C2), 27.91 (C3), 33.39 (C1), 40.15 (C4), 61.41 (C13), 170.74 (C10), 197.83 (C5) and 199.26 (C7); m/z : (EI) 188 (M^+ , 19%), 134 (41), 98 (65), 86 (100), 72 (45) and 64 (32); HRMS Found (188.1917 $\text{C}_9\text{H}_{12}\text{O}_9$ requires 188.1918).

Preparation of (*E*)-3-cyclohexyl-acrylic acid ethyl ester (204)⁵⁴



A 100 ml round bottom flask was charged with (carbethoxymethyl)-triphenylphosphonium bromide (2.29 g, 5.35 mmol) in THF (8 ml) under a nitrogen atmosphere. Butyllithium (2.14 ml, 2.5 M, 5.35 mmol) was added dropwise at 0°C and the mixture stirred for 20 min. The aldehyde (0.20 g, 1.78 mmol) was added immediately to the reaction, and the mixture was stirred for a further 3 h, upon which it was quenched with H₂O (10 ml), and extracted into DCM (3 × 15 ml). The organic layer was dried over MgSO₄ and reduced *in vacuo* to give the crude product as an orange oil which was further purified *via* flash chromatography on silica gel (petrol:EtOAc, 4:1) to give the product as a colourless oil (0.22 g, 68%). Data the same as that reported in the literature.

Preparation of 1-(S),3-(R)-2-(2-hydroxyethyl)-3-hydroxymethylcyclopropanecarboxylic acid ethyl ester (211)



Bicyclo [3.1.0] hex-2-ene-6-carboxylic acid methyl ester (**197**) (1.00 g, 6.60 mmol) in DCM (20 ml) was treated with ozone with stirring. Once the reaction mixture had turned blue, MeOH (25 ml) was added followed by NaBH₄ (0.55 g, 14.50 mmol). This was left to stir for 2 hours at room temperature. Conc. HCl (1.5 ml) was then added dropwise at 0°C and this was quenched with H₂O (20 ml). The MeOH was removed *in vacuo* and then extracted into DCM (3 × 20 ml), washed with brine and dried over MgSO₄. The organic layer was reduced *in vacuo* to furnish the diol as a colourless oil (0.53 g, 32%).

$\nu_{\max}(\text{neat})/\text{cm}^{-1}$: 3395, 2936, 1716, 1651, 1446, 1180, 1028 and 667; δ_{H} (CDCl₃, 400 MHz) 1.19 (3H, t, *J* 7.2 Hz, CH₂CH₃), 1.40-1.45 (1H, m, HOCH₂CH₂CH), 1.53-1.70 (1H, m, HOCH₂CH₂CH), 1.74-1.84 (1H, m, HOCH₂CH), 1.89-1.99 (2H, m, HOCH₂CH₂CHCH), 3.20-3.26 (1H, m, HOCHHCH), 3.57-3.67 (1H, m, HOCHHCH₂CH), 3.73-3.80 (1H, m, HOCHHCH), 3.88 (1H, dd, *J* 4.8 & 11.6 Hz, HOCHHCH₂CH) and 4.05 (2H, q, *J* 7.2 Hz, CH₂CH₃); δ_{C} (CDCl₃, 100 MHz) 14.18 (C14), 25.34 (C3), 28.59 (C1), 29.13 (C2), 56.47 (C4), 50.68 (C5), 60.61 (C7), 62.30 (C13) and 173.78 (C9); *m/z*: (FAB) 189 (M⁺H, 15 %), 169 (48), 147 (57), 136 (62), 95 (31), 81 (36), 73 (100), 69 (47) and 55 (59); HRMS Found (189.1122 C₉H₁₇O₄ requires 189.1048).

128.34 (C23), 137.25 (C18), 144.58 (C6), 166.19 (C8), 168.65 (C16) and 170.90 (C17); m/z : (EI) 362 (M^+ , 8%), 256 (15), 236 (100), 121 (45), 120 (34), 112 (32), 105 (48), 98 (16) and 59 (29); HRMS Found (362.1374 $C_{19}H_{22}O_7$ requires 362.1368).

Trans Isomer:

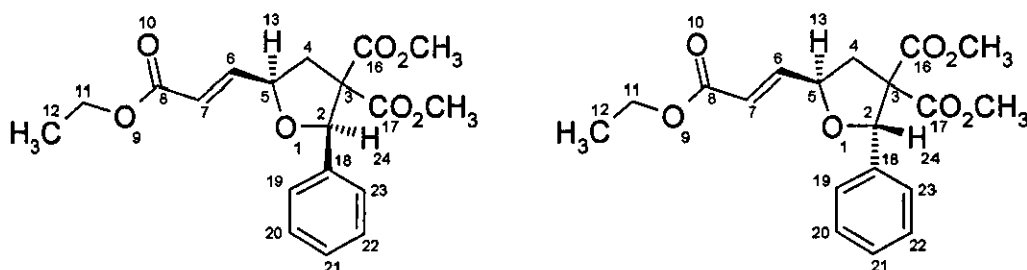
$\nu_{\max}(\text{neat})/\text{cm}^{-1}$: 2952, 1731, 1662, 1454, 1434 and 1268; δ_H ($CDCl_3$, 400MHz) 1.21 (3H, t, J 7.0 Hz, $CO_2CH_3CH_2$), 2.14 (1H, dd, J 7.0 & 13.0 Hz, $CH=CHCHCHH$), 3.03 (1H, dd, J 7.0 & 13.0 Hz, $CH=CHH$), 3.12 (3H, s, OCH_3), 3.69 (3H, s, OCH_3), 4.13 (2H, q, J 7.0 Hz, $CO_2CH_2CH_3$), 5.15-5.20 (1H, m, $CH=CHCHCH_2$), 5.71 (1H, s, $CH=CHCHOCHAr$), 6.06 (1H, dd, J 2.0 & 16.0 Hz, $CH=CHCHCH_2$), 6.89 (1H, dd, J 5.0 & 16.0 Hz, $CH=CHCHCH_2$) and 7.20-7.36 (5H, m, Ar- H); δ_C ($CDCl_3$, 100 MHz) 14.24 (C12), 40.03 (C4), 52.32 (OCH_3), 52.95 (OCH_3), 60.57 (C11), 65.88 (C5), 83.85 (C2), 114.54 (C3), 120.96 (C3), 126.45 (C19 & C23), 127.98 (C20 & C22), 128.24 (C21), 137.62 (C18), 146.78 (C6), 166.25 (C8), 168.86 (C16) and 169.87 (C17); m/z : (EI) 362 (M^+ , 3%), 256 (15), 236 (100), 121 (40), 112 (37), 105 (58) and 59 (19); HRMS Found (362.1372 $C_{19}H_{22}O_7$ requires 362.1365).

Preparation of allylmagnesium bromide



Allyl bromide (12.00 g, 99.19 mmol) was added dropwise to magnesium turnings (2.41 g, 99.19 mmol) in anhydrous Et_2O (200 ml) under a nitrogen atmosphere. An ice bath was used to cool the reaction when it became too vigorous and after the addition the reaction was stirred for 1 h at rt.

Preparation of (*E*)-2-(*S*),5-(*S*)-5-(2-ethoxycarbonyl-vinyl)-2-phenyl-dihydro-furan-3,3-dicarboxylic acid dimethyl ester (*cis:trans*; 1:1).

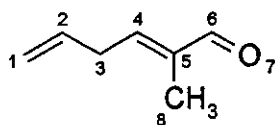


To a stirred solution of 2-(2-ethoxycarbonyl-vinyl)-cyclopropane-1,1-dicarboxylic acid dimethyl ester (**249**) (0.11 g, 0.53 mmol) in THF (6 ml) was added benzaldehyde (**166**) (0.06 g, 0.53 mmol) and ZnBr_2 (0.24 g, 1.05 mmol) at room temperature. This was left to stir for 10 min under a nitrogen atmosphere, before a catalytic amount of tetrakis(triphenylphosphine)Pd(0) (0.06 g, 0.05 mmol) was added. The resulting mixture was allowed to stir at room temperature for 48 h. After which, the solvent was removed *in vacuo* and the residue dissolved in EtOAc (8 ml). The palladium catalyst was filtered under suction through a plug of silica, and the organic layer was washed several times with distilled H_2O (3×5 ml). The organics were dried over MgSO_4 and concentrated *in vacuo* to give a yellow oil which was further purified *via* flash chromatography (hexane:EtOAc, 6:1) to give the desired product as a colourless oil (0.06 g, 29%).

Cis isomer:

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$: 2952, 1731, 1662, 1454, 1434 and 1268; δ_{H} (CDCl_3 , 400MHz) 1.25 (3H, t, J 7.0 Hz, $\text{CO}_2\text{CH}_3\text{CH}_2$), 2.50 (1H, dd, J 6.0 & 13.0 Hz, $\text{CH}=\text{CHCHCHH}$), 2.73 (1H, dd, J 10.0 & 13.0 Hz, $\text{CH}=\text{CHCHCHH}$), 3.05 (3H, s, OCH_3), 3.75 (3 H, s, OCH_3), 4.17 (2H, q, J 7.0 Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 4.49-4.54 (1H, m, $\text{CH}=\text{CHCHCH}_2$), 5.65 (1H, s, $\text{CH}=\text{CHCHOCHAr}$), 6.11 (1H, dd, J 1.0 & 15.0 Hz, $\text{CH}=\text{CHCHCH}_2$), 7.04 (1H, dd, J 5.0 & 15.0 Hz, $\text{CH}=\text{CHCHCH}_2$) and 7.19-7.24 (5H, m, Ar-H); δ_{C} (CDCl_3 , 100 MHz) 14.27 (C12), 39.94 (C4), 52.66 (OCH_3), 53.13 (OCH_3), 60.65 (C11), 65.97 (C5), 84.54 (C2), 114.54 (C3), 122.16 (C7), 126.45 (C19), 126.92 (C20), 127.92 (C21), 127.99 (C22),

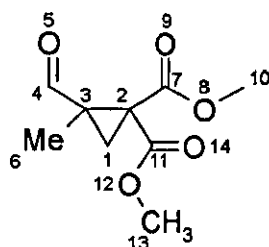
Preparation of (*E*)-2-methyl-hexa-2,5-dienal (220)⁶⁰



To 3-ethoxymethacrolein (5.00 g, 43.80 mmol) dissolved in anhydrous Et₂O (15 ml) was added allylmagnesium bromide (14.00 g, 96.36 mmol) dropwise at 0°C. The resulting mixture was left to stir at room temperature for 15 min, after which NH₄⁺Cl/ice/H₂O (20 ml) was added. The organics were extracted into Et₂O (3 x 20 ml) and washed with 3M HCl (2 ml) and brine (3 x 5 ml), and dried with MgSO₄. The organics were reduced *in vacuo* to yield the alkadienal (4.50 g, 93 %) as an orange oil.

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$: 3079, 2976, 2923, 2819, 1687, 1636 and 1404; δ_{H} (CDCl₃, 400 MHz) 1.70 (3H, s, CH₃), 3.02-3.06 (2H, m, =CH-CH₂), 5.03-5.08 (2H, m, =CH₂), 5.74-5.83 (1H, m, H₂C=CH), 6.42-6.47 (1H, m, HC=C(CH₃)) and 9.43 (1H, s, CHO); δ_{C} (CDCl₃, 100 MHz) 9.15 (C8), 32.97 (C3), 116.81 (C1), 133.64 (C2), 140.02 (C5), 150.98 (C4) and 195.07 (C6); m/z : (EI) 110 (M⁺, 2%), 109 (18), 95 (78), 81 (100), 79 (52), 77 (28), 67 (64), 53 (59) and 41 (93); HRMS Found (110.0729, C₇H₁₀O requires 110.0731).

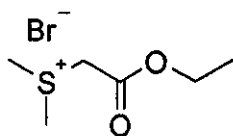
Preparation of 2-formyl-2-methylcyclopropane-1,1-dicarboxylic acid dimethyl ester (219)⁵⁹



Dimethyl bromomalonate (**216**) (0.40 g, 0.25 ml, 2.27 mmol), methacrolein (**218**) (0.16 g, 0.19 ml, 2.27 mmol), potassium carbonate (0.53 g, 3.80 mmol) and DMF (10 ml) were stirred vigorously for 2 h at room temperature. The mixture was treated with dilute HCl (2 ml) and extracted into Et₂O (3 x 10 ml). The organic phase was washed with H₂O and dried over MgSO₄. The organic phase was concentrated *in vacuo* to give the aldehyde as a colourless oil (0.31 g, 82 %).

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$: 2955, 1735, 1702, 1681, 1453 and 1246; $\delta_{\text{H}}(\text{CDCl}_3, 400 \text{ MHz})$ 1.36 (3H, s, CHOCH(CH₃)), 1.91 (1H, d, *J* 5.6 Hz, CHHC(CO₂CH₃)₂), 2.12 (1H, d, *J* 5.6 Hz, CHHC(CO₂CH₃)₂), 3.76 (3H, s, OCH₃), 3.80 (3H, s, OCH₃) and 9.26 (1H, s, CHO); $\delta_{\text{C}}(\text{CDCl}_3, 100 \text{ MHz})$ 12.63 (C6), 24.43 (C3), 38.39 (C1), 41.88 (C2), 53.18 (C13), 53.23 (C10), 166.74 (C7), 167.66 (C11) and 198.24 (C4); *m/z*: (EI) 200 (M⁺, 2%), 185 (46), 184 (45), 167 (37), 153 (43), 152 (100), 124 (42), 113 (57), 112 (57), 97 (40), 82 (57), 59 (83) and 43 (60); HRMS Found (200.0681, C₉H₁₂O₅ requires 200.0684).

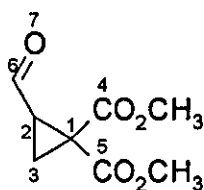
Preparation of ethoxycarbonylmethyl-dimethyl-sulfonium (223)⁶³



Ethyl bromoacetate ester (226) (8.87 g, 53.12 mmol), dimethyl sulfide (3.00 g, 48.29 mmol) were stirred in acetone at 0°C. The mixture was allowed to warm to room temperature and left to stir for a further 16 h. The mixture was concentrated *in vacuo* and placed under high vacuum for a further 6 h to yield the salt (10.00 g, 90 %) as a white crystalline solid.

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$: 2992, 2357, 1732, 1635, 1317 and 1203; $\delta_{\text{H}}(\text{CDCl}_3, 400 \text{ MHz})$ 1.27 (3H, t, J 7.0 Hz, CH_2CH_3), 3.42 (6H, s, $\text{S}(\text{CH}_3)_2$), 4.23 (2H, q, J 7.0 Hz, CH_2CH_3) and 5.21 (2H, s, SCH_2); $\delta_{\text{C}}(\text{CDCl}_3, 100 \text{ MHz})$ 14.03 (C1), 25.26 (C5), 44.16 (C2), 63.69 (C4) and 164.37 (C3).

Preparation of 2-formyl-cyclopropane-1, 1-dicarboxylic acid dimethyl ester (201) Method A.



Vinylcyclopropane (161) (1.00 g, 5.40 mmol) in DCM (25 ml) was treated with ozone with stirring. Once the mixture had turned blue, the reaction was quenched with DMS (2

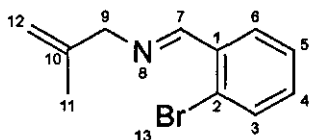
ml) and the solvent removed *in vacuo* to give the desired product as a colourless oil (0.80g, 80%).

$\nu_{\max}(\text{neat})/\text{cm}^{-1}$: 3008, 2956, 2850, 1734, 1437, 1300, 1269 and 1130; δ_{H} (CDCl_3 , 400 MHz) 1.74-1.78 (1H, m, CHOCHCHH), 2.00-2.03 (1H, m, CHOCHCHH), 2.68-2.73 (1H, m, CHOCHCH_2), 3.71 (6H, s, OCH_3) and 9.30 (1H, d, J 3.0 Hz, CHOCHCH_2); δ_{C} (CDCl_3 , 100 MHz) 19.51 (C3), 34.73 (C2), 37.43 (C1), 53.09 (OCH_3), 53.26 (OCH_3), 166.33 (C4), 168.28 (C5) and 196.22 (C6); m/z : (EI) 185 (M^+ , 3%), 171 (88), 142 (38), 126 (100), 98 (55), 95 (43), 68 (55), 67 (41) and 59 (81); HRMS Found (185.0448 $\text{C}_8\text{H}_{10}\text{O}_5$ requires 185.0450).

Preparation of 2-formyl-cyclopropane-1, 1-dicarboxylic acid dimethyl ester (201)⁵⁹ Method B.

Dimethyl bromomalonate (**216**) (0.20 g, 0.95 mmol), acrolein (**217**) (0.06 g, 1.14 mmol), potassium carbonate (0.26 g, 1.90 mmol) and DMF (5 ml) were stirred vigorously for 3 h at room temperature. After which the mixture was treated with dilute HCl (2 ml) and extracted into Et_2O (3×10 ml). The organics were washed with H_2O (2×15 ml), dried over MgSO_4 and reduced *in vacuo* to give the desired product as a colourless oil (0.19 g, 90%) data as shown in **Method A**.

Preparation of (*E*)-(2-bromobenzylidene)-(2-methylallyl)-amine (232)

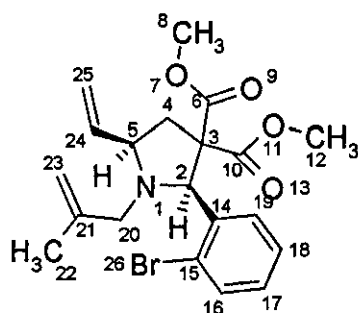


To a stirred solution of diethyl ether (15 ml) under nitrogen was added molecular sieves (2.50 g 4 Å), 2-methylallylamine (0.25 g, 3.52 mmol) and 2-bromobenzaldehyde (0.65 g, 3.52 mmol). This mixture was left to stir overnight, after which time it was filtered under

suction and washed several times with Et₂O (3 x 5 ml). The filtrate was concentrated *in vacuo* to give the imine (0.80 g, 95 %) as an orange oil.

ν_{max} (neat)/cm⁻¹: 3254, 3069, 2969, 2886, 2811, 2360, 1653 and 1635; δ_{H} (CDCl₃, 400 MHz) 1.76 (3H, s, CH₃), 4.13 (2H, s, CH₂N), 4.82-4.84 (2H, m, =CH₂), 7.17-7.29 (2H, m, Ar-H), 7.48-7.51 (1H, m, Ar-H), 7.98-8.00 (1H, m, Ar-H) and 8.57 (1H, s, N=CH); δ_{C} (CDCl₃, 100 MHz) 21.20 (C11), 67.15 (C9), 111.74 (C12), 125.11 (C10), 127.66 (C5), 128.93 (C3), 131.85 (C4), 133.08 (C6), 134.67 (C1), 143.41 (C2) and 161.03 (C7); *m/z*: (EI) 239 (M⁺, Br⁸¹, 42%), 237, (M⁺, Br⁷⁹, 41 %), 184 (91), 182 (91), 116 (58), 89 (100), 56 (86) and 55 (86); HRMS Found (237.0153, C₁₁H₁₂NBr⁷⁹ requires 237.0152).

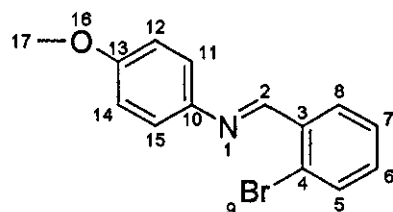
Preparation of 2-(R),5-(R)-2-(2-bromophenyl)-1-(2-methylallyl)-5-vinylpyrrolidine-3,3-dicarboxylic acid dimethyl ester (231)



To a stirred solution of 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester (**162**) (0.25 g, 1.36 mmol) in THF (10 ml) was added (2-bromobenzylidene)-(2-methylallyl)-amine (**231**) (0.32 g, 1.36 mmol) and ZnBr₂ (0.61 g, 2.72 mmol) at room temperature. This mixture was left to stir for 10 min under nitrogen before a catalytic amount of Pd(PPh₃)₄ (0.16 g, 0.14 mmol) was added. The resulting mixture was allowed to stir at room temperature for 24 h. The solvent was removed *in vacuo* and the residue dissolved in EtOAc (5 ml). The palladium catalyst was filtered under suction through a plug of silica, and the organic layer was washed several times with distilled H₂O (3 x 10 ml). The organic phase was dried over MgSO₄ and concentrated *in vacuo* to give the crude product as a colourless oil, which was further purified by column chromatography on silica gel (petrol:EtOAc, 3:1) to give the desired product as a colourless oil (0.28 g, 48 %).

$\nu_{\max}(\text{neat})/\text{cm}^{-1}$: 3073, 2950, 2819, 1736, 1434 and 1275; δ_{H} (CDCl_3 , 400 MHz) 1.43 (3H, s, $=\text{C}(\text{CH}_3)$), 2.24 (1H, dd, J 8.2 & 13.2 Hz, $\text{CHHC}(\text{CO}_2\text{CH}_3)_2$), 2.27 (1H, dd, J 5.0 & 13.2 Hz, $\text{CHHC}(\text{CO}_2\text{CH}_3)_2$), 3.08-3.12 (2H, m, CH_2N), 3.13 (3H, s, OCH_3), 3.17-3.24 (1H, m, $=\text{CHCH}$), 3.82 (3H, s, OCH_3), 4.50 (1H, s, $\text{HHC}=\text{C}(\text{CH}_3)$), 4.91 (1H, s, $\text{HHCC}(\text{CH}_3)$), 5.02 (1H, s, NCHAr), 5.16-5.19 (1H, m, $\text{HHC}=\text{CH}$), 5.24-5.31 (1H, m, $\text{HHC}=\text{CH}$), 5.80-5.88 (1H, m, $\text{H}_2\text{C}=\text{CH}$), 6.98-7.04 (1H, m, Ar- H), 7.21-7.25 (1H, m, Ar- H), 7.39 (1H, dd, J 1.0 & 8.0 Hz, Ar- H) and 7.58 (1H, d, J 7.0 Hz, Ar- H); δ_{C} (CDCl_3 , 100 MHz) 20.54 (C22), 39.53 (C4), 51.78 (C12), 53.18 (C8), 60.42 (C20), 64.32 (C3), 66.10 (C5), 69.80 (C2), 113.74 (C23), 117.44 (C25), 124.71 (C14), 126.63 (C17), 128.52 (C18), 131.21 (C16), 131.91 (C19), 139.52 (C24), 140.62 (C21), 142.82 (C15), 168.69 (C10) and 171.68 (C6); m/z : (EI) 423 (M^+ , Br^{81} , 25%), 421 (M^+ , Br^{79} , 25%), 380 (40), 368 (97), 366 (100), 364 (51), 123 (80) and 55 (40); HRMS Found (421.0895, $\text{C}_{20}\text{H}_{24}\text{O}_4\text{NBr}^{79}$ requires 421.0888).

Preparation of (*E*)-(2-bromo-benzylidene)-(4-methoxy-phenyl)-amine

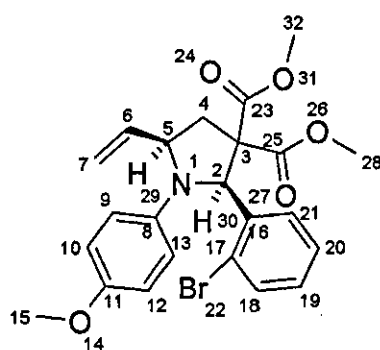


To a solution of Et_2O (10 ml) under a nitrogen atmosphere was added molecular sieves (3.00 g, 4 Å), *p*-anisidine (0.25 g, 2.02 mmol) and 2-bromobenzaldehyde (0.37 g, 0.24 ml, 2.02 mmol). The reaction mixture was left to stir overnight, after which it was filtered under suction and washed several times with Et_2O (3×10 ml). The filtrate was concentrated *in vacuo* to give the imine as a orange oil (0.6 g, 95%).

$\nu_{\max}(\text{neat})/\text{cm}^{-1}$: 2832, 2362, 1698, 1614, 1503, 1245, 1023, 827 and 751 δ_{H} (CDCl_3 , 400 MHz) 3.85 (3H, s, OCH_3), 6.93-6.97 (1H, m, Ar- H), 7.26-7.33 (1H, m, Ar- H), 7.38-7.42 (1H, m, Ar- H), 7.43-7.46 (1H, m, Ar- H), 7.61 (2H, dd, J 1.2 & 8.0 Hz, Ar- H), 8.22 (2H,

dd, J 1.8 & 7.8 Hz, Ar- H) and 8.87 (1H, s, NCHAr); δ_c (CDCl₃, 100 MHz) 55.52 (OCH₃), 114.41 (C11 & C15), 122.56 (C12 & C14), 125.87 (C3), 127.70 (C8), 127.92 (C7), 132.07 (C6), 133.18 (C5), 135.36 (C13), 144.45 (C4), 157.15 (C2) and 158.65 (C5); m/z : (EI) 291 (M^{+H} , Br⁸¹, 97%), 289 (M^{+H} , Br⁷⁹, 97%), 276 (100), 274 (81), 167 (41), 92 (15), and 77 (35); HRMS Found (289.0101 C₁₄H₁₂NOBr⁷⁹ requires 289.0102).

Preparation of 2-(R),5-(R)-2-(2-bromophenyl)-1-(4-methoxyphenyl)-5-vinylpyrrolidine-3, 3-dicarboxylic acid dimethyl ester

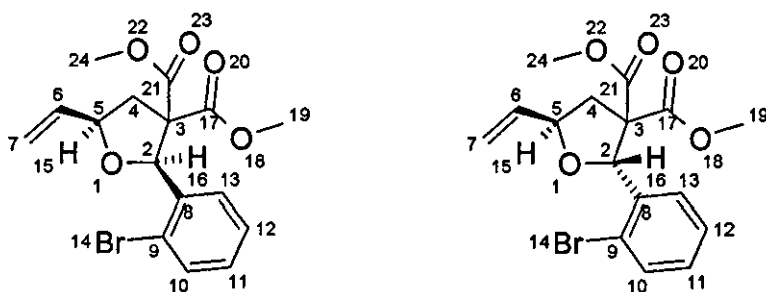


To a stirred solution of 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester (**162**) (0.25 g, 1.36 mmol) in THF (5 ml) was added (2-bromobenzylidene)-(4-methoxyphenyl) amine (0.39 g, 1.36 mmol) and ZnCl₂ (0.37 g, 2.72 mmol) at room temperature. This mixture was left to stir for 10 min under nitrogen before a catalytic amount of Pd(PPh₃)₄ (0.16 g, 0.14 mmol) was added. The resulting mixture was allowed to stir at room temperature for 48 h. The solvent was removed *in vacuo* and the residue dissolved in EtOAc. The palladium catalyst was filtered under suction through a plug of silica, and the organic layer was washed several times with distilled H₂O (3 x 10 ml). The organics were dried over MgSO₄ and concentrated *in vacuo* to give the crude product which was purified using flash chromatography on silica gel (petrol:EtOAc, 5:1) to give the desired product as a colourless oil (0.38 g, 56 %).

ν_{\max} (neat)/cm⁻¹: 2997, 2950, 2832, 2358, 1736, 1510, 1434 and 1243; δ_H (CDCl₃, 400 MHz) 2.64 (1H, dd, J 6.0 & 13.6 Hz, CHHC(CO₂CH₃)₂), 2.90 (1H, dd, J 11.0 & 13.6 Hz, CHHC(CO₂CH₃)₂), 3.36 (3H, s, OCH₃), 3.65 (3H, s, -CO₂CH₃), 3.79 (3H, s, -CO₂CH₃), 4.05-4.14 (1H, m, =CHCH), 5.30 (1H, dt, J 1.1 & 10.4 Hz, HHC=CH), 5.40 (1H, dt, J 1.1 & 17.2 Hz, HHC=CH), 5.96 (1H, s, -CHAr), 6.00-6.09 (1H, m, H₂C=CH), 6.54-6.57 (2H,

m, Ar-*H*), 6.69-6.74 (2H, m, Ar-*H*), 7.03-7.05 (1H, m, Ar-*H*), 7.11-7.15 (1H, m, Ar-*H*), 7.28-7.30 (1H, m, Ar-*H*) and 7.55-7.58 (1H, m, Ar-*H*); δ_c (CDCl₃, 100 MHz) 38.94 (C4), 52.23 (C15), 53.34 (C32), 55.60 (C28), 60.78 (C5), 63.66 (C3), 70.06 (C2), 114.32 (C12), 114.94 (C13), 115.16 (C9), 116.31 (C16), 116.75 (C7), 123.42 (C8), 123.43 (C18), 127.77 (C19), 129.40 (C21), 130.38 (C20), 139.51 (C6), 141.71 (C11), 152.48 (C17), 167.93 (C25) and 170.63 (C23); *m/z*: (EI) 476 (*M*⁺, Br⁸¹, 15%), 474 (*M*⁺, Br⁷⁹, 15%), 424 (52), 400 (48), 380 (51), 366 (100), 123 (65), and 84 (45); HRMS Found (474.3517, C₂₃H₂₄O₅NBr⁷⁹ requires 474.3513).

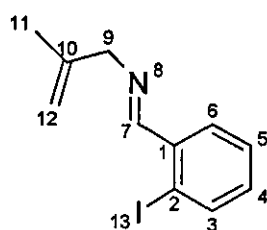
Preparation of 2-(*R*),5-(*R*)-2-(2-bromophenyl)-5-vinyldihydrofuran-3, 3-dicarboxylic acid dimethyl ester (1:1 *cis:trans*)



To a stirred solution of 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester (**161**) (0.15 g, 0.82 mmol) in THF (5 ml) was added 2-bromobenzaldehyde (**234**) (0.15 g, 0.82 mmol) and ZnCl₂ (0.11 g, 1.64 mmol) at room temperature. This mixture was left to stir for 10 min under nitrogen before a catalytic amount of Pd(PPh₃)₄ (0.09 g, 0.08 mmol) was added. The resulting mixture was allowed to stir at room temperature for 48 h. The solvent was removed *in vacuo* and the residue dissolved in EtOAc (5 ml). The palladium catalyst was filtered under suction through a plug of silica, and the organic layer was washed several times with distilled H₂O (3 x 10 ml). The organic phase was dried over MgSO₄ and reduced under pressure to give the crude product which was purified further using column chromatography on silica gel (petrol:EtOAc, 5:1) to give the title compound as a colourless oil (0.19 g, 62 %).

$\nu_{\max}(\text{neat})/\text{cm}^{-1}$: 3065, 2994, 2950, 2878, 2842, 1736, 1645, 1470 and 1434; δ_{H} (CDCl_3 , 400 MHz) 2.37 (1H, dd, J 1.2 & 9.0 Hz, $\text{CH}_2=\text{CHCHCHH}$), 2.43 (1H, dd, J 4.7 & 13.2 Hz, $\text{CH}_2=\text{CHCHCHH}$), 2.81 (1H, dd, J 11.6 & 13.2 Hz, $\text{CH}_2=\text{CHCHCHH}$), 3.11-3.14 (1H, m, $\text{CH}_2=\text{CHCHCHH}$), 3.14 (3H, s, OCH_3), 3.23 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 4.42-4.47 (1H, m, $\text{CH}_2=\text{CHCH}$), 5.03-5.06 (1H, m, $\text{CH}_2=\text{CHCH}$), 5.18 (1H, dt, J 1.4 & 10.4 Hz, $\text{HHC}=\text{CH}$), 5.28 (1H, dt, J 1.3 & 9.3 Hz, $\text{HH}'\text{C}=\text{CHCH}$), 5.35 (1H, dt, J 1.4 & 15.7 Hz, $\text{HHC}=\text{CH}$), 5.43 (1H, dt, J 1.3 & 16.0 Hz, $\text{H}'\text{HC}=\text{CHCH}$), 5.84-5.93 (1H, m, $\text{H}_2\text{C}=\text{CH}$), 6.00-6.08 (1H, m, $\text{H}_2\text{C}=\text{CHCH}$), 6.29 (1H, s, OCHAr), 6.38 (1H, s, OCHAr), 7.09-7.11 (1H, m, Ar- H), 7.11-7.13 (1H, m, Ar- H), 7.26-7.28 (1H, m, Ar- H), 7.28-7.31 (1H, m, Ar- H), 7.37 (1H, dd, J 1.8 & 7.9 Hz, Ar- H), 7.42 (1H, dd, J 1.7 & 7.8 Hz, Ar- H), 7.50 (1H, dd, J 1.3 & 10.8 Hz, Ar- H) and 7.51 (1H, dd, J 1.2 & 8.0 Hz, Ar- H); δ_{C} (CDCl_3 , 100 MHz) 40.60 (C_4), 41.15 (C_4'), 52.09 (C_{24}), 52.27 (C_{24}), 53.09 (C_{19}), 53.25 (C_{19}'), 65.84 (C_3), 65.92 (C_3'), 79.25 (C_5'), 80.55 (C_5), 82.76 (C_2'), 83.27 (C_2), 116.36 (C_7), 118.11 (C_7'), 123.06 (C_9), 123.49 (C_9'), 127.16 (C_{13}'), 128.22 (C_{11}), 129.03 (C_{13}), 129.35 (C_{11}'), 129.46 (C_{12}), 129.53 (C_{12}'), 132.34 (C_{10}'), 132.64 (C_{10}), 135.73 (C_6'), 137.61 (C_6), 138.09 (C_8'), 138.74 (C_8), 168.52 (C_{17}'), 168.72 (C_{17}), 170.90 (C_{21}') and 171.15 (C_{21}); m/z : (EI) 370 (M^+ , Br^{81} , 3%), 368 (M^+ , Br^{79} , 3%), 289 (42), 235 (62), 203 (57), 184 (100), 152 (90) and 124 (61); HRMS Found (368.0265, $\text{C}_{16}\text{H}_{17}\text{O}_5\text{Br}^{79}$ requires 368.0259).

Preparation of (*E*)-(2-iodobenzylidene)-(2-methylallyl)-amine (**243**)

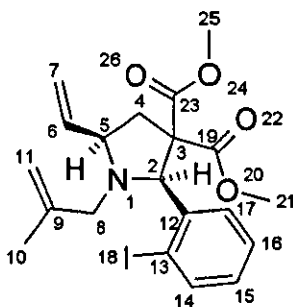


To a stirred solution of Et_2O (15 ml) in a nitrogen atmosphere was added molecular sieves (2.50 g 4 Å), 2-methylallylamine (**233**) (0.25 g, 3.52 mmol) and 2-iodobenzaldehyde (**242**) (0.87 g, 3.52 mmol). The reaction mixture was left to stir

overnight, after which time it was filtered under suction and washed several times with Et₂O (3 × 5 ml). The filtrate was concentrated *in vacuo* to give the imine as a colourless oil (0.35 g, 90 %).

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$: 3060, 2968, 2932, 2878, 2809, 1652, 1634, 1459 and 1433; δ_{H} (CDCl₃, 400 MHz) 1.84 (3H, s, H₂C=C(CH₃)), 4.21 (2H, s, CH₂N), 4.90-4.92 (2H, m, H₂C=C(CH₃)), 7.11 (1H, dt, *J* 1.8 & 7.7 Hz, Ar-*H*), 7.35-7.39 (1H, m, Ar-*H*), 7.86 (1H, dd, *J* 1.2 & 8.0 Hz, Ar-*H*), 8.00 (1H, dd, *J* 1.8 & 7.8 Hz, Ar-*H*) and 8.44 (1H, s, N=CHAr); δ_{C} (CDCl₃, 100 MHz) 21.07 (C11), 66.87 (C9), 100.08 (C10), 111.73 (C12), 128.42 (C4), 128.88 (C5), 132.03 (C6), 136.96 (C1), 139.61 (C3), 143.30 (C2) and 165.19 (C7); *m/z*: (EI) 285 (M⁺, 22%), 144 (100), 101 (48), 67 (55) and 55 (49); HRMS Found (285.1277, C₁₁H₁₂Nl requires 285.1275).

Preparation of 2-(R),5-(R)-2-(2-iodophenyl)-1-(2-methylallyl)-5-vinylpyrrolidine-3,3-dicarboxylic acid dimethyl ester (244)

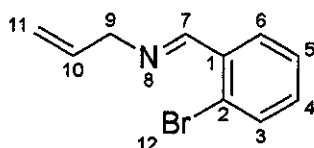


To a stirred solution of 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester (**161**) (0.25 g, 1.36 mmol) in THF (5 ml) was added (2-iodobenzylidene)-(2-methylallyl)-amine (**243**) (0.38 g, 1.36 mmol) and ZnCl₂ (0.37 g, 2.72 mmol) at room temperature. This mixture was left to stir for 10 min under nitrogen before a catalytic amount of Pd(PPh₃)₄ (0.16 g, 0.14 mmol) was added. The resulting mixture was allowed to stir at room temperature for 48 h. The solvent was removed *in vacuo* and the residue dissolved in EtOAc (5 ml). The palladium catalyst was filtered under suction through a plug of silica, and the organic layer was washed several times with distilled H₂O (3 × 10 ml). The

organic phase was dried over MgSO_4 and concentrated *in vacuo* to give the crude product as a colourless oil, which was further purified *via* flash chromatography (petrol:EtOAc, 15:1) on silica gel to give the desired product as a white crystalline solid (0.25 g, 37 %).

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$: 3072, 2949, 2818, 2359, 1736 and 1275; $\delta_{\text{H}}(\text{CDCl}_3, 400 \text{ MHz})$ 1.30 (1H, s, $\text{H}_2\text{C}=\text{C}(\text{CH}_3)$), 2.24 (1H, dd, J 5.0 & 13.2 Hz, $\text{CHHC}(\text{CO}_2\text{CH}_3)_2$), 2.74 (1H, t, J 12.0 Hz, $\text{H}_2\text{C}=\text{CHCH}$), 3.12 (3H, s, OCH_3), 3.14 (1H, dd, J 8.8 & 13.2 Hz, $\text{CHHC}(\text{CO}_2\text{CH}_3)_2$), 3.18-3.21 (2H, m, CH_2N), 3.82 (3H, s, OCH_3), 4.51 (1H, s, $\text{HHC}=\text{CCH}_3$), 4.96 (1H, s, $\text{HHC}=\text{CCH}_3$), 5.09 (1H, s, NCHAr), 5.18 (1H, dd, J 1.6 & 10.1 Hz, $\text{HHC}=\text{CH}$), 5.28 (1H, dt, J 0.8 & 16.7 Hz, $\text{HHC}=\text{CH}$), 5.78-5.87 (1H, m, $\text{H}_2\text{C}=\text{CH}$), 6.83-6.87 (1H, m, Ar- H), 7.24-7.28 (1H, m, Ar- H), 7.54 (1H, dd, J 1.7 & 7.9 Hz, Ar- H) and 7.69 (1H, dd, J 1.3 & 7.9 Hz, Ar- H); $\delta_{\text{C}}(\text{CDCl}_3, 100 \text{ MHz})$ 20.45 (C2), 39.50 (C4), 51.68 (C25), 53.20 (C21), 60.28 (C8), 64.47 (C3), 66.13 (C5), 74.74 (C10), 101.39 (C9), 114.00 (C11), 117.48 (C7), 127.44 (C15), 128.77 (C16), 130.87 (C17), 138.76 (C14), 139.58 (C6), 142.73 (C12), 143.36 (C13), 168.57 (C19) and 171.51 (C23); mp: 68-70°C; m/z : (EI) 470 (M^+ , 97%), 270 (65), 229 (38), 114 (59), 59 (89), 55 (100) and 39 (60); HRMS Found (470.0823, $\text{C}_{20}\text{H}_{25}\text{O}_4\text{NI}$ requires 470.0823).

Preparation of (*E*)-allyl-[1-(2-bromophenyl)-methylidene]-amine (246)

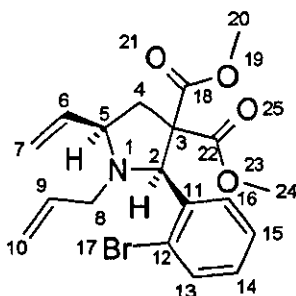


To a stirred solution of Et_2O (15 ml) in a nitrogen atmosphere was added molecular sieves (2.50 g 4 Å), allyamine (247) (0.25 g, 4.38 mmol) and 2-bromobenzaldehyde (234) (0.81 g, 4.38 mmol). The reaction mixture was left to stir overnight, after which it was filtered under suction and washed several times with Et_2O ($3 \times 5 \text{ ml}$). The filtrate was concentrated *in vacuo* to give the imine as a brown oil (0.89 g, 90 %).

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$: 3065, 2887, 2359, 1635, 1588, 1464, 1437, 1019 and 755; $\delta_{\text{H}}(\text{CDCl}_3, 400 \text{ MHz})$ 4.29-4.32 (2H, m, $\text{H}_2\text{C}=\text{CHCH}_2$), 5.16-5.27 (2H, m, $\text{H}_2\text{C}=\text{CH}$), 6.05-6.09 (1H, m, $\text{H}_2\text{C}=\text{CH}$), 7.26-7.28 (1H, m, Ar- H), 7.34-7.36 (1H, m, Ar- H), 7.56 (1H, dd, J

1.2 & 7.7 Hz, Ar-*H*), 8.04 (1H, dd, *J* 1.8 & 7.7 Hz, Ar-*H*) and 8.67 (1H, s, N=CHAr); δ_c (CDCl₃, 100 MHz) 63.54 (C9), 116.34 (C11), 125.06 (C1), 127.61 (C3), 128.80 (C4), 131.84 (C6), 133.04 (C5), 134.56 (C2), 135.63 (C10) and 161.01 (C7); *m/z*: (FAB) 226 ($M^{+H} Br^{81}$ 3%) 224 ($M^{+H} Br^{79}$ 3%), 169 (100), 154 (41), 136 (78), 105 (41), 91 (58) and 77 (42); HRMS Found (224.0071, C₁₀H₁₀NBr⁷⁹ requires 224.0074).

Preparation of 2-(R),5-(R)-1-allyl-2-(2-bromophenyl)-5-vinylpyrrolidine-3,3-dicarboxylic acid dimethyl ester (245)

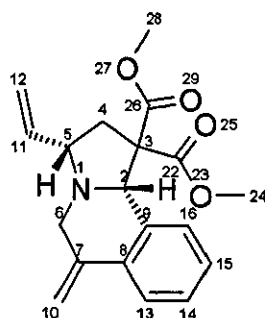


To a stirred solution of 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester (**161**) (0.25 g, 1.36 mmol) in THF (3 ml) was added allyl-[1-(2-bromophenyl)-methylidene]-amine (**246**) (0.31g, 1.36 mmol) and ZnCl₂ (0.37 g, 2.72 mmol) at room temperature. This mixture was left to stir for 10 min under nitrogen before a catalytic amount of Pd(PPh₃)₄ (0.16, 0.14 mmol) was added. The resulting mixture was allowed to stir at room temperature for 48 h. The solvent was removed *in vacuo* and the residue dissolved in EtOAc (5 ml). The palladium catalyst was filtered under suction through a plug of silica, and the organic layer was washed several times with distilled H₂O (3 × 10 ml). The organic phase was dried over MgSO₄ and concentrated *in vacuo* to give the crude product as a colourless oil, which was further purified using flash chromatography (petrol:EtOAc, 15:1) on silica gel to give the desired product as a colourless oil (0.30 g, 54 %).

$\nu_{max}(\text{neat})/\text{cm}^{-1}$: 3073, 2950, 2813, 1753, 1643, 1483, 1274, 921 and 755; δ_H (CDCl₃, 400 MHz) 2.14 (1H, dd, *J* 4.8 & 13.2 Hz, NCHCHH), 2.66 (1H, dd, *J* 5.2 & 13.2 Hz, NCHCHH), 3.01 (3H, s, OCH₃), 3.07-3.14 (1H, m, =CHCH), 3.18-3.24 (2H, m, =CHCH₂), 3.72 (3H, s, OCH₃), 4.87-4.89 (1H, m, HHC=CHCH), 5.00-5.05 (1H, m,

$HHC=CHCH_2$), 5.12 (1H, dd, J 1.6 & 10.0 Hz, $HHC=CHCH$), 5.18-5.22 (1H, m, $HHC=CHCH_2$), 5.30 (1H, s, $NCHAr$), 5.50-5.61 (1H, m, $=CHCH_2$), 5.65-5.78 (1H, m, $=CHCH$), 6.95-7.01 (1H, m, $Ar-H$), 7.15-7.21 (1H, m, $Ar-H$), 7.36 (1H, dd, J 1.2 & 8.0 Hz, $Ar-H$) and 7.52 (1H, dd, J 1.6 & 8.0 Hz, $Ar-H$); δ_c ($CDCl_3$, 100 MHz) 39.78 (C4), 52.01 (C24), 53.00 (C20), 53.61 (C8), 63.92 (C5), 67.90 (C2), 117.55 (C7), 117.66 (C11), 117.87 (C10), 125.07 (C3), 126.87 (C16), 128.76 (C15), 131.19 (C14), 131.95 (C13), 133.97 (C9), 139.19 (C6), 140.50 (C12), 168.92 (C22) and 171.61 (C18); m/z (EI) 410, (M^{+H} , Br^{81} , 96%), 408, (M^{+H} , Br^{79} , 96%), 366 (52), 274 (48), 252 (100) and 59 (75); HRMS Found (408.0801, $C_{19}H_{23}O_4NBr^{79}$ requires 408.0805).

Preparation of 2-(S),5-(R)-6-methylene-3-vinyl-2,3,6,10b-tetrahydro-5H-pyrrolo[2,1a]isoquinoline-1,1-dicarboxylic acid dimethyl ester (248)

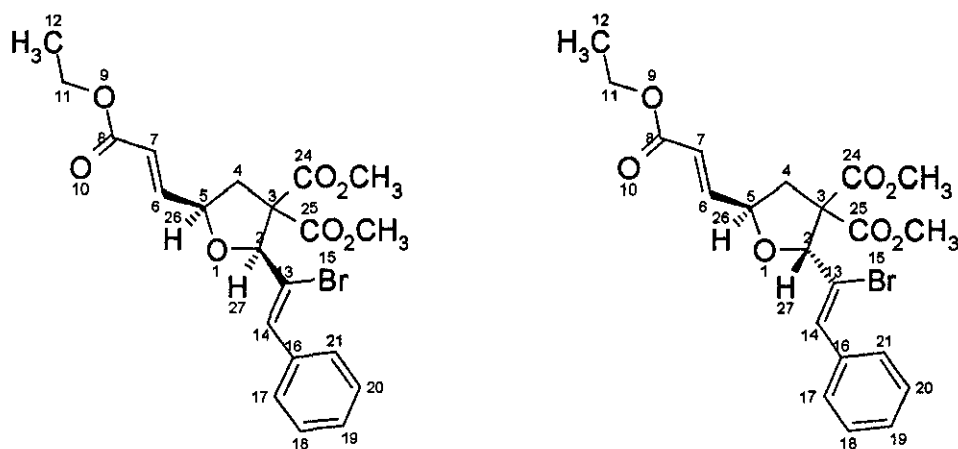


To a flame dried round bottom flask was added 1-allyl-2-(2-bromophenyl)-5-vinylpyrrolidine-3, 3-dicarboxylic acid dimethyl ester (**244**) (0.25 g, 0.25 mmol), $Pd(PPh_3)_4$, (0.14 g, 0.12 mmol), and Et_3N (5 ml). This mixture was heated at $100^\circ C$ for 24 h, after which it was washed with H_2O (15 ml), and extracted into DCM (3×10 ml). The organics were dried over $MgSO_4$, and reduced *in vacuo* to give a dark brown oil, which was purified *via* flash chromatography (petrol: Et_2O , 1:1) to give the desired product as a colourless oil (0.09 g, 42 %).

ν_{max} (neat)/ cm^{-1} : 2924, 1716, 1635, 1365, 1143 and 602; δ_H ($CDCl_3$, 400 MHz) 2.18-2.24 (1H, m, $CH_2=CHCHCHH$), 2.50-2.58 (1H, m, $CH_2=CHCHCHH$), 3.11 (3H, s, OCH_3), 3.46-3.57 (2H, m, $CH_2=CCH_2$), 3.85 (1H, s, OCH_3), 3.86-3.93 (1H, m, $CH_2=CHCHCH_2$), 4.96 (1H, s, $CHH=CCH_2N$), 5.21-5.37 (2H, m, $CH_2=CHCHCH_2$), 5.57 (1H, s,

CH₂=CHCHNCH), 5.58 (1H, s, CHH=CCH₂N), 7.14-7.26 (2H, m, Ar-H), 7.35-7.41 (1H, m, Ar-H) and 7.44-7.49 (1H, m, Ar-H); δ_c (CDCl₃, 100 MHz) 21.02 (C4), 50.84 (C24), 51.85 (C28), 52.96 (C5), 60.37 (C2), 64.46 (C6), 65.92 (C3), 103.90 (C10), 114.41 (C12), 124.18 (C14 & C15), 127.38 (C13), 127.44 (C16), 134.70 (C8), 137.10 (C9), 140.67 (C11), 146.84 (C7), 174.56 (C26) and 177.34 (C22); *m/z*: (EI) 328 (M⁺H, 14 %), 248 (28), 115 (34), 88 (16), 77 (17), 65 (22) and 57 (100); HRMS Found (327.3864 C₁₉H₂₁NO₄ requires 327.3801).

Preparation of (*E,E*)-2-(*R*),5-(*R*)-2-(1-bromo-2-phenylvinyl)-5-(2-ethoxycarbonylvinyl)-dihydrofuran-3,3-dicarboxylic acid dimethyl ester (265) (*cis:trans*; 3:1)



To a stirred solution of 2-(2-ethoxycarbonyl-vinyl)-cyclopropane-1,1-dicarboxylic acid dimethyl ester (**249**) (0.20 g, 0.78 mmol) in THF (5 ml) was added α -bromo-cinnamaldehyde (**264**) (0.17 g, 0.78 mmol) and ZnBr₂ (0.35 g, 1.56 mmol) at room temperature. This mixture was left to stir for 10 min under a nitrogen atmosphere before a catalytic amount of Pd(PPh₃)₄ (0.09 g, 0.08 mmol) was added. This was stirred at room temperature for 24 h, after which the solvent was removed *in vacuo* and the residue dissolved in EtOAc. The palladium catalyst was filtered under suction through a plug of silica, and the organic layer was washed several times with distilled H₂O (3 \times 10 ml). The organics were dried over MgSO₄ and reduced *in vacuo* to give a dark yellow oil, which

was further purified *via* flash chromatography (petrol:EtOAc, 4:1) to give the desired product as a yellow oil (0.13 g, 36%).

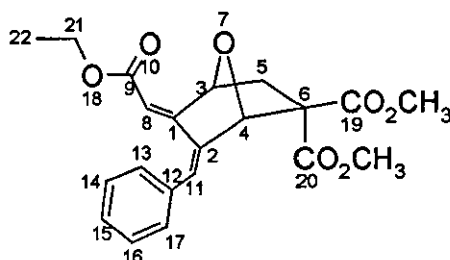
Cis Isomer:

$\nu_{\max}(\text{neat})/\text{cm}^{-1}$: 2952, 2358, 1732, 1434 and 1267; δ_{H} (CDCl_3 , 400 MHz) 1.23 (3H, t, J 7.2 Hz, CH_2CH_3), 2.48 (1H, dd, J 5.6 & 13.2 Hz, $\text{CH}=\text{CHCHCHH}$), 2.83 (1H, dd, J 11.2 & 13.2 Hz, $\text{CH}=\text{CHCHCHH}$), 3.61 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 4.15 (2H, q, J 7.2 Hz, CH_2CH_3), 4.47-4.52 (1H, m, $\text{CH}=\text{CHCHCH}_2$), 5.44 (1H, d, J 0.4 Hz, $\text{CHC}(\text{Br})=\text{CHAr}$), 6.11 (1H, dd, J 1.2 & 15.6 Hz, $\text{CH}=\text{CHCHCH}_2$), 6.98 (1H, dd, 5.6 & 15.6 Hz, $\text{CH}=\text{CHCHCH}_2$), 7.11 (1H, s, $\text{CHC}(\text{Br})=\text{CHAr}$), 7.23-7.32 (3H, m, Ar- H) and 7.50-7.52 (2H, m, Ar- H); δ_{C} (CDCl_3 , 100 MHz) 14.25 (C12), 39.71 (C4), 53.18 (OCH_3), 53.58 (OCH_3), 60.67 (C11), 65.34 (C3), 77.27 (C5), 87.04 (C2), 122.43 (C16), 122.74 (C7), 128.21 (C18 & C20), 128.43 (C19), 129.15 (C17 & C21), 132.18 (C14), 134.88 (C13), 144.10 (C6), 166.06 (C24), 167.71 (C25) and 170.45 (C8); m/z : (FAB) 469 (M^+ , Br^{81} , 30%), 467 (M^+ , Br^{79} , 30%), 387 (100), 257 (91), 211 (52), 154 (49) and 136 (41); HRMS Found (467.0709 $\text{C}_{21}\text{H}_{23}\text{O}_7\text{Br}^{79}$ requires 467.0705).

Trans Isomer:

$\nu_{\max}(\text{neat})/\text{cm}^{-1}$: 2952, 2359, 1735, 1444 and 1268; δ_{H} (CDCl_3 , 400 MHz) 1.22 (3H, t, J 7.2 Hz, CH_2CH_3), 2.20 (1H, dd, J 6.4 & 13.2 Hz, $\text{CH}=\text{CHCHCHH}$), 3.14 (1H, dd, J 7.2 & 13.2 Hz, $\text{CH}=\text{CHCHCHH}$), 3.63 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 4.13 (2H, q, J 7.2 Hz, CH_2CH_3), 5.09-5.12 (1H, m, $\text{CH}=\text{CHCHCH}_2$), 5.55 (1H, d, J 0.8 Hz, $\text{CHC}(\text{Br})=\text{CHAr}$), 6.03 (1H, dd, J 1.6 & 15.6 Hz $\text{CH}=\text{CHCHCH}_2$), 6.80 (1H, dd, J 4.8 & 15.6 Hz, $\text{CH}=\text{CHCHCH}_2$), 7.14 (1H, s, $\text{CHC}(\text{Br})=\text{CHAr}$), 7.19-7.31 (3H, m, Ar- H) and 7.49-7.52 (2H, m, Ar- H); δ_{C} (CDCl_3 , 100 MHz) 14.24 (C12), 39.49 (C4), 53.28 (OCH_3), 53.31 (OCH_3), 60.60 (C11), 64.66 (C3), 78.40 (C5), 86.86 (C2), 121.41 (C7), 122.39 (C16), 128.19 (C18 & C20), 128.36 (C19), 129.18 (C17 & C21), 131.03 (C14), 134.93 (C13), 146.06 (C6), 166.12 (C24), 168.00 (C25) and 169.59 (C8); m/z : (FAB) 469 (M^+ , Br^{81} , 30%), 467 (M^+ , Br^{79} , 30%), 387 (100), 225 (33), 211 (52), 154 (50), 137 (31), and 121 (20); HRMS Found (467.0711 $\text{C}_{21}\text{H}_{23}\text{O}_7\text{Br}^{79}$ requires 467.0705).

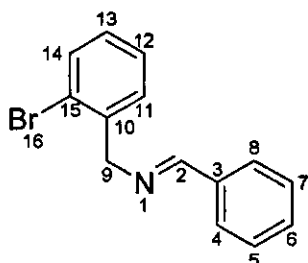
Preparation of 6-benzylidene-1-ethoxycarbonylmethylene-7-oxa-bicyclo[2.2.1]heptane-6,6-dicarboxylic acid dimethyl ester.(262)



To a flame dried round bottom flask was added 2-(1-bromo-2-phenyl-vinyl)-5-(2-ethoxycarbonyl-vinyl)-dihydro-furan-3, 3-dicarboxylic acid dimethyl ester (**265**) (0.07 g, 0.15 mmol), Pd(OAc)₂ (3 mg, 0.02 mmol), PPh₃ (0.02 g, 0.15 mmol) and ⁱPrNEt₂ (0.04 g, 0.05 ml, 0.30 mmol) in anhydrous DMF (2ml). This mixture was heated at 100°C for 24 h, after which it was washed with H₂O (15 ml), and extracted into DCM (3 × 10 ml). The organics were dried over MgSO₄, and reduced *in vacuo* to give a dark brown oil, which was purified *via* flash chromatography on silica gel (petrol:EtOAc, 10:1), to give the desired product as a colourless oil (0.03 g, 43%).

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$: 3359, 2360, 1734, 1527, 1350, 1042, 802 and 731; δ_{H} (CDCl₃, 400 MHz) 1.21 (3H, t, *J* 7.2 Hz, CH₃CH₂), 2.40 (1H, dd, *J* 8.0 & 12.0 Hz, CH=CCHCHH), 2.65 (1H, d, *J* 8.0 Hz, CH=CCHCHH), 3.68 (3H, s, OCH₃), 3.76 (3H, s, OCH₃), 4.08 (2H, q, *J* 7.2 Hz, CH₃CH₂), 5.35 (1H, s, ArCH=CHC(CO₂CH₃)₂), 5.86 (1H, s, C=CHAr), 5.89-5.92 (1H, m, CH=CCHCH₂), 6.68 (1H, s, CH=CCHCH₂), 7.27-7.43 (4H, m, Ar-H) and 7.51-7.54 (1H, m, Ar-H); δ_{C} (CDCl₃, 100 MHz) 14.09 (C22), 37.84 (C5), 53.13 (OCH₃), 53.20 (OCH₃), 60.37 (C21), 63.27 (C6), 80.92 (C3), 85.09 (C4), 111.27 (C11), 126.63 (C12), 128.16 (C8), 128.31 (C13), 128.47 (C14), 129.15 (C15), 129.23 (C16), 129.32 (C17), 135.03 (C1), 136.63 (C2), 169.60 (C9), 170.25 (C19) and 171.12 (C20); *m/z*: (FAB) 387 (M⁺H, 2%), 243 (26), 191 (25), 169 (20), 159 (140, 154 (23), 149 (51), 136 (27), 131 (45), 119 (45), 95 (56), 83 (40), 81 (49), 71 (41), 69 (74), 57 (100) and 55 (92); HRMS Found (387.1450 C₂₁H₂₂O₇ requires 387.1443).

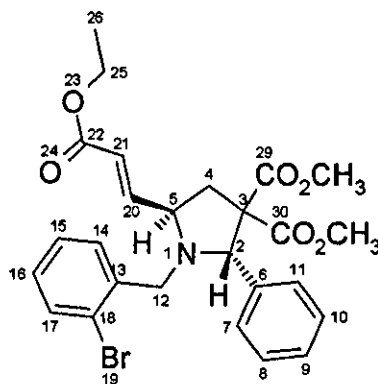
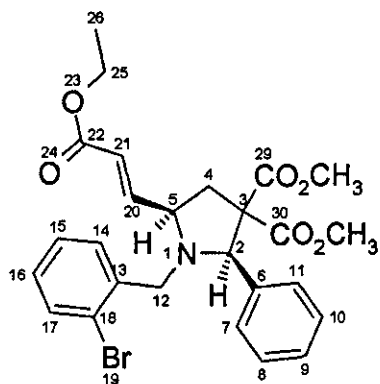
Preparation of (*E*)-benzylidene-(2-bromobenzyl)-amine (**258**)



To a stirred solution of Et₂O (15 ml) in a nitrogen atmosphere was added molecular sieves (2.50 g 4 Å), 2-bromobenzylamine hydrochloride (**259**) (0.25 g, 1.12 mmol) and benzaldehyde (0.12 g, 0.14 ml, 1.12 mmol). The reaction mixture was left to stir overnight, after which time it was filtered under suction and washed several times with Et₂O (3 × 5 ml). The filtrate was concentrated *in vacuo* to give the imine as a brown oil (0.30 g, 96%).

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$: 3059, 2846, 1644, 1438, 1024, 750 and 692; δ_{H} (CDCl₃, 400 MHz) 4.82 (2H, s, CH₂N=CH), 7.05-7.09 (1H, m, Ar-*H*), 7.20-7.25 (1H, m, Ar-*H*), 7.33-7.39 (4H, m, Ar-*H*), 7.49-7.52 (1H, dd, *J* 1.2 & 8.0 Hz Ar-*H*), 7.73-7.76 (2H, m, Ar-*H*) and 8.35 (1H, t, *J* 1.2 Hz, CH₂N=CH); δ_{C} (CDCl₃, 100 MHz) 64.30 (C9), 123.58 (C15), 127.54 (C11), 128.33 (C4 & C8), 128.49 (C12), 128.67 (C5 & C7), 129.77 (C13), 130.94 (C6), 132.55 (C14), 136.08 (C3), 138.73 (C10) and 162.98 (C2); *m/z* (FAB) 276 (M⁺, Br⁸¹, 7%), 274 (M⁺, Br⁷⁹, 7%), 171 (48), 169 (100), 91 (27) and 73 (49); HRMS Found (274.0236 C₁₄H₁₂NBr⁷⁹ requires 274.0231).

Preparation of (*E*)-2-(*R*),5-(*R*)-1-(2-bromobenzyl)-5-(2-ethoxycarbonylvinyl)-2-phenyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (257**) (*cis:trans*; 4:1)**



To a stirred solution of 2-(2-ethoxycarbonyl-vinyl)-cyclopropane-1, 1-dicarboxylic acid dimethyl ester (**249**) (0.30 g, 1.16 mmol) in THF (5 ml) was added benzylidene-(2-bromo-benzyl)-amine (**257**) (0.32 g, 1.16 mmol) and ZnBr_2 (0.52 g, 2.32 mmol) at room temperature. This was left to stir for 10 min under a nitrogen atmosphere before a catalytic amount of $\text{Pd}(\text{PPh}_3)_4$ (0.13 g, 0.12 mmol) was added. The reaction mixture was allowed to stir at room temperature for 24 h. The solvent was removed *in vacuo* and the residue dissolved in EtOAc. The palladium catalyst was filtered under suction through a plug of silica, and the organic phase collected and washed several times with H_2O (3×10 ml). The organic phase was dried over MgSO_4 and concentrated *in vacuo* to give the crude oily product, which was further purified by flash chromatography on silica gel (petrol:EtOAc, 4:1) to give the pyrrolidine as a yellow oil (0.29 g, 48%).

Cis Isomer:

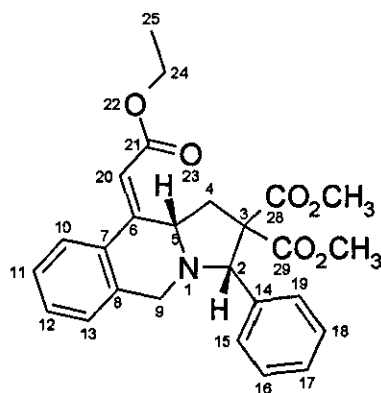
$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$: 2981, 2951, 2358, 1753, 1736, 1434 and 1267; δ_{H} (CDCl_3 , 400 MHz) 1.18 (3H, t, J 7.2 Hz, CH_3CH_2), 2.21 (1H, dd, J 6.0 & 13.2 Hz, $\text{CH}=\text{CHCHCHH}$), 2.72 (1H, dd, J 10.8 & 13.2 Hz, $\text{CH}=\text{CHCHCHH}$), 3.01 (3H, s, OCH_3), 3.33-3.39 (1H, m, $\text{CH}=\text{CHCHCH}_2$), 3.72 (3H, s, OCH_3), 3.75 (1H, d, J 1.2 Hz, CH_2Ar), 4.06 (2H, q, J 7.2

Hz, CH₃CH₂), 4.71 (1H, s, NCHAr), 5.79 (1H, dd, *J* 0.4 & 15.6 Hz, CH=CHCHCH₂), 6.69 (1H, dd, *J* 8.4 & 15.6 Hz, CH=CHCHCH₂), 6.80-6.84 (1H, m, Ar-*H*), 7.00 (1H, td, *J* 1.2 & 7.6 Hz, Ar-*H*), 7.05-7.14 (3H, m, Ar-*H*), 7.20-7.24 (2H, m, Ar-*H*) and 7.27-7.29 (2H, m, Ar-*H*); δ_c (CDCl₃, 100 MHz) 14.25 (C26), 38.68 (C4), 52.10 (OCH₃), 53.14 (OCH₃), 56.69 (C12), 60.23 (C25), 64.45 (C3), 64.55 (C5), 72.62 (C2), 121.79 (C21), 124.62 (C6), 126.76 (C17), 127.34 (C8 & C9 & C10), 128.49 (C7 & C11), 128.55 (C14), 132.28 (C15), 132.50 (C16), 137.40 (C13), 139.32 (C18), 148.56 (C20), 165.91 (C29), 168.79 (C30) and 171.78 (C22); *m/z*: (FAB) 532 (M⁺, Br⁸¹, 20%), 530 (M⁺, Br⁷⁹, 20%), 360 (100), 171 (53), 169 (55), 154 (52), 105 (35) and 91 (45); HRMS Found (530.1174 C₂₆H₂₈O₆NBr⁷⁹ requires 530.1178).

Trans Isomer:

*v*_{max}(neat)/cm⁻¹: 2981, 2955, 2360, 1750, 1733, 1434 and 1267; δ_H (CDCl₃, 400 MHz) 1.19 (3H, t, *J* 7.2 Hz, CH₃CH₂), 2.41 (1H, dd, *J* 6.8 & 13.2 Hz, CH=CHCHCHH), 2.54 (1H, dd, *J* 10.4 & 13.2 Hz, CH=CHCHCHH), 3.03 (3H, s, OCH₃), 3.72 (3H, s, OCH₃), 3.74 (2H, s, CH₂Ar), 4.05 (2H, q, *J* 7.2 Hz, CH₃CH₂), 4.45-4.48 (1H, m, CH=CHCHCH₂), 4.68 (1H, s, NCHAr), 5.42 (1H, dd, *J* 1.2 & 11.6 Hz, CH=CHCHCH₂), 6.08 (1H, dd, *J* 8.0 & 11.6 Hz, CH=CHCHCH₂), 6.88-6.90 (1H, m, Ar-*H*), 7.00 (1H, td, *J* 1.2 & 7.2 Hz, Ar-*H*), 7.08-7.20 (3H, m, Ar-*H*), 7.23-7.26 (2H, m, Ar-*H*) and 7.33-7.35 (2H, m, Ar-*H*); δ_c (CDCl₃, 100 MHz) 14.21 (C26), 37.88 (C4), 52.04 (OCH₃), 53.00 (OCH₃), 57.50 (C12), 60.07 (C25), 60.69 (C5), 64.46 (C3), 73.13 (C2), 119.47 (C21), 125.03 (C6), 126.66 (C17), 127.58 (C8 & C9 & C10), 128.57 (C7 & C11), 128.65 (C14), 132.37 (C15), 132.41 (C16), 137.73 (C13), 139.24 (C18), 151.23 (C20), 166.08 (C29), 171.70 (C30) and 173.00 (C22); *m/z*: (FAB) 532 (M⁺, Br⁸¹, 19%), 530 (M⁺, Br⁷⁹, 19%), 360 (100), 171 (43), 169 (45), and 91 (25); HRMS Found (530.1171 C₂₆H₂₈O₆NBr⁷⁹ requires 530.1178).

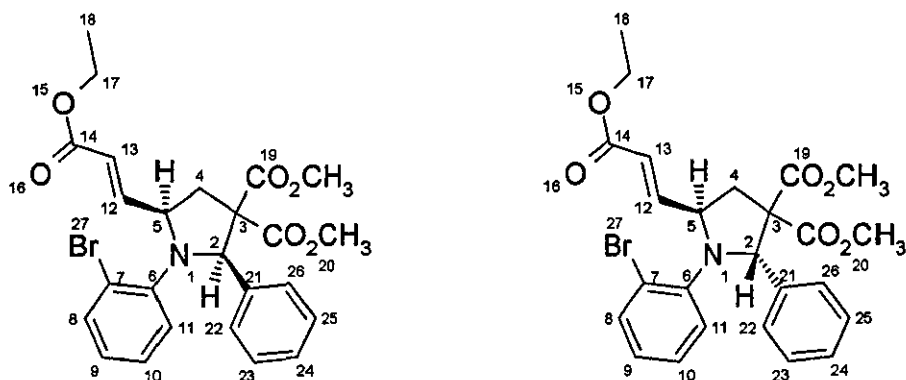
Preparation of (Z)-2-(S),5-(S)-6-ethoxycarbonylmethylene-2-phenyl-1,5,10,10a-tetrahydro-pyrrolo[1,2-*b*]isoquinoline-3,3-dicarboxylic acid dimethyl ester (256)



To a flame dried round bottom flask was added 1-(2-bromo-benzyl)-5-(2-ethoxycarbonyl-vinyl)-2-phenyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (**257**) (0.11 g, 0.21 mmol), Pd(OAc)₂ (5 mg, 0.02 mmol), PPh₃ (0.02 g, 0.08 mmol) and ⁱPrNEt₂ (0.05 g, 0.07 ml, 0.42 mmol) in anhydrous DMF (3ml). This mixture was heated at 100°C for 24 h, after which it was washed with H₂O (15 ml), and extracted into DCM (3 × 10 ml). The organics were dried over MgSO₄, and reduced *in vacuo* to give a dark brown oil, which was purified *via* flash chromatography (petrol:Et₂O, 1:1) to give the desired product as a yellow/green oil (0.07 g, 78%).

ν_{max} (neat)/cm⁻¹: 3395, 2950, 1731, 1172 and 702; δ_{H} (CDCl₃, 400 MHz) 1.33 (3H, t, *J* 7.2 Hz, CH₃CH₂), 2.78 (1H, dd, *J* 10.4 & 12.8 Hz, CH=CCHCHH), 2.97 (OCH₃), 3.24 (1H, dd, *J* 6.0 & 12.8 Hz, CH=CCHCHH), 3.30 (1H, d, *J* 14.0 Hz, CH=CCHNCHH), 3.64 (1H, d, *J* 14.0 Hz, CH=CCHNCHH), 3.82 (3H, s, OCH₃), 3.88-3.92 (1H, m, CH=CCHCH₂), 4.23 (2H, q, *J* 7.2 Hz, CH₃CH₂), 4.58 (1H, s, NCHAr), 6.41 (1H, d, *J* 2.8 Hz, CH=CCHCH₂), 6.98-7.00 (1H, m, Ar-*H*), 7.22-7.31 (5H, m, Ar-*H*), 7.36-7.38 (2H, m, Ar-*H*) and 7.74-7.76 (1H, m, Ar-*H*); δ_{C} (CDCl₃, 100 MHz) 14.26 (C25), 36.95 (C4), 51.80 (C9), 52.03 (OCH₃), 52.93 (OCH₃), 60.29 (C24), 63.10 (C5), 64.22 (C3), 71.36 (C2), 114.56 (C20), 124.45 (C17), 126.71 (C16), 127.17 (C18), 127.86 (C15 & C19),

Preparation of (*E*)-2-(*R*),5-(*R*)-1-(2-bromophenyl)-5-(2-ethoxycarbonylvinyl)-2-phenylpyrrolidine-3,3-dicarboxylic acid dimethyl ester (254**) (*cis:trans*; 1.5:1)**

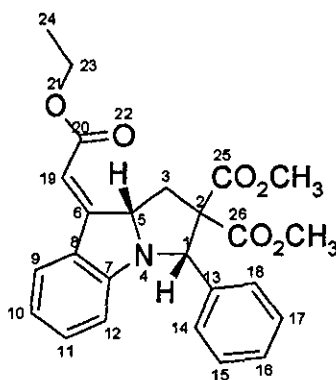


To a stirred solution of 2-(2-ethoxycarbonyl-vinyl)-cyclopropane-1, 1-dicarboxylic acid dimethyl ester.(**249**) (0.18 g, 0.70 mmol) in THF (5 ml) was added benzylidene-(2-bromophenyl)-amine (**255**) (0.18 g, 0.70 mmol) and ZnBr_2 (0.31 g, 1.40 mmol) at room temperature. This was left to stir for 10 minutes under a nitrogen atmosphere before a catalytic amount of $\text{Pd}(\text{PPh}_3)_4$ (0.08 g, 0.07 mmol) was added. The reaction mixture was allowed to stir at room temperature for 24 h. The solvent was removed *in vacuo* and the residue dissolved in EtOAc. The palladium catalyst was filtered under suction through a plug of silica, and the organic phase collected and washed several times with H_2O (3×10 ml). The organic phase was dried over MgSO_4 and concentrated *in vacuo* to give the crude oily product, which was further purified by flash chromatography on silica gel (petrol:EtOAc, 4:1) to give the pyrrolidine as a yellow oil (0.14 g, 38%).

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$: 2950, 1733, 1653, 1474, 1257, 1028 and 734; δ_{H} (CDCl_3 , 400 MHz) 1.20 (3H, t, J 7.2 Hz, CH_3CH_2), 1.25 (3H, t, J 6.8 Hz, $\text{CH}_3'\text{CH}_2$), 2.14 (1H, dd, J 7.2 & 13.2 Hz, $\text{CH}=\text{CHCHCHH}$), 2.50 (1H, dd, J 6.4 & 13.2 Hz, $\text{CH}=\text{CHCHCH}'\text{H}$), 2.73 (1H, dd, J 10.4 & 13.2 Hz, $\text{CH}=\text{CHCHCHH}'$), 3.00-3.03 (1H, m, $\text{CH}=\text{CHCHCHH}$), 3.04 (3H, s, OCH_3), 3.22 (3H, s, OCH_3'), 3.73 (3H, s, OCH_3'), 3.75 (3H, s, OCH_3), 4.10 (2H, q, J 6.8 Hz, $\text{CH}_3\text{CH}_2'$), 4.17 (2H, q, J 7.2 Hz, CH_3CH_2), 4.49-4.55 (1H, m, $\text{CH}=\text{CHCH}'\text{CH}_2$),

5.16-5.18 (1H, m, CH=CHCHCH₂), 5.65 (1H, s, NCH'Ar), 5.71 (1H, s, NCHAr), 6.05 (1H, dd, *J* 1.6 & 15.6 Hz, CH=CHCHCH₂), 6.13 (1H, dd, *J* 1.6 & 16.0 Hz, CH=CH'CHCH₂), 6.70-7.06 (1H, m, CH=CHCHCH₂), 6.86-6.92 (2H, m, Ar-*H*'), 6.86-6.92 (2H, m, Ar-*H*'), 6.97-7.06 (1H, m, CH'=CHCHCH₂), 7.15-7.28 (4H, m, Ar-*H*'), 7.15-7.28 (4H, m, Ar-*H*'), 7.32-7.36 (2H, m, Ar-*H*'), 7.32-7.36 (2H, m, Ar-*H*'), 7.48 (1H, d, *J* 8.0 Hz, Ar-*H*) and 7.75 (1H, d, *J* 8.0 Hz, Ar-*H*); δ_c (CDCl₃, 100 MHz) 14.28 (C18'), 14.30 (C18), 30.84 (C4'), 31.00 (C4), 39.93 (C17), 52.34 (OCH₃'), 52.64 (OCH₃'), 53.14 (OCH₃'), 53.54 (OCH₃'), 60.57 (C17'), 64.64 (C5'), 65.96 (C3), 69.57 (C3'), 77.62 (C5), 83.85 (C2), 84.53 (C2'), 99.20 (C21'), 118.61 (C13'), 122.15 (C13), 126.45 (C23' & C24' & C25'), 126.92 (C23 & C24 & C25), 127.35 (C22' & C26'), 127.93 (C22 & C26), 127.99 (C11'), 128.25 (C11), 128.35 (C10'), 128.46 (C9 & C10), 128.71 (C9'), 129.26 (C8), 131.91 (C8'), 132.65 (C6'), 135.83 (C6), 137.25 (C7), 138.70 (C7'), 144.59 (C12'), 146.79 (C12), 166.20 (C14), 167.63 (C14'), 168.66 (C19), 170.49 (C20'), 170.90 (C19'), and 171.83 (C20); *m/z*: (FAB), 518 (M⁺, Br⁸¹, 7%), 516 (M⁺, Br⁷⁹, 7%), 488 (40), 486 (54), 436 (42), 298 (43), 260 (100) and 121 (52); HRMS Found (516.1024 C₂₅H₂₆O₆NBr⁷⁹ requires 516.1021).

Preparation of (Z)-1-(R),5-(R)-6-ethoxycarbonylmethylene-1-phenyl-8,8a-dihydro-1*H*-3a-aza-cyclopenta[α]indene-2,2-dicarboxylic acid dimethyl ester (253)

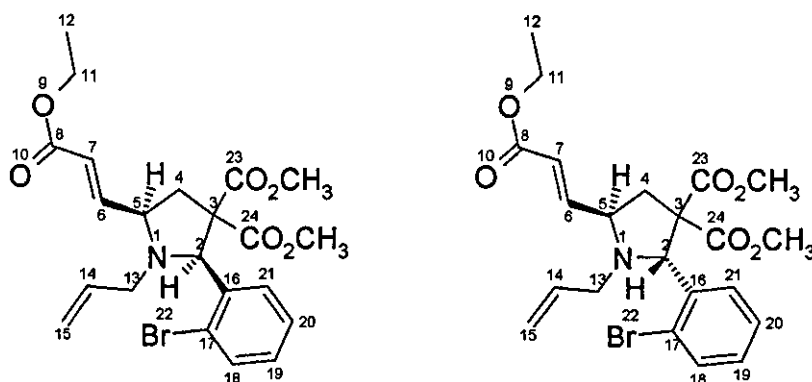


To a flame dried round bottom flask was added 1-(2-bromophenyl)-5-(2-ethoxycarbonylmethylene)-2-phenylpyrrolidine-3,3-dicarboxylic acid dimethyl ester (254)

(0.14 g, 0.27 mmol), Pd(OAc)₂ (6 mg, 0.03 mmol), PPh₃ (0.03 g, 0.11 mmol) and ⁱPrNEt₂ (0.07 g, 0.09 ml, 0.53 mmol) in anhydrous DMF (3ml). This mixture was heated at 100°C for 24 h, after which it was washed with H₂O (15 ml), and extracted into DCM (3 × 10 ml). The organics were dried over MgSO₄, and reduced *in vacuo* to give a dark brown oil, which was purified *via* flash chromatography (petrol:Et₂O, 1:1), to give the desired product as a colourless oil (0.06 g, 54%).

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$: 3375, 2935, 1736, 1110, 1072 and 712; δ_{H} (CDCl₃, 400 MHz) 1.32-1.38 (3H, t, *J* 7.2 Hz, CH₃CH₂), 1.84 (1H, dd, *J* 10.4 & 12.8 Hz, CH=CCHCHH), 3.10 (3H, s, OCH₃), 3.40 (1H, dd, *J* 8.0 & 12.8 Hz, CH=CCHCHH), 3.63 (3H, s, OCH₃), 4.18 (2H, q, *J* 7.2 Hz, CH₃CH₂), 5.27 (1H, s, NCHAr), 5.88-5.98 (1H, m, CH=CCHCH₂), 6.17 (1H, d, *J* 2.7 Hz, CH=CCHCH₂), 6.49 (2H, dd, *J* 8.0 & 24.0 Hz, Ar-*H*), 6.80-6.87 (1H, m, Ar-*H*), 7.21-7.29 (2H, m, Ar-*H*), 7.35-7.37 (2H, m, Ar-*H*), 7.45-7.49 (1H, m, Ar-*H*) and 7.57-7.59 (1H, m, Ar-*H*); δ_{C} (CDCl₃, 100 MHz) 14.27 (C24), 38.22 (C3), 52.11 (OCH₃), 53.49 (OCH₃), 60.77 (C23), 68.74 (C2), 71.02 (C1), 105.83 (C19), 109.89 (C5), 11.79 (C9), 112.10 (C12), 120.51 (C18), 122.22 (C14), 127.27 (C10 & C11), 127.78 (C15), 128.20 (C17), 128.25 (C16), 132.67 (C13), 133.24 (C6), 138.61 (C8), 139.61 (C7), 166.58 (C20), 170.49 (C25) and 171.79 (C26); *m/z*: (FAB) 435 (M⁺, 23%), 406 (44), 307 (26), 154 (100), 136 (63) and 105 (37); HRMS Found (435.1671 C₂₅H₂₅O₆N requires 435.1676).

Preparation of (*E*)-2-(*R*),5-(*R*)-1-allyl-2-(2-bromophenyl)-5-(2-ethoxycarbonylvinyl)-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (261) (*cis:trans*; 2:1).

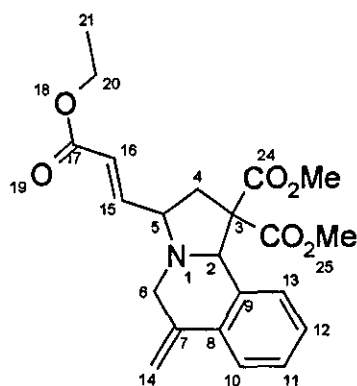


To a stirred solution of 2-(2-ethoxycarbonyl-vinyl)-cyclopropane-1, 1-dicarboxylic acid dimethyl ester (**249**) (0.47 g, 1.85 mmol) in THF (5 ml) was added allyl-[1-(2-bromophenyl)-methylidene]-amine (**247**) (0.41 g, 1.85 mmol) and ZnBr_2 (0.83 g, 3.70 mmol) at room temperature. This was left to stir for 10 min under a nitrogen atmosphere before a catalytic amount of $\text{Pd}(\text{PPh}_3)_4$ (0.21 g, 0.19 mmol) was added. The reaction mixture was allowed to stir at room temperature for 24 h. The solvent was removed *in vacuo* and the residue dissolved in EtOAc. The palladium catalyst was filtered under suction through a plug of silica, and the organic phase collected and washed several times with H_2O (3×10 ml). The organic phase was dried over MgSO_4 and concentrated *in vacuo* to give the crude oily product, which was further purified by flash chromatography on silica gel (petrol:Et₂O, 1:1) to give the pyrrolidine as a colourless oil (0.25 g, 30%).

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$: 2950, 2359, 1735, 1718, 1266, 1194 and 702; δ_{H} (CDCl_3 , 400 MHz) 1.30 (3H, t, J 7.2 Hz, CH_3CH_2), 1.32 (3H, t, J 7.2 Hz, $\text{CH}_3'\text{CH}_2$), 2.27 (1H, dd, J 5.2 & 8.0 Hz, $\text{CH}=\text{CHCHCH}'\text{H}$), 2.39 (1H, dd, J 5.2 & 8.0 Hz, $\text{CH}=\text{CHCHCHH}$), 2.64-2.70 (1H, m, $\text{CH}=\text{CHCHCHH}$), 2.76-2.82 (1H, m, $\text{CH}=\text{CHCHCHH}'$), 3.10 (3H, s, OCH_3), 3.12 (3H, s, OCH_3'), 3.14-3.20 (2H, m, $\text{CH}_2=\text{CHCH}_2'\text{N}$), 3.14-3.20 (2H, m, $\text{CH}_2=\text{CHCH}_2\text{N}$), 3.45-3.51 (1H, m, $\text{CH}=\text{CHCH}'\text{CH}_2$), 3.81 (3H, s, OCH_3'), 3.82 (3H, s, OCH_3), 4.17 (2H, q, J 7.2 Hz, CH_3CH_2), 4.23 (2H, q, J 7.2 Hz, $\text{CH}_3\text{CH}_2'$), 4.47-4.55 (1H, m, $\text{CH}=\text{CHCHCH}_2$), 4.93-5.00 (2H, m, $\text{CH}_2=\text{CHCH}_2\text{N}$), 5.06-5.14 (2H, m, $\text{CH}_2'=\text{CHCH}_2\text{N}$), 5.37 (1H, s, NCHAr), 5.41 (1H, s, $\text{NCH}'\text{Ar}$), 5.57-5.62 (1H, m, $\text{CH}_2=\text{CHCH}_2\text{N}$), 5.63-5.66 (1H, m, $\text{CH}_2=\text{CH}'\text{CH}_2\text{N}$), 5.90-5.93 (1H, m, $\text{CH}=\text{CHCHCH}_2$), 6.06 (1H, dd, J 0.8 & 14.8 Hz, $\text{CH}'=\text{CHCHCH}_2$), 6.24-6.29 (1H, m, $\text{CH}=\text{CHCHCH}_2$), 6.89 (1H, dd, J 7.6 & 14.8 Hz, $\text{CH}=\text{CH}'\text{CHCH}_2$), 7.04-7.09 (1H, m, $\text{Ar-H}'$), 7.04-7.09 (1H, m, Ar-H), 7.23-7.29 (2H, m, $\text{Ar-H}'$), 7.23-7.29 (2H, m, Ar-H), 7.44-7.46 (1H, m, $\text{Ar-H}'$), 7.44-7.46 (1H, m, Ar-H), 7.58-7.60 (1H, m, $\text{Ar-H}'$) and 7.58-7.60 (1H, m, Ar-H); δ_{C} (CDCl_3 , 100 MHz) 14.22 ($\text{C12}'$), 14.27 (C12), 38.54 (C4), 39.43 ($\text{C4}'$), 51.84 (OCH_3'), 51.90 (OCH_3), 53.20 (OCH_3'), 54.14 (OCH_3), 54.21 ($\text{C13}'$), 55.06 (C13), 58.35 (C5), 60.25 (C11), 60.57 ($\text{C11}'$), 61.81 ($\text{C5}'$), 64.05 ($\text{C3}'$), 64.36 (C3), 68.54 ($\text{C2}'$), 68.71 (C2), 117.84 (C15), 118.18 ($\text{C15}'$), 122.21 (C7), 123.31 ($\text{C7}'$), 124.99 ($\text{C16}'$), 126.86 ($\text{C19}'$), 127.02 (C19), 128.83 ($\text{C21}'$), 128.95 (C21), 131.10 ($\text{C17}'$), 132.05 (C17), 133.51 ($\text{C18}'$ & $\text{C20}'$), 134.15 (C18 & C20), 140.05 (C16), 148.39 ($\text{C14}'$), 150.59 (C14), 166.10 ($\text{C8}'$), 166.19 (C8), 168.51 ($\text{C24}'$), 168.48 (C24), 171.27 (C23) and 171.38 ($\text{C23}'$); m/z : (FAB) 482 (M^+ , Br^{81} ,

41%), 480 (M^+ , Br^{79} , 41%), 452 (44), 440 (100), 438 (62), 154 (20) and 136 (20); HRMS Found (480.1016 $C_{22}H_{26}O_6NBr^{79}$ requires 480.1021).

Preparation of (*E*)-3-(2-ethoxycarbonyl-vinyl)-6-methylene-2,3,6,10b-tetrahydro-5*H*-pyrrolo[2,1-*a*]isoquinoline-1,1-dicarboxylic acid dimethyl ester (260)

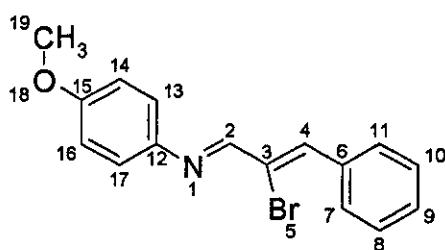


To a flame dried round bottom flask was added 1-allyl-2-(2-bromophenyl)-5-(2-ethoxycarbonylvinyl)-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (260) (0.23 g, 0.47 mmol), $Pd(OAc)_2$ (0.01 g, 0.05 mmol), PPh_3 (0.05 g, 0.19 mmol) and $iPrNEt_2$ (0.12 g, 0.16 ml, 0.94 mmol) in anhydrous DMF (2ml). This mixture was heated in a microwave for 1 h, after which it was washed with H_2O (15 ml), and extracted into DCM (3×10 ml). The organics were dried over $MgSO_4$, and reduced *in vacuo* to give a dark brown oil, which was purified *via* flash chromatography on silica gel (petrol:EtOAc, 10:1), to give a trace amount of the product as a colourless oil.

$\nu_{max}(\text{neat})/\text{cm}^{-1}$: 2358, 1731, 1698, 1454, 1372, 1172, 1028 and 667; δ_H ($CDCl_3$, 400 MHz) 1.27 (2H, t, J 7.2 Hz, CH_3CH_2), 1.93-2.03 (1H, m, $CHCHHC(CO_2CH_3)_2$), 2.16 (1H, dd, J 4.0 & 8.0 Hz, $CHCHHC(CO_2CH_3)_2$), 2.96-3.01 (1H, m, $CHCH_2C(CO_2CH_3)_2$), 3.06-3.16 (2H, m, $CHNCH_2$), 3.71 (3H, s, CO_2CH_3), 3.84 (3H, s, CO_2CH_3), 4.16 (2H, q, J 7.2 Hz, CH_3CH_2), 4.85-4.87 (1H, $CH=CHCHCH_2$), 5.23 (1H, s, $CHH=CCH_2N$), 5.25-5.28 (1H, m, $CH=CHCHCH_2$), 5.33 (1H, s, $CHH=CCH_2N$), 5.73 (1H, s, $CHNCHC(CO_2CH_3)_2$), 6.20-6.30 (2H, m, Ar-*H*), 6.97-7.00 (1H, m, Ar-*H*) and 7.25-7.29 (1H, m, Ar-*H*); δ_C

(CDCl₃, 100 MHz) 13.29 (C21), 20.28 (C4), 48.74 (C5), 49.17 (C2), 50.29 (OCH₃), 50.59 (OCH₃), 51.47 (C3), 59.27 (C20), 59.80 (C6), 106.10 (C14), 118.18 (C16), 122.14 (C11), 123.54 (C10), 124.91 (C8), 126.68 (C12), 127.93 (C13), 131.08 (C9), 146.63 (C15), 151.97 (C7), 171.50 (C17), 172.20 (C24) and 172.54 (C25).

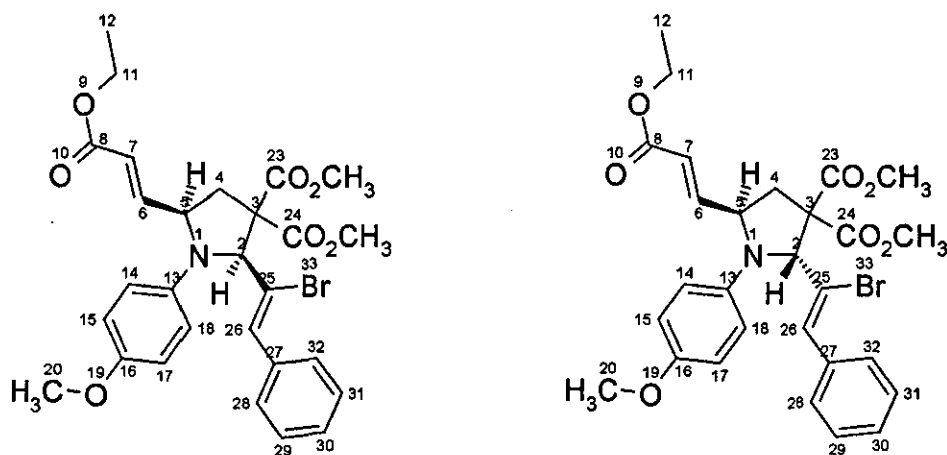
Preparation of (*E*)-(2-bromo-3-phenylallylidene)-(4-methoxyphenyl)-amine (266)



To a stirred solution of diethyl ether (15 ml) under a nitrogen atmosphere was added molecular sieves (3.00 g, 4 Å), *p*-anisidine (0.25 g, 2.03 mmol) and α -bromocinnamaldehyde (264) (0.43 g, 0.15 ml, 2.03 mmol). The reaction mixture was left to stir overnight, after which it was filtered under suction and washed several times with Et₂O (3 × 10 ml). The filtrate was concentrated *in vacuo* to give the imine as a green/yellow oil (0.59 g, 92%).

ν_{max} (neat)/cm⁻¹: 2358, 2339, 1611, 1501, 1245 and 668; δ_{H} (CDCl₃, 400 MHz) 3.84 (3H, s, OCH₃), 6.87-6.95 (2H, m, Ar-*H*), 7.16-7.25 (3H, m, Ar-*H*), 7.39-7.47 (2H, m, Ar-*H*), 7.56 (1H, s, N=CHC(Br)=CHAr), 7.90-7.92 (2H, m, Ar-*H*) and 8.30 (1H, s, N=CH); δ_{C} (CDCl₃, 100 MHz) 55.50 (OCH₃), 114.37 (C7 & C11), 118.04 (C6), 122.60 (C8 & C10), 128.45 (C13 & C17), 129.74 (C9), 130.18 (C14 & C16), 131.62 (C15), 135.26 (C12), 140.88 (C4), 150.76 (C3) and 157.03 (C2); *m/z*: (FAB) 318 (M⁺, Br⁸¹, 15%), 316 (M⁺, Br⁷⁹, 15%), 314 (100), 307 (13), 236 (21), and 195 (22); HRMS Found (316.0331 C₁₆H₁₄NOBr⁷⁹ requires 316.0337).

Preparation of (*E*)-2-(*R*),5-(*R*)-2-(1-bromo-2-phenylvinyl)-5-(2-ethoxycarbonylvinyl)-1-(4-methoxyphenyl)-pyrrolidine-3,3 dicarboxylic acid dimethyl ester (267**) (*cis:trans* 1:1)**

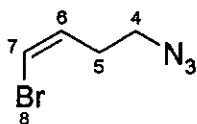


To a stirred solution of 2-(2-ethoxycarbonyl-vinyl)-cyclopropane-1, 1-dicarboxylic acid dimethyl ester (**249**) (0.20 g, 0.77 mmol) in THF (5 ml) was added (2-bromo-3-phenylallylidene)-(4-methoxyphenyl)-amine (**266**) (0.24 g, 0.77 mmol) and ZnBr_2 (0.35 g, 1.54 mmol) at room temperature. This was left to stir for 10 minutes under a nitrogen atmosphere before a catalytic amount of $\text{Pd}(\text{PPh}_3)_4$ (0.09 g, 0.07 mmol) was added. The reaction mixture was allowed to stir at room temperature for 24 h. The solvent was removed *in vacuo* and the residue dissolved in EtOAc. The palladium catalyst was filtered under suction through a plug of silica, and the organic phase collected and washed several times with H_2O (3×10 ml). The organic phase was dried over MgSO_4 and concentrated *in vacuo* to give the crude oily product, which was further purified by flash chromatography on silica gel (petrol:Et₂O 1:1) to give the pyrrolidine as a colourless oil (0.26 g, 60%).

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$: 2952, 2358, 1736, 1511, 1257, 1177, 1038 and 732; δ_{H} (CDCl_3 , 400 MHz) 1.17 (3H, t, J 7.2 Hz, CH_3CH_2), 1.20 (3H, t, J 7.2 Hz, $\text{CH}_3'\text{CH}_2$), 2.49 (1H, d, J 14.0 Hz, $\text{CH}=\text{CHCHCHH}$), 2.61 (1H, dd, J 6.0 & 13.2 Hz, $\text{CH}=\text{CHCHCH}'\text{H}$), 2.97 (1H, dd, J 11.2 & 13.2 Hz, $\text{CH}=\text{CHCHCHH}'$), 3.43-3.49 (1H, m, $\text{CH}=\text{CHCHCHH}$), 3.61 (3H,

s, OCH₃Ar), 3.62 (3H, s, OCH₃'Ar), 3.63 (3H, s, OCH₃'), 3.64 (3H, s, OCH₃), 3.66 (3H, s, OCH₃), 3.70 (3H, s, OCH₃'), 4.07 (2H, q, *J* 7.2 Hz, CH₃CH₂'), 4.09 (2H, q, *J* 7.2 Hz, CH₃CH₂), 4.19-4.22 (1H, m, CH=CHCH'CH₂), 4.66-4.70 (1H, m, CH=CHCHCH₂), 5.05 (1H, s, NCHC(Br)=CHAr), 5.61 (1H, s NCH'C(Br)=CHAr), 5.70 (1H, dd, *J* 1.6 & 16.0 Hz, CH=CHCHCH₂), 6.06 (1H, dd, *J* 1.2 & 16.0 Hz, CH=CHCHCH₂), 6.46-6.49 (2H, m, Ar-*H*), 6.57-6.61 (2H, m, Ar-*H*'), 6.69-6.71 (1H, m, CH=CHCHCH₂), 6.72-6.75 (2H, m, Ar-*H*'), 6.72-6.75 (2H, m, Ar-*H*), 6.93-6.99 (1H, m, CH=CH'CHCH₂), 7.14 (1H, s, =CHAr), 7.17 (=CH'Ar), 7.19-7.31 (3H, m, Ar-*H*'), 7.19-7.31 (3H, m, Ar-*H*), 7.37-7.39 (2H, m, Ar-*H*) and 7.53 (2H, m, Ar-*H*); δ_c (CDCl₃, 100 MHz) 14.23 (C12'), 14.34 (C12), 35.90 (C4), 37.87 (C4'), 53.08 (OCH₃), 53.22 (OCH₃), 53.25 (OCH₃'), 53.56 (OCH₃'), 55.58 (C20), 55.63 (C20'), 58.22 (C5), 58.91 (C5'), 60.47 (C11), 60.63 (C11'), 63.80 (C3), 63.88 (C3'), 70.92 (C2), 75.59 (C2'), 114.67 (C28 & C32), 115.00 (C28' & C32'), 115.14 (C30), 115.21 (C30'), 122.08 (C7), 122.38 (C27), 123.08 (C7'), 123.86 (C27'), 128.20 (C29 & C31), 128.24 (C29' & C31'), 128.38 (C15 & C17), 128.51 (C15' & C17'), 129.15 (C14 & C18), 129.23 (C14' & C18'), 131.40 (C26), 134.97 (C25), 137.61 (C25'), 140.70 (C16), 140.99 (16'), 147.46 (C6), 148.08 (C6'), 152.00 (C13), 153.10 (C13'), 166.01 (C8), 166.21 (C8'), 167.32 (C23), 167.38 (C23'), 170.09 (C24) and 170.14 (C24'); *m/z*: (EI) 574.(M⁺, Br⁸¹, 96%), 572 (M⁺, Br⁷⁹, 96%), 494 (48), 468 (40), 276 (62), 238 (59), 212 (48), 162 (82), 150 (85), 124 (100) and 98 (46); HRMS Found (572.1279 C₂₈H₃₀O₇NBr⁷⁹ requires 572.1278).

Preparation of (Z)-4-azido-1-bromobut-1-ene (285)

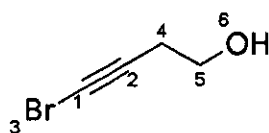


4-Bromobut-3-en-1-ol (281) (1.00 g, 6.63 mmol) was dissolved in THF (30 ml) and cooled to 0°C. To this was added triphenylphosphine (2.61 g, 9.95 mmol), diphenylphosphoryl azide (2.74 g, 2.14 ml, 9.95 mmol) and finally diisopropyl azodicarboxylate (2.01 g, 1.96 ml, 9.95 mmol). This mixture was allowed to warm to

room temperature whilst stirring, and monitored by TLC. After 3 hours, the reaction was quenched with H₂O (20 ml), and then extracted into DCM (3 × 15 ml) and concentrated *in vacuo* to give an oil. The oily residue was then stirred in hexane (300 ml) for 24 h. The solid triphenylphosphine oxide was removed *via* filtration, and the organics were reduced *in vacuo* to give the crude azide as an orange oil, which was further purified *via* flash chromatography (petrol:EtOAc, 4:1) to give the azide as a yellow oil (0.99, 97%).

$\nu_{\max}(\text{neat})/\text{cm}^{-1}$: 2984, 2170, 1774, 1488, 1245 and 1182; δ_{H} (CDCl₃, 400 MHz) 2.56 (2H, q, *J* 6.5 Hz, CH=CHCH₂CH₂N₃), 4.13-4.18 (2H, m, CH=CHCH₂CH₂N₃), 6.15-6.17 (1H, m, CH=CHCH₂CH₂N₃) and 6.30-6.32 (1H, m, CH=CHCH₂CH₂N₃); δ_{C} (CDCl₃, 100 MHz) 29.43 (C4), 60.42 (C5), 110.34 (C6) and 130.37 (C7).

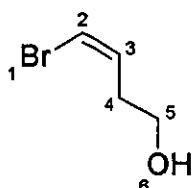
Preparation of 4-bromo-but-3-yn-1-ol (280) ⁶⁸



To a solution of potassium hydroxide (11.49 g, 206.80 mmol) in H₂O (200 ml) was added bromine (9.30 g, 56.90 mmol), and the solution was cooled to 0°C. The flask was covered with aluminium foil and then 3-butyn-1-ol (3.57 g, 51.70 mmol) was added. The mixture was stirred for 24 h after warming to room temperature. The mixture was extracted with Et₂O (2 × 50 ml), and the organic layer was dried over Na₂SO₄, and concentrated *in vacuo* to give the desired product as a colourless oil (6.86 g, 89%).

$\nu_{\max}(\text{neat})/\text{cm}^{-1}$: 3335, 2884, 1419, 1050 and 845; δ_{H} (CDCl₃, 400 MHz) 1.77 (1H, s, CH₂OH), 2.49 (2H, t, *J* 3.2 Hz, CH₂CH₂OH) and 3.77 (2H, t, *J* 3.2 Hz, CH₂CH₂OH); δ_{C} (CDCl₃, 100 MHz) 15.26 (C2), 24.02 (C4), 40.09 (C1) and 60.79 (C5); *m/z*: (EI) 150 (M⁺, Br⁸¹, 5%), 148 (M⁺, Br⁷⁹, 5%), 120 (95), 118 (100) and 69 (25); HRMS Found (147.9522, C₄H₅OBr⁷⁹, requires 147.9523).

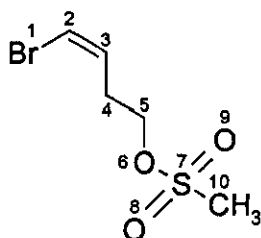
Preparation of (Z)-4-bromo-but-3-en-1-ol (281)⁶⁸



A dry 10 ml round bottomed flask was charged with 4-bromo-but-3-en-1-ol (280) (0.25 g, 1.68 mmol), dissolved in THF/H₂O (10 ml 1:1). To this was added *p*-toluensulfonhydrazide (0.63 g, 3.36 mmol) and sodium acetate (0.41 g, 5.04 mmol). This mixture was stirred under reflux for 4 h, after which the reaction was allowed to cool, and then extracted with DCM (2 × 10 ml). The organics were dried over MgSO₄, then concentrated *in vacuo* to give the desired product as a colourless oil (0.21 g 83 %).

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$: 662, 1048, 1290, 1623, 1706, 2882, 2449 and 3329 (OH); δ_{H} (CDCl₃, 400 MHz) 2.45-2.50 (2H, m, HC=CHCH₂), 3.71 (2H, t, *J* 6.4 Hz, HC=CHCH₂CH₂OH), 6.19 (1H, q, *J* 7.2 Hz, HC=CHCH₂) and 6.28 (1H, dt, *J* 1.2 & 7.2 Hz, HC=CHCH₂); δ_{C} (CDCl₃, 100 MHz) 33.14 (C4), 60.59 (C5), 109.86 (C2) and 131.20 (C3); *m/z*: (EI) 152 (M⁺, Br⁸¹, 8%), 150, (M⁺, Br⁷⁹, 8%), 122 (49), 120 (52) and 71 (100); HRMS Found (149.9678, C₄H₇OBr⁷⁹ requires 149.9680).

Preparation of (Z)-methanesulfonic acid 4-bromobut-3-enyl ester (282)⁶⁹

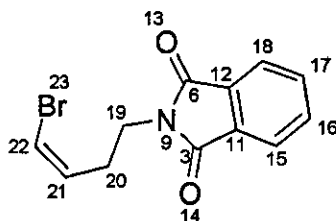


A 10 ml round bottomed flask was charged with 4-bromobut-3-en-1-ol (**281**) (4.74 g, 31.41 mmol) dissolved in DCM (3 ml). To this mixture was added triethylamine (3.50 g, 34.55 mmol) and the reaction mixture was cooled to 0°C. Methanesulfonyl chloride (3.60 g, 31.41 mmol) was added dropwise, and the reaction was stirred whilst allowed to warm to room temperature overnight. The reaction was quenched with H₂O (30 ml) followed by a saturated sodium bicarbonate solution (20 ml). The organics were extracted into DCM (3 × 20 ml), dried over MgSO₄ and concentrated *in vacuo* to give the crude product which was further purified *via* flash chromatography (hexane:EtOAc, 1:1) to give the desired product as an orange oil (6.41 g, 89 %).

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$: 1351, 1171, 964, 920 and 803; δ_{H} (CDCl₃, 400 MHz) 2.65-2.70 (2H, m, HC=CHCH₂CH₂OCH₃), 3.04 (3H, s, OCH₃), 4.29 (2H, t, *J* 6.8 Hz, HC=CHCH₂CH₂OCH₃), 6.19 (1H, q, *J* 7.2 Hz, HC=CHCH₂) and 6.37 (1H, dt, *J* 1.6 & 7.2 Hz, HC=CHCH₂); δ_{C} (CDCl₃, 100 MHz) 29.87 (C4), 37.58 (C7), 67.53 (C5), 111.51 (C2) and 128.93 (C3) *m/z*: (EI) 248 (M⁺, Br⁸¹, 98%), 246 (M⁺, Br⁷⁹, 98%), 134 (90), 118 (52), 109 (56), 91 (48), 79 (100) and 53 (80); HRMS Found (245.9791, C₅H₉O₃SBr⁷⁹ requires 245.9794).

Preparation of (Z)-4-bromobut-3-enylisoindole-1, 3-dione (283)⁷¹

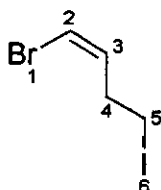
Method A



A solution of methanesulfonic acid 4-bromobut-3-enyl ester (**282**) (4.63g, 17.75 mmol) and potassium phthalamide (6.58 g, 35.50 mmol) in DMF (100 ml) was heated under reflux for 24 h under a nitrogen atmosphere. After cooling to room temperature, the resulting residue was diluted with EtOAc, and the solids filtered. The organic phase was washed with H₂O (3 × 30 ml), dried over MgSO₄ and concentrated *in vacuo* to give the crude product which was further purified by flash chromatography on silica gel (petrol:EtOAc, 1:1) to give the phthalamide product as a yellow crystalline solid (2.55 g, 29 %).

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$: 2935, 1765, 1735, 1280, 1055, 770 and 689; δ_{H} (CDCl₃, 400 MHz) 2.60-2.66 (2H, m, CH₂N), 3.82 (2H, t, *J* 6.7 Hz, =CHCH₂), 6.16 (1H, q, *J* 7.0 Hz, HC=CH), 6.24 (1H, dt, *J* 1.4 & 7.0 Hz, BrCH=CH), 7.72-7.78 (2H, m, Ar-*H*) and 7.80-7.91 (2H, m, Ar-*H*); δ_{C} (CDCl₃, 100 MHz) 29.21 (C20), 36.10 (C19), 110.59 (C21), 123.26 (C16 & C17), 130.79 (C22), 132.06 (C11 & C12), 133.95 (C15 & C18) and 168.29 (2 × CO); mp: 62.1-65.8°C; *m/z*: (FAB) 282 (M⁺, Br⁸¹, 2%), 280 (M⁺, Br⁷⁹, 2%), 160 (39), 95 (30), 81 (.8), 69 (570, 57 (67), 55 (100) and 41 (40); HRMS Found (279.9977 C₁₂H₁₀O₂NBr⁷⁹ requires 279.9973).

Preparation of (Z)-1-bromo-4-iodo-but-1-ene (287)⁷⁵



Methanesulfonic acid 4-bromobut-3-enyl ester (**282**) (5.00 g, 21.84 mmol) and sodium iodide (49.11 g, 327.65 mmol) were added to anhydrous acetone (350 ml) and heated under reflux for 24 h. The resulting precipitate was removed by filtration on a Celite bed, and the filtrate was reduced *in vacuo*. The white solid was washed with Et₂O (5 × 20 ml) and the solution was reduced *in vacuo* a second time to give the desired product as an orange oil (4.62 g, 82%).

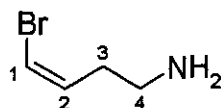
$\nu_{\max}(\text{neat})/\text{cm}^{-1}$: 3357, 2358, 1361 and 1166; δ_{H} (CDCl₃, 400 MHz) 2.62-2.68 (2H, m, BrCH=CHCH₂CH₂I), 3.04 (2H, t, *J* 7.2 Hz, BrCH=CHCH₂CH₂I), 5.99 (1H, q, *J* 6.8 Hz, BrCH=CHCH₂CH₂I) and 6.18 (1H, dt, *J* 1.2 & 6.8 Hz BrCH=CHCH₂CH₂I), δ_{C} (CDCl₃, 100 MHz) 2.53 (C3), 33.51 (C4), 110.02 (C2) and 133.34 (C1); *m/z*: (EI) 262 (M⁺, Br⁸¹, 98%), 260 (M⁺, Br⁷⁹, 98%), 209 (35), 139 (39), 91 (100), 65 (52), 55 (61) and 43 (91); HRMS Found (259.8693 C₄H₆Br⁷⁹I requires 259.8692).

Preparation of 4-bromobut-3-enylisoindole-1,3-dione (**283**) Method B

A solution of 1-bromo-4-iodobut-1-ene (**287**) (4.63 g, 17.75 mmol) and potassium phthalimide (6.58 g, 35.50 mmol) in 2-butanone (100 ml) was heated under reflux for 24 h under a nitrogen atmosphere. After cooling to room temperature, the resulting residue was diluted with EtOAc, and the solids filtered. The organic phase was washed with H₂O (3 × 30 ml), dried over MgSO₄ and concentrated *in vacuo* to give the crude product which was further purified by flash chromatography on silica gel (petrol:EtOAc, 1:1) to

give the phthalamide product as a yellow crystalline solid (3.55 g, 72%). Data as shown in Method A.

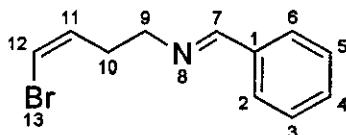
Preparation of (Z)-4-bromobut-3-enylamine (284)⁷⁶



Phthalamide (**283**) (2.00 g, 7.15 mmol) in EtOH (60 ml) was treated with hydrazine monohydrate (0.36 g, 0.347 ml, 7.15 mmol). The reaction mixture was refluxed for 24 h. Once the reaction was complete, it was cooled and the solids filtered and washed with EtOH (3 × 10 ml). The filtrate was concentrated *in vacuo*, whereupon the white precipitate was treated with H₂O (20 ml) and 2M HCl (pH 1-2). This solution was again filtered and washed with H₂O (2 × 10 ml). The filtrate was basified with NaOH (pH 12-14), and then extracted with DCM (5 × 10 ml). The organic phase was dried over MgSO₄, concentrated *in vacuo* to give the crude amine, which was further purified by flash column chromatography on silica gel (99.9% Et₂O, 0.1%NEt₃) to give the amine as an orange oil (0.67 g, 62%).

ν_{max} (neat)/cm⁻¹: 3294, 2925, 2358, 1289, 1050 and 689; δ_{H} (CDCl₃, 400 MHz) 2.42-2.56 (2H, m, =CHCH₂), 3.73 (2H, t, *J* 7.0 Hz, CH₂NH₂), 6.20 (1H, q, *J* 7.0 Hz, =CHCH₂) and 6.30 (1H dt, *J* 1.4 & 7.0 Hz HC(Br)=CH); δ_{C} (CDCl₃, 100 MHz) 33.12 (C3), 60.88 (C4), 109.82 (C2) and 131.10 (C1); *m/z*: (FAB) 152 (M⁺, Br⁸¹, 46%), 150 (M⁺, Br⁷⁹, 46%), 136 (58), 105 (75), 81 (49), 69 (76) and 55 (100); HRMS Found (149.9921 C₄H₈NBr⁷⁹ requires 149.9918).

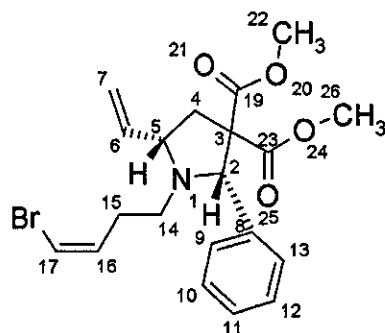
**Preparation of (Z,E)-4-(bromobut-3-enyl)-[1-phenylmethylidene]-amine
(286)**



To a stirred solution of Et₂O (15 ml) in a nitrogen atmosphere was added molecular sieves (2.50 g 4 Å), 4-bromobut-3-enylamine (**284**) (0.20 g, 1.33 mmol) and benzaldehyde (**166**) (0.14 g, 0.14 ml, 1.33 mmol). The reaction mixture was left to stir overnight, after which time it was filtered under suction and washed several times with Et₂O (3 × 5 ml). The filtrate was concentrated *in vacuo* to give the imine as an orange oil (0.33 g, 88%).

ν_{max} (neat)/cm⁻¹: 2925, 2359, 1289, 1055, 772 and 689; δ_{H} (CDCl₃, 400 MHz) 2.62 (2H, q, *J* 6.6 Hz, =CHCH₂), 3.70-3.74 (2H, m, CH₂N), 6.10-6.19 (1H, m, =CH), 6.22-6.30 (1H, m, HC(Br)=CH), 7.40-7.42 (1H, m, Ar-*H*), 7.43-7.49 (2H, m, Ar-*H*), 7.72-7.78 (2H, m, Ar-*H*) and 8.29 (1H, s, N=CH); δ_{C} (CDCl₃, 100 MHz) 31.29 (C9), 59.64 (C10), 109.09 (C11), 128.08 (C3 & 5), 128.56 (C2 & 6), 130.65 (C4), 132.27 (C7), 136.03 (C1) and 161.58 (C12); *m/z*: (FAB) 240 (M⁺, Br⁸¹, 10%), 238 (M⁺, Br⁷⁹, 10%), 136 (27), 118 (28), 95 (37), 91 (38), 81 (38), 69 (55), 57 (50) and 55 (100); HRMS Found (238.0234 C₁₁H₁₂NBr⁷⁹ requires 238.0231).

Preparation of (Z)-2-(S),5-(R)-4-bromobut-3-enyl-2-phenyl-5-vinylpyrrolidine-3,3-dicarboxylic acid dimethyl ester (288)

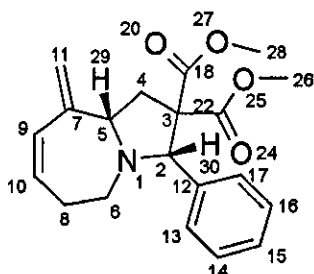


To a stirred solution of 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester (**161**) (0.26 g, 1.39 mmol) in THF (5 ml) was added 4-(bromobut-3-enyl)-[1-phenylmethylidene]-amine (**286**) (0.32 g, 1.39 mmol) and ZnCl_2 (0.38 g, 2.78 mmol) at room temperature. This was left to stir for 10 minutes under a nitrogen atmosphere before a catalytic amount of $\text{Pd}(\text{PPh}_3)_4$ (0.16 g, 0.14 mmol) was added. The reaction mixture was allowed to stir at room temperature for 24 h. The solvent was removed *in vacuo* and the residue dissolved in EtOAc. The palladium catalyst was filtered under suction through a plug of silica, and the organic phase collected and washed several times with H_2O (3×10 ml). The organic phase was dried over MgSO_4 and concentrated *in vacuo* to give the crude oily product, which was further purified by flash chromatography on silica gel (hexane:EtOAc, 15:1) to give the pyrrolidine as a colourless oil (0.31 g, 52%).

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$: 2981, 2951, 2358, 1753, 1733, 1436, 1257 and 772; δ_{H} (CDCl_3 , 400 MHz) 2.01-2.25 (2H, m, $=\text{CHCH}_2$), 2.26-2.31 (1H, m, NCHCHH), 2.63-2.68 (1H, m, NCHCHH), 2.69-2.73 (2H, m, CH_2N), 3.10 (3H, s, OCH_3), 3.13-3.24 (1H, m, $=\text{CHCH}$), 3.78 (3H, s, OCH_3), 4.75 (1H, s, NCHAr), 5.18 (1H, dd, J 1.5 & 10.0 Hz, $\text{HHC}=\text{CH}$), 5.29 (1H, dd, J 1.0 & 10.0 Hz, $\text{HHC}=\text{CH}$), 5.80-5.84 (1H, m, $\text{H}_2\text{C}=\text{CH}$), 5.90-5.93 (1H, m, $\text{BrCH}=\text{CH}$), 6.00-6.06 (1H, m, $\text{BrCH}=\text{CH}$), 7.20-7.24 (2H, m, Ar-H), 7.30-7.33 (1H, m, Ar-H) and 7.39 (2H, d, J 7.0 Hz, Ar-H); δ_{C} (CDCl_3 , 100 MHz) 27.78 (C15), 39.00 (C4), 49.80 (C14), 51.96 (C22), 53.00 (C26), 64.55 (C3), 65.46 (C5), 71.39 (C2), 108.21 (C17), 117.22 (C7), 127.62 (C13), 127.72 (C10), 127.91 (C9), 128.57 (C11 & C12),

132.89 (C16), 139.86 (C6), 140.57 (C8), 169.07 (CO) and 172.07 (CO); m/z : (EI) 424 (M^+ , Br^{81} , 97%), 422 (M^+ , Br^{79} , 97%), 302 (100), 121 (48), 91 (45) and 59 (70); HRMS Found (422.0960 $C_{20}H_{24}O_4NBr^{79}$ requires 422.0961).

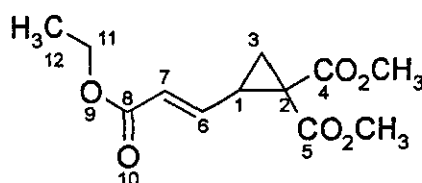
Preparation of 2-(R),5-(S)-7-methylene-2-phenyl-5,6,9,9a-tetrahydro-1H-pyrrolo[1,2-a]azepine-3,3-dicarboxylic acid diethyl ester (289)



To a solution of 4-bromobut-3-enyl-2-phenyl-5-vinylpyrrolidine-3, 3-dicarboxylic acid dimethyl ester (288) (0.10 g, 0.24 mmol) in CH_3CN (3ml) was added NEt_3 (0.07 g, 0.10 ml, 0.71 mmol) and $Pd(PPh_3)_4$ (0.01 g, 0.01 mmol). This mixture was heated in a microwave for 15 minutes at $150^\circ C$. The reaction mixture was filtered through Celite, washed with EtOAc and then concentrated *in vacuo* to give the crude product which was further purified by flash chromatography on silica gel (hexane:DCM, 1:1) to give the desired product as a colourless oil (0.022 g, 27%).

$\nu_{max}(neat)/cm^{-1}$: 2924, 1736, 1733, 1630, 1355, 1259, 1143 and 702; δ_H ($CDCl_3$, 400 MHz) 2.14-2.22 (2H, m, NCH_2CH_2), 2.54 (1H, m, $NCHHCH_2$), 2.50-2.58 (1H, m, $NCHCHH$), 2.89-2.92 (1H, m, $NCHHCH_2$), 3.00-3.03 (1H, m, $NCHCHH$), 3.06 (3H, s, OCH_3), 3.33-3.39 (1H, m, $H_2C=CCH$), 3.79 (3H, s, OCH_3), 4.63 (1H, s, $NCHAr$), 5.09 (2H, d, J 17.7 Hz, $H_2C=C$), 5.60-5.70 (1H, m, $HC=CHCH_2$), 6.13 (1H, d, J 12.1 Hz, $HC=CHCH_2$), 7.23-7.29 (3H, m, Ar-H) and 7.45 (2H, d, J 7.2 Hz, Ar-H); δ_C ($CDCl_3$, 100 MHz) 30.83 (C8), 39.04 (C4), 52.03 (C26), 52.93 (C28), 53.31 (C6), 66.45 (C5), 74.98 (C2), 116.28 (C11), 127.65 (C13), 127.80 (C14), 128.62 (C17), 128.74 (C16 & C15), 130.06 (C10), 131.01 (C9), 140.0 (C12), 168.0 (C7), 170.0 (C18) and 172.0 (C22); m/z : (EI) 342 (M^+H , 99%), 282 (51), 250 (53), 222 (61) and 59 (100); HRMS Found (342.1702 $C_{20}H_{24}O_4N$ requires 342.1700).

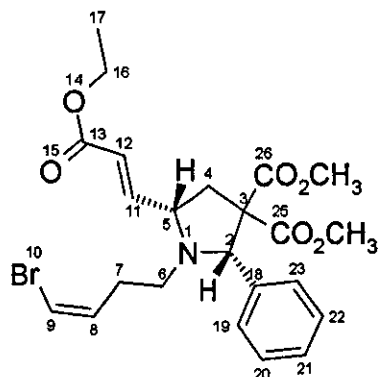
Preparation of (*E*)-2-(2-ethoxycarbonyl-vinyl)-cyclopropane-1,1-dicarboxylic acid dimethyl ester (249)



A 100 ml round bottom flask was charged with (carbethoxymethyl)triphenylphosphonium bromide (1.38 g, 3.23 mmol) and THF (15 ml) under a nitrogen atmosphere. Butyllithium (1.29 ml, 2.5 M, 3.23 mmol) was added dropwise at 0°C and the mixture stirred for 3 min. The aldehyde (0.30 g, 1.61 mmol) was added immediately to the reaction, and the mixture was stirred for a further 3 min, upon which it was quenched with H₂O (10 ml), and extracted into DCM (3 × 15 ml). The organic layer was dried over MgSO₄ and reduced *in vacuo* to give the desired product as a colourless oil (0.27 g, 64%)

ν_{max} (neat)/cm⁻¹: 2981, 2955, 1725, 1650 and 1437; δ_{H} (CDCl₃, 400MHz) 1.20 (3H, t, *J* 7.2 Hz, CO₂CH₃CH₂), 1.65 (1H, dd, *J* 5.0 & 7.0 Hz, CH=CHCHCHH), 1.75 (1H, dd, *J* 5.0 & 7.0 Hz, CH=CHCHCHH), 2.57-2.62 (1H, m, CH=CHCHCH₂), 3.70 (6H, s, OCH₃), 4.10 (2H, q, *J* 7.2 Hz, CO₂CH₃CH₂), 5.97-6.01 (1H, m, CH=CHCHCH₂) and 6.37 (1H, dd, *J* 10.0 & 15.0 Hz, CH=CHCHCH₂); δ_{C} (CDCl₃, 100 MHz) 14.15 (C12), 21.41 (C3), 29.70 (C1), 36.47 (C2), 52.92 (2 × OCH₃), 60.35 (C11), 124.38 (C7), 143.03 (C6), 165.55 (C8), 167.16 (C4) and 169.07 (C5); *m/z*: (EI) 256 (M⁺, 5%), 211 (26), 143 (21), 120 (73), 112 (100) and 84 (45); HRMS Found (256.0947 C₁₂H₁₆O₆ requires 256.0946).

Preparation of (*E,Z*)-2-(*R*),5-(*S*)-1-(4-bromobut-3-enyl)-5-(2-ethoxycarbonylvinyl)-2-phenylpyrrolidine-3,3-dicarboxylic acid dimethyl ester (294)

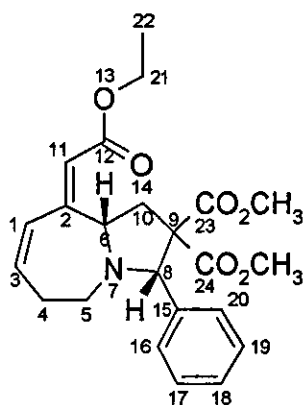


To a stirred solution of 2-vinylcyclopropane-1,1-dicarboxylic acid dimethyl ester (**249**) (0.20 g, 0.78 mmol) in THF (5 ml) was added 4-(bromobut-3-enyl)-[1-phenylmethylidene]-amine (**286**) (0.19 g, 0.78 mmol) and ZnBr_2 (0.35 g, 1.56 mmol) at room temperature. This was left to stir for 10 minutes under a nitrogen atmosphere before a catalytic amount of $\text{Pd}(\text{PPh}_3)_4$ (0.09 g, 0.08 mmol) was added. The reaction mixture was allowed to stir at room temperature for 24 h. The solvent was removed *in vacuo* and the residue dissolved in EtOAc. The palladium catalyst was filtered under suction through a plug of silica, and the organic phase collected and washed several times with H_2O (3×10 ml). The organic phase was dried over MgSO_4 and concentrated *in vacuo* to give the crude oily product, which was further purified by flash chromatography on silica gel (petrol:Et₂O, 1:1) to give the pyrrolidine as a colourless oil (0.24 g, 62%).

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$: 2950, 1731, 1656, 1434 and 1265; δ_{H} (CDCl_3 , 400 MHz) 1.25 (3H, t, J 7.2 Hz, CH_3CH_2), 1.97-2.14 (2H, m, $\text{CH}=\text{CHCH}_2\text{CH}_2$), 2.24 (1H, dd, J 7.6 & 13.2 Hz, $\text{CH}=\text{CHCHCHH}$), 2.50-2.57 (1H, m, $\text{CH}=\text{CHCH}_2\text{CHH}$), 2.63-2.69 (1H, m, $\text{CH}=\text{CHCH}_2\text{CHH}$), 2.63-2.69 (1H, m, $\text{CH}=\text{CHCHCHH}$), 3.05 (3H, s, OCH_3), 3.29-3.35 (1H, m, $\text{CH}=\text{CHCHCH}_2$), 3.72 (3H, s, OCH_3), 4.16 (2H, q, J 7.2 Hz, CH_3CH_2), 4.72 (1H, s, NCHAr), 5.79-5.86 (1H, m, $\text{CH}=\text{CHCH}_2\text{CH}_2$), 5.97-5.99 (1H, m, $\text{CH}=\text{CHCH}_2\text{CH}_2$),

6.03 (1H, d, J 0.8 Hz, $\text{CH}=\text{CHCHCH}_2$), 6.89 (1H, dd, J 0.8 & 15.6 Hz, $\text{CH}=\text{CHCHCH}_2$), 7.14-7.24 (3H, m, Ar- H) and 7.31-7.35 (2H, m, Ar- H); δ_{C} (CDCl_3 , 100 MHz) 14.29 (C17), 27.99 (C7), 38.53 (C4), 50.46 (C6), 52.09 (OCH_3), 52.29 (OCH_3), 60.22 (C16), 63.22 (C2), 64.66 (C3), 71.59 (C5), 108.66 (C9), 122.91 (C12), 127.85 (C20 & C21 & C22), 128.50 (C19 & C23), 132.39 (C8), 140.18 (C18), 148.87 (C11), 166.19 (C13), 168.63 (C25) and 171.74 (C26); m/z (FAB) 496 (M^+ , Br^{81} , 30%), 494 (M^+ , Br^{79} , 30%), 374 (100), 225 (25), 176 (31), 168 (45), 141 (37), 108 (30), 90 (22) and 55 (33); HRMS Found (494.1175 $\text{C}_{23}\text{H}_{28}\text{O}_6\text{NBr}^{79}$ requires 494.1178).

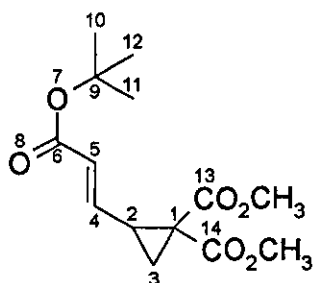
Preparation of (Z)-6-(S),8-(R)-2-ethoxycarbonylmethylene-8-phenyl-5,6,9,9a-tetrahydro-1H-pyrrolo[1,2-a]azepine-9,9-dicarboxylic acid dimethyl ester (295)



To a flame dried round bottom flask was added 1-(4-bromo-but-3-enyl)-5-(2-ethoxycarbonyl-vinyl)-2-phenyl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (**294**) (0.12 g, 0.24 mmol), $\text{Pd}(\text{OAc})_2$ (5 mg, 0.02 mmol), PPh_3 (0.03 g, 0.10 mmol) and $i\text{PrNEt}_2$ (0.06 g, 0.08 ml, 0.48 mmol) in anhydrous DMF (3ml). This mixture was heated at 100°C for 24 h, after which it was washed with H_2O (15 ml), and extracted into DCM (3×10 ml). The organics were dried over MgSO_4 , and reduced *in vacuo* to give a dark brown oil, which was purified *via* flash chromatography (petrol: Et_2O , 1:1) to give the desired product as a colourless oil (0.07 g, 67%).

$\nu_{\max}(\text{neat})/\text{cm}^{-1}$: 2935, 1736, 1110, 1072 and 712; $\delta_{\text{H}}(\text{CDCl}_3, 400 \text{ MHz})$ 1.20 (3H, t, J 7.2 Hz, CH_3CH_2), 1.98-2.04 (1H, m, $\text{CH}=\text{CHCHHCH}_2$), 2.18-2.23 (1H, m, $\text{CH}=\text{CHCHHCH}_2$), 2.51-2.59 (1H, m, $\text{CH}=\text{CHCH}_2\text{CHH}$), 2.51-2.59 (1H, m, $\text{CH}=\text{CCHCHH}$), 2.64-2.69 (1H, m, $\text{CH}=\text{CHCH}_2\text{CHH}$), 2.78 (1H, dd, J 6.0 & 12.8 Hz, $\text{CH}=\text{CCHCHH}$), 2.92 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 4.07 (2H, q, J 7.2 Hz, CH_3CH_2), 4.37-4.41 (1H, m, $\text{CH}=\text{CCHCH}_2$), 4.64 (1H, s, CHNCHAr), 5.68 (1H, s, $\text{CH}=\text{CCHCH}_2$), 5.77-5.81 ($\text{CH}=\text{CCH}=\text{CHCH}_2$), 6.03-6.07 (1H, m, $\text{CH}=\text{CCH}=\text{CHCH}_2$), 7.14-7.21 (2H, m, Ar- H), 7.32-7.39 (2H, m, Ar- H) and 7.55-7.57 (1H, m, Ar- H); $\delta_{\text{C}}(\text{CDCl}_3, 100 \text{ MHz})$ 14.29 (C22), 33.32 (C5), 38.81 (C10), 47.36 (C4), 51.95 (OCH_3), 52.87 (OCH_3), 59.82 (C21), 63.83 (C9), 66.61 (C6), 72.84 (C8), 118.85 (C11), 127.83 (C1), 128.30 (C16 & C20), 128.42 (C17 & C19), 128.99 (C18), 136.30 (C3), 139.59 (C15), 158.90 (C2), 165.98 (C12), 169.66 (C23) and 172.07 (C24); m/z : (EI) 414 (M^+ , 98%), 384 (100), 292 (18), 248 (22), 233 (28), 115 (39), 91 (62) and 77 (70); HRMS Found 414.1904 $\text{C}_{23}\text{H}_{28}\text{NO}_6$ requires 414.1911).

Preparation of (*E*)-2-(2-*tert*-butoxycarbonylvinyl)-cyclopropane-1,1-dicarboxylic acid dimethyl ester (300)

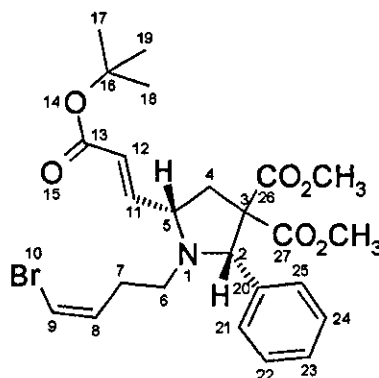


A 100 ml round bottom flask was charged with (*tert*-butoxycarbonylmethyl)-triphenylphosphonium bromide (0.89 g, 1.94 mmol) in THF (8 ml) under a nitrogen atmosphere. Butyllithium (0.78 ml, 2.5 M, 1.94 mmol) was added dropwise at 0°C and the mixture stirred for 3 min. The aldehyde (0.30 g, 1.61 mmol) was added immediately to the reaction, and the mixture was stirred for a further 3 min, upon which it was quenched with H_2O (10 ml), and extracted into DCM ($3 \times 15 \text{ ml}$). The organic layer was

dried over MgSO_4 and reduced *in vacuo* to give the crude product as an orange oil which was further purified *via* flash chromatography on silica gel (petrol:EtOAc, 4:1) to give the product as a colourless oil (0.28 g, 61%).

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$: 3418, 1731, 1715, 1651, 1437, 1142 and 721; δ_{H} (CDCl_3 , 400 MHz) 1.39 (9H, s, $\text{OC}(\text{CH}_3)_3$), 1.63 (1H, dd, J 4.0 & 7.2 Hz, $\text{CH}=\text{CHCHCHH}$), 1.73 (1H, dd, J 2.0 & 7.2 Hz, $\text{CH}=\text{CHCHCHH}$), 2.56-2.59 (1H, m, $\text{CH}=\text{CHCHCH}_2$), 3.68 (3H, s, OCH_3), 3.69 (3H, s, OCH_3), 5.91 (1H, dd, J 0.4 & 15.6 Hz, $\text{CH}=\text{CHCHCH}_2$) and 6.27 (1H, dd, J 6.0 & 15.6 Hz, $\text{CH}=\text{CHCHCH}_2$); δ_{C} (CDCl_3 , 100 MHz) 21.36 (C3), 27.83 (C10 & C11 & C12), 29.70 (C2), 36.36 (C9), 52.78 (OCH_3), 52.92 (C12), 80.42 (C1), 126.17 (C4), 141.74 (C5), 165.27 (C6), 169.21 (C13) and 169.33 (C14); m/z : (EI) 302 (M^+ , 98%), 246 (79), 211 (33), 145 (80), 120 (54), 113 (61), 98 (40), 65 (37), 57 (100) and 41 (72); HRMS Found (302.1598 $\text{C}_{14}\text{H}_{20}\text{O}_6$ requires 302.1598)

Preparation of (*E,Z*)-2-(*R*),5-(*S*)-1-(4-bromobut-3-enyl)-5-(2-*tert*-butoxycarbonylvinyl)-2-phenylpyrrolidine-3,3-dicarboxylic acid dimethyl ester (301)

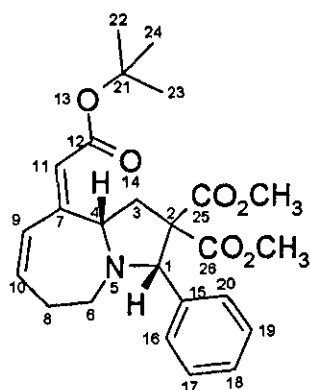


To a stirred solution of 2-(2-*tert*-butoxycarbonyl-vinyl)-cyclopropane-1,1-dicarboxylic acid dimethyl ester (**300**) (0.71 g, 2.49 mmol) in THF (15 ml) was added 4-(bromobut-3-enyl)-[1-phenylmethylidene]-amine (**286**) (0.59 g, 2.49 mmol) and ZnBr_2 (1.12 g, 4.98 mmol) at room temperature. This was left to stir for 10 min under a nitrogen atmosphere before a catalytic amount of $\text{Pd}(\text{PPh}_3)_4$ (0.29 g, 0.25 mmol) was added. The reaction

mixture was allowed to stir at room temperature for 24 h. The solvent was removed *in vacuo* and the residue dissolved in EtOAc. The palladium catalyst was filtered under suction through a plug of silica, and the organic phase collected and washed several times with H₂O (3 × 10 ml). The organic phase was dried over MgSO₄ and concentrated *in vacuo* to give the crude oily product, which was further purified by flash chromatography on silica gel (petrol:EtOAc, 4:1) to give the pyrrolidine as a colourless oil (0.97 g, 74%).

$\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$: 3465, 1735, 1711, 1257, 1151, 721 and 667; δ_{H} (CDCl₃, 400 MHz) 1.51 (9H, s, OC(CH₃)₃), 2.09-2.21 (2H, m, CH=CHCH₂CH₂), 2.29 (1H, dd, *J* 7.6 & 13.6 Hz, CH=CHCHCHH), 2.58-2.65 (1H, m, CH=CHCH₂CHH), 2.69-2.76 (1H, m, CH=CHCHCHH), 2.69-2.76 (1H, m, CH=CHCH₂CHH), 3.11 (3H, s, OCH₃), 3.76 (3H, s, OCH₃), 3.33-3.39 (1H, m, CH=CHCHCH₂), 4.78 (1H, s, HCNCHAr), 5.89-5.92 (1H, m, CH=CHCH₂CH₂), 5.99 (1H, m, CH=CHCHCH₂), 6.04-6.06 (1H, m, CH=CHCH₂CH₂), 6.84 (1H, dd, *J* 7.6 & 15.7 Hz, CH=CHCHCH₂), 7.22-7.30 (3H, m, Ar-*H*) and 7.38-7.40 (2H, m, Ar-*H*); δ_{C} (CDCl₃, 100 MHz) 28.04 (C6), 28.15 (C17 & C18 & C19), 38.57 (C4), 50.45 (C7), 52.07 (OCH₃), 53.14 (OCH₃), 63.23 (C5), 64.73 (C3), 71.60 (C2), 80.60 (C16), 108.70 (C8), 124.74 (C12), 127.79 (C23), 127.82 (C22 & C24), 128.51 (C21 & C25), 132.46 (C9), 140.27 (C20), 147.53 (C11), 165.30 (C13), 168.66 (C26) and 171.80 (C27); *m/z*: (EI) 524 (M⁺, Br⁸¹, 97%), 522 (M⁺, Br⁷⁹, 97%), 402 (92), 346 (45), 121 (25), 91 (22), 59 (40) and 57 (100); HRMS Found (522.1488 C₂₅H₃₂O₆NBr⁷⁹ requires 522.1486).

Preparation of (Z)-1-(R),5-(S)-7-*tert*-butoxycarbonylmethylene-1-phenyl-5,6,9,9a-tetrahydro-1*H*-pyrrolo[1,2*a*]azepine-2,2-dicarboxylic acid dimethyl ester (302)

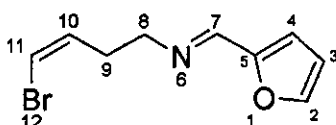


To a flame dried round bottom flask was added 1-(4-bromo-but-3-enyl)-5-(2-*tert*-butoxycarbonyl-vinyl)-2-phenyl-pyrrolidine-3, 3-dicarboxylic acid dimethyl ester (**301**) (0.17 g, 0.33 mmol), Pd(OAc)₂ (8 mg, 0.03 mmol), PPh₃ (0.04 g, 0.13 mmol) and ⁱPrNEt₂ (0.09 g, 0.12 ml, 0.67 mmol) in anhydrous DMF (2ml). This mixture was heated at 100°C for 24 h, after which it was washed with H₂O (15 ml), and extracted into DCM (3 × 10 ml). The organics were dried over MgSO₄, and reduced *in vacuo* to give a dark brown oil, which was purified *via* flash chromatography on alumina (petrol:EtOAc, 10:1), to give the desired product as a colourless oil (0.06 g, 42%).

ν_{max} (neat)/cm⁻¹: 2924, 1736, 1631, 1365, 1269, 1143 and 702; δ_{H} (CDCl₃, 400 MHz) 1.47 (9H, s, OC(CH₃)₃), 2.08-2.09 (1H, m, CH=CHCHHCH₂), 2.24-2.57 (1H, m, CH=CHCHHCH₂), 2.60-2.66 (1H, m, CH=CHCH₂CHH), 2.60-2.66 (1H, m, CH=CCHCHH), 2.67-2.72 (1H, m, CH=CHCH₂CHH), 2.81 (1H, dd, *J* 6.8 & 18.8 Hz, CH=CCHCHH), 2.99 (3H, s, OCH₃), 3.79 (3H, s, OCH₃), 4.42-4.46 (1H, m, CH=CCHCH₂), 4.71 (1H, s, CHNCHAr), 5.67 (1H, d, *J* 0.8 Hz, CH=CCHCH₂), 5.76-5.83 (1H, m, CH=CHCH₂CH₂), 6.06-6.09 (1H, m, CH=CHCH₂CH₂), 7.23-7.30 (3H, m, Ar-*H*) and 7.45-7.47 (2H, m, Ar-*H*); δ_{C} (CDCl₃, 100 MHz) 28.14 (C22 & C23 & C24), 33.22 (C6), 38.99 (C3), 47.54 (C8), 51.93 (OCH₃), 52.73 (OCH₃), 63.23 (C3), 66.33

(C4), 72.87 (C2), 79.92 (C21), 120.97 (C11), 127.77 (C17 & C18 & C19), 127.80 (C16 & C20), 129.75 (C9), 135.51 (C10), 156.39 (C15), 156.86 (C7), 165.70 (C12), 169.63 (C25) and 172.05 (C26); m/z : (EI) 442 (M^+ , 98%), 384 (83), 248 (22), 115 (31), 91 (26), 77 (17) and 57 (100); HRMS Found (442.2223 $C_{25}H_{32}O_6N$ requires 442.2224).

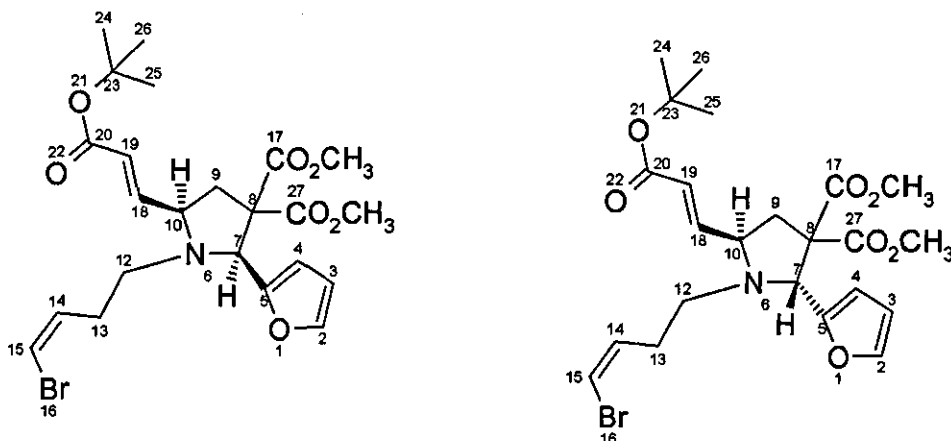
Preparation of (Z,E)-(4-bromobut-3-enyl)-furan-2-ylmethyleamine (308)



To a solution of diethyl ether (10 ml) under a nitrogen atmosphere was added molecular sieves (3.00 g, 4 Å), 4-bromobut-3-enylamine (0.28 g, 1.85 mmol) and 2-furaldehyde (0.14 g, 0.12 ml, 1.85 mmol). The reaction mixture was left to stir overnight, after which it was filtered under suction and washed several times with Et_2O (3 × 10 ml). The filtrate was concentrated *in vacuo* to give the imine as an orange oil (0.19 g, 44%).

ν_{max} (neat)/ cm^{-1} : 2929, 2856, 1718, 1437, 1165 and 749; δ_H ($CDCl_3$, 400 MHz) 2.49-2.55 (2H, m, $CH=CHCH_2CH_2$), 3.55-3.59 (2H, m, $CH=CHCH_2CH_2$), 6.07-6.10 (1H, m, $CH=CHCH_2CH_2$), 6.12-6.17 (1H, m, $CH=CHCH_2CH_2$), 6.38-6.40 (1H, m, $N=CHC=CHCH=CH$), 6.67 (1H, d, J 3.6 Hz, $N=CHC=CHCH=CH$), 7.43 (1H, s, $N=CHC=CHCH=CH$), and 8.01 (1H, d, J 1.2 Hz, $N=CH$); δ_C ($CDCl_3$, 100 MHz) 31.23 (C8), 65.74 (C9), 109.17 (C10), 111.61 (C3), 114.27 (C2), 131.58 (C11), 144.74 (C4), 150.19 (C7), and 152.85 (C5); m/z : (FAB) 230 (M^+ , Br^{81} , 22%), 228 (M^+ , Br^{79} , 22%), 154 (21), 148 (33), 136 (31), 120 (24), 108 (44), 96 (100), 91 (26) and 77 (23); HRMS Found (228.0028 $C_9H_{10}NOBr^{79}$ requires 228.0024).

Preparation of (*E,Z*)-7-(*R*),10-(*R*)-1-(4-bromobut-3-enyl)-5-(2-*tert*-butoxycarbonylvinyl)-2-furan-2-yl-pyrrolidine-3,3-dicarboxylic acid dimethyl ester (310) (*cis:trans*; 2:1)



To a stirred solution of 2-(2-*tert*-butoxycarbonylvinyl)-cyclopropane-1, 1-dicarboxylic acid dimethyl ester (**300**) (0.45 g, 1.59 mmol) in THF (10 ml) was added (4-bromo-but-3-enyl)-furan-2-ylmethylene-amine (**308**) (0.36 g, 1.59 mmol) and ZnBr₂ (0.72 g, 3.18 mmol) at room temperature. This was left to stir for 10 min under a nitrogen atmosphere before a catalytic amount of Pd(PPh₃)₄ (0.18 g, 0.16 mmol) was added. The reaction mixture was allowed to stir at room temperature for 24 h. The solvent was removed *in vacuo* and the residue dissolved in EtOAc. The palladium catalyst was filtered under suction through a plug of silica, and the organic phase collected and washed several times with H₂O (3 × 10 ml). The organic phase was dried over MgSO₄ and concentrated *in vacuo* to give the crude oily product, which was further purified by flash chromatography on silica gel (petrol:EtOAc, 4:1) to give the pyrrolidine as a colourless oil (0.42 g, 52%).

ν_{\max} (neat)/cm⁻¹: 2359, 2088, 1734, 1647, 1436, 1256, 1207, 1148, 1072 and 668; δ_{H} (CDCl₃, 400 MHz) 1.39 (9H, s, OC(CH₃)₃), 1.43 (9H, s, OC(CH₃)₃), 1.64 (1H, dd, *J* 5.2 & 7.6 Hz, CH=CHCHCHH), 1.73 (1H, dd, *J* 5.2 & 7.6 Hz, CH=CHCHCHH), 2.08-2.17 (2H, m, CH=CHCH₂CH₂), 2.21-2.28 (2H, m, CH=CHCH₂CH₂), 2.35-2.44 (1H, m, CH=CHCHCHH), 2.53-2.62 (2H, m, CH=CHCH₂CH₂), 2.53-2.62 (1H, m,

CH=CHCHCH[']), 2.65-2.71 (2H, m, CH=CHCH₂'CH₂), 3.18-3.25 (1H, m, CH=CHCH[']CH₂), 3.38 (3H, s, OCH₃[']), 3.39 (3H, s, OCH₃), 3.69 (3H, s, OCH₃), 3.70 (3H, s, OCH₃[']), 3.71-3.73 (1H, m, CH=CHCHCH₂), 4.76 (1H, s, NCH[']Ar), 5.06 (1H, s, NCH), 5.78 (1H, dd, *J* 0.8 & 15.6 Hz, CH=CHCHCH₂), 5.89 (1H, dd, *J* 1.4 & 15.6 Hz, CH[']=CHCHCH₂), 5.90-5.98 (1H, m, CH=CHCH₂CH₂), 6.01-6.11 (1H, m, CH=CH[']CH₂CH₂), 6.01-6.11 (1H, m, CH=CHCH₂CH₂), 6.21-6.25 (1H, m, CH=CH[']CH₂CH₂), 6.21-6.25 (2H, m, Ar-*H*), 6.21-6.25 (2H, m, Ar-*H*[']), 6.55 (1H, dd, *J* 8.0 & 15.6 Hz, CH=CHCHCH₂), 6.70 (1H, dd, *J* 8.0 & 15.6 Hz, CH=CHCHCH₂), 7.26-7.28 (1H, m, Ar-*H*[']) and 7.30-7.32 (1H, m, Ar-*H*); δ_c (CDCl₃, 100 MHz) 21.46 (C9), 28.14 (C24['] & C25['] & C26[']), 28.11 (C24 & C25 & C26), 28.77 (C9[']), 36.41 (C11), 38.23 (C11[']), 46.19 (C12), 50.61 (C13[']), 52.73 (OCH₃), 52.89 (OCH₃[']), 53.02 (OCH₃), 53.19 (OCH₃[']), 62.41 (C10), 62.53 (C10[']), 63.01 (C8), 63.04 (C8[']), 63.14 (C7[']), 65.29 (C7), 80.47 (C23), 80.54 (C23[']), 108.72 (C14), 110.41 (C14[']), 124.84 (C19), 126.25 (C19[']), 132.40 (C15[']), 132.64 (C15), 141.77 (C4), 141.81 (C4[']), 142.23 (C3), 142.35 (C3[']), 142.80 (C2), 142.81 (C2[']), 147.34 (C18[']), 148.35 (C18), 151.22 (C5), 153.73 (C5[']), 165.47 (C20), 165.71 (C20[']), 167.27 (C17), 168.29 (C17[']), 168.42 (C27) and 169.44 (C27[']); *m/z*: (EI) 514 (M⁺, Br⁸¹, 99%), 512 (M⁺, Br⁷⁹, 99%), 434 (25), 392 (21), 162 (33), 150 (100), 96 (41) and 72 (51); HRMS Found (512.1285 C₂₃H₃₀O₇NBr⁷⁹ requires 512.1278).

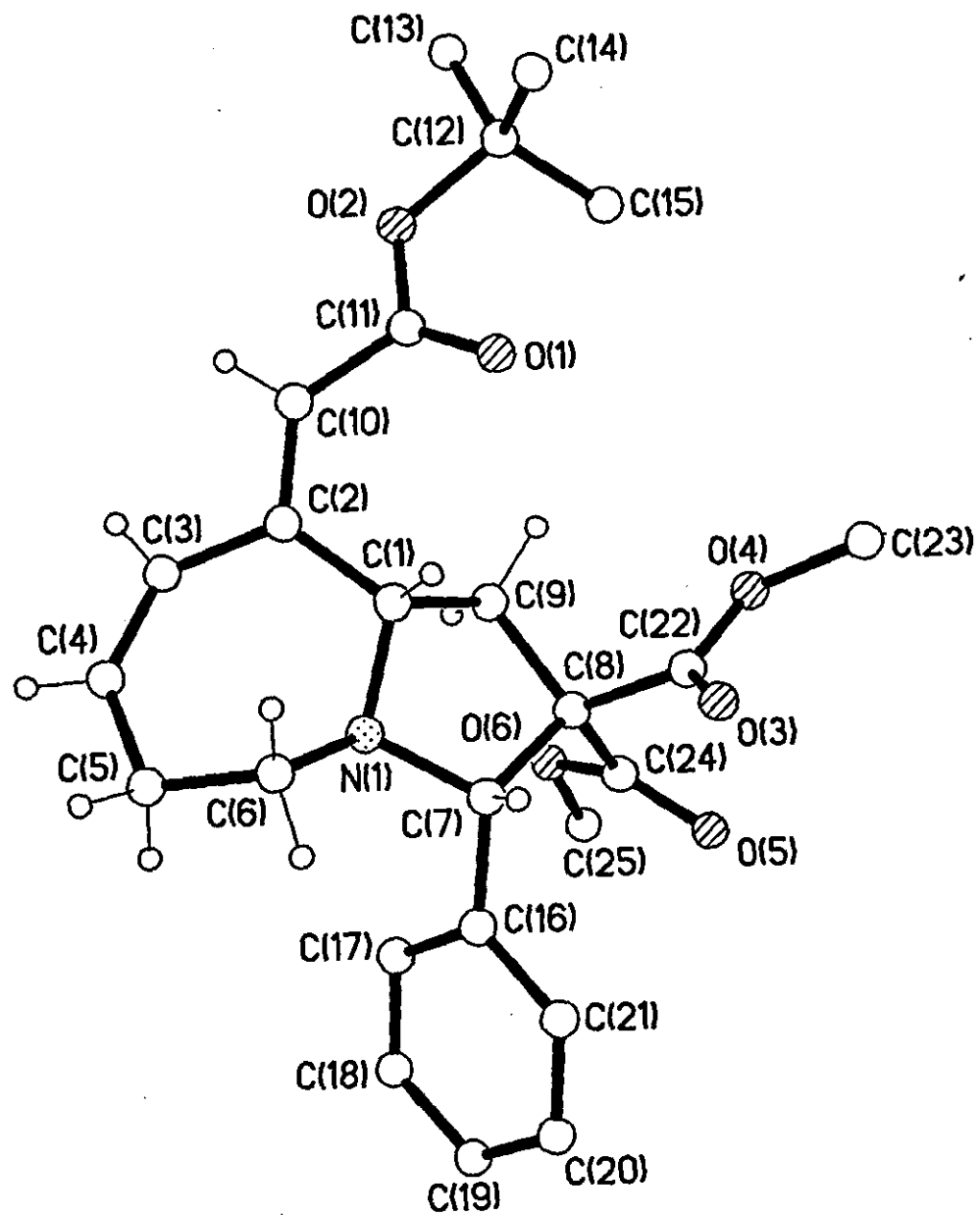
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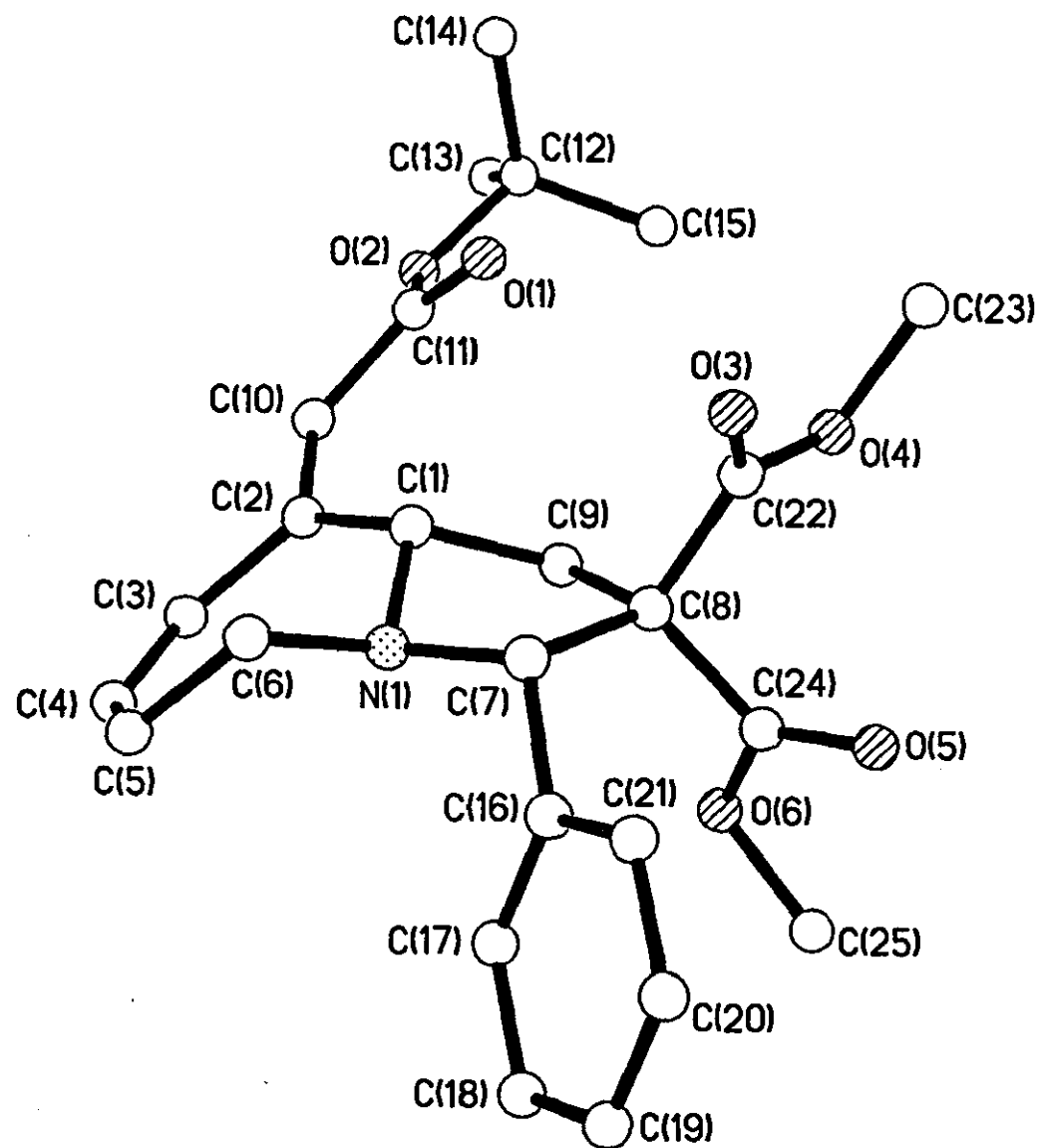


Table 1. Crystal data and structure refinement for gp7.

Identification code	gp7	
Chemical formula	$C_{25}H_{31}NO_6$	
Formula weight	441.51	
Temperature	150(2) K	
Radiation, wavelength	MoK α , 0.71073 Å	
Crystal system, space group	monoclinic, P2 ₁	
Unit cell parameters	$a = 9.3057(8)$ Å	$\alpha = 90^\circ$
	$b = 13.1079(11)$ Å	$\beta = 95.186(2)^\circ$
	$c = 9.5560(8)$ Å	$\gamma = 90^\circ$
Cell volume	1160.85(17) Å ³	
Z	2	
Calculated density	1.263 g/cm ³	
Absorption coefficient μ	0.090 mm ⁻¹	
F(000)	472	
Crystal colour and size	pale yellow, 0.31 × 0.15 × 0.14 mm ³	
Reflections for cell refinement	3096 (θ range 2.65 to 26.34°)	
Data collection method	Bruker APEX 2 CCD diffractometer	
	ω rotation with narrow frames	
θ range for data collection	2.14 to 26.41°	
Index ranges	$h -11$ to 11, $k -16$ to 16, $l -11$ to 11	
Completeness to $\theta = 26.00^\circ$	100.0 %	
Intensity decay	0%	
Reflections collected	10450	
Independent reflections	2488 ($R_{int} = 0.0471$)	
Reflections with $F^2 > 2\sigma$	2094	
Absorption correction	semi-empirical from equivalents	
Min. and max. transmission	0.973 and 0.988	
Structure solution	direct methods	
Refinement method	Full-matrix least-squares on F^2	
Weighting parameters a, b	0.0389, 0.1009	
Data / restraints / parameters	2488 / 1 / 294	
Final R indices [$F^2 > 2\sigma$]	$R1 = 0.0343$, $wR2 = 0.0715$	
R indices (all data)	$R1 = 0.0502$, $wR2 = 0.0796$	
Goodness-of-fit on F^2	1.037	
Absolute structure parameter	10(10), Friedels merged; absolute structure unknown.	
Largest and mean shift/su	0.000 and 0.000	
Largest diff. peak and hole	0.173 and -0.179 e Å ⁻³	

Table 2. Atomic coordinates and equivalent isotropic displacement parameters (\AA^2) for gp7. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U_{eq}
N(1)	0.2733(2)	0.73848(15)	-0.0190(2)	0.0205(4)
C(1)	0.3343(3)	0.69201(19)	0.1119(3)	0.0207(5)
C(2)	0.4970(3)	0.70097(19)	0.1377(3)	0.0223(5)
C(3)	0.5862(3)	0.7501(2)	0.0372(3)	0.0274(6)
C(4)	0.5550(3)	0.8205(2)	-0.0627(3)	0.0316(6)
C(5)	0.4180(3)	0.8738(2)	-0.1087(3)	0.0310(6)
C(6)	0.2922(3)	0.84917(19)	-0.0255(3)	0.0248(6)
C(7)	0.1216(2)	0.70588(19)	-0.0371(3)	0.0206(5)
C(8)	0.1250(3)	0.59516(18)	0.0283(2)	0.0202(5)
C(9)	0.2833(3)	0.58198(19)	0.0885(3)	0.0233(5)
C(10)	0.5694(3)	0.6603(2)	0.2534(3)	0.0245(5)
C(11)	0.5062(3)	0.6100(2)	0.3715(3)	0.0272(6)
O(1)	0.3833(2)	0.61989(18)	0.4025(2)	0.0411(5)
O(2)	0.60640(18)	0.55093(15)	0.44140(19)	0.0283(4)
C(12)	0.5695(3)	0.4829(2)	0.5567(3)	0.0326(7)
C(13)	0.7114(4)	0.4289(3)	0.5942(4)	0.0560(10)
C(14)	0.5259(4)	0.5446(3)	0.6802(3)	0.0448(8)
C(15)	0.4542(4)	0.4083(3)	0.5017(4)	0.0513(9)
C(16)	0.0588(3)	0.71297(18)	-0.1882(3)	0.0210(5)
C(17)	0.1432(3)	0.69730(19)	-0.2993(3)	0.0246(6)
C(18)	0.0813(3)	0.7003(2)	-0.4370(3)	0.0295(6)
C(19)	-0.0641(3)	0.7178(2)	-0.4653(3)	0.0331(7)
C(20)	-0.1484(3)	0.7344(2)	-0.3557(3)	0.0350(7)
C(21)	-0.0875(3)	0.7317(2)	-0.2182(3)	0.0275(6)
C(22)	0.0237(3)	0.58842(19)	0.1465(3)	0.0222(5)
O(3)	-0.0544(2)	0.65473(14)	0.18068(19)	0.0326(5)
O(4)	0.03545(19)	0.49691(14)	0.20727(19)	0.0287(4)
C(23)	-0.0539(3)	0.4800(2)	0.3213(3)	0.0315(6)
C(24)	0.0706(3)	0.51604(18)	-0.0806(3)	0.0224(5)
O(5)	-0.0548(2)	0.49393(16)	-0.1037(2)	0.0356(5)
O(6)	0.17617(19)	0.47742(14)	-0.14906(19)	0.0289(4)
C(25)	0.1299(4)	0.4078(2)	-0.2623(3)	0.0404(8)

Table 3. Bond lengths [Å] and angles [°] for gp7.

N(1)–C(1)	1.459(3)	N(1)–C(6)	1.463(3)
N(1)–C(7)	1.470(3)	C(1)–C(2)	1.517(3)
C(1)–C(9)	1.528(4)	C(2)–C(10)	1.352(4)
C(2)–C(3)	1.473(4)	C(3)–C(4)	1.341(4)
C(4)–C(5)	1.485(4)	C(5)–C(6)	1.509(4)
C(7)–C(16)	1.511(3)	C(7)–C(8)	1.579(3)
C(8)–C(24)	1.523(3)	C(8)–C(22)	1.538(3)
C(8)–C(9)	1.542(3)	C(10)–C(11)	1.474(4)
C(11)–O(1)	1.214(3)	C(11)–O(2)	1.343(3)
O(2)–C(12)	1.482(3)	C(12)–C(15)	1.511(4)
C(12)–C(13)	1.512(4)	C(12)–C(14)	1.516(4)
C(16)–C(21)	1.387(3)	C(16)–C(17)	1.392(3)
C(17)–C(18)	1.389(4)	C(18)–C(19)	1.374(4)
C(19)–C(20)	1.381(4)	C(20)–C(21)	1.383(4)
C(22)–O(3)	1.197(3)	C(22)–O(4)	1.333(3)
O(4)–C(23)	1.446(3)	C(24)–O(5)	1.203(3)
C(24)–O(6)	1.329(3)	O(6)–C(25)	1.451(3)
C(1)–N(1)–C(6)	114.3(2)	C(1)–N(1)–C(7)	105.92(18)
C(6)–N(1)–C(7)	113.61(19)	N(1)–C(1)–C(2)	114.3(2)
N(1)–C(1)–C(9)	100.20(19)	C(2)–C(1)–C(9)	112.9(2)
C(10)–C(2)–C(1)	115.9(2)	C(10)–C(2)–C(1)	121.3(2)
C(3)–C(2)–C(1)	122.8(2)	C(4)–C(3)–C(2)	131.8(3)
C(3)–C(4)–C(5)	131.3(3)	C(4)–C(5)–C(6)	115.5(2)
N(1)–C(6)–C(5)	109.6(2)	N(1)–C(7)–C(16)	112.28(19)
N(1)–C(7)–C(8)	103.64(18)	C(16)–C(7)–C(8)	115.3(2)
C(24)–C(8)–C(22)	105.95(19)	C(24)–C(8)–C(9)	115.2(2)
C(22)–C(8)–C(9)	110.4(2)	C(24)–C(8)–C(7)	111.24(19)
C(22)–C(8)–C(7)	110.59(19)	C(9)–C(8)–C(7)	103.58(19)
C(1)–C(9)–C(8)	102.84(19)	C(2)–C(10)–C(11)	126.8(2)
O(1)–C(11)–O(2)	124.5(2)	O(1)–C(11)–C(10)	126.1(2)
O(2)–C(11)–C(10)	109.3(2)	C(11)–O(2)–C(12)	121.3(2)
O(2)–C(12)–C(15)	109.7(2)	O(2)–C(12)–C(13)	101.6(2)
C(15)–C(12)–C(13)	110.9(3)	O(2)–C(12)–C(14)	110.7(2)
C(15)–C(12)–C(14)	112.6(2)	C(13)–C(12)–C(14)	110.7(3)
C(21)–C(16)–C(17)	118.6(2)	C(21)–C(16)–C(7)	119.7(2)
C(17)–C(16)–C(7)	121.6(2)	C(18)–C(17)–C(16)	120.3(2)
C(19)–C(18)–C(17)	120.5(3)	C(18)–C(19)–C(20)	119.6(3)
C(19)–C(20)–C(21)	120.3(3)	C(20)–C(21)–C(16)	120.7(2)
O(3)–C(22)–O(4)	124.2(2)	O(3)–C(22)–C(8)	125.9(2)
O(4)–C(22)–C(8)	109.9(2)	C(22)–O(4)–C(23)	115.8(2)
O(5)–C(24)–O(6)	124.4(2)	O(5)–C(24)–C(8)	123.1(2)
O(6)–C(24)–C(8)	112.4(2)	C(24)–O(6)–C(25)	115.1(2)

Table 4. Hydrogen coordinates and isotropic displacement parameters (\AA^2) for gp7.

	x	y	z	U
H(1)	0.2880	0.7222	0.1928	0.025
H(3)	0.6838	0.7278	0.0446	0.033
H(4)	0.6344	0.8396	-0.1129	0.038
H(5A)	0.3908	0.8566	-0.2085	0.037
H(5B)	0.4355	0.9482	-0.1034	0.037
H(6A)	0.3100	0.8771	0.0708	0.030
H(6B)	0.2033	0.8810	-0.0707	0.030
H(7)	0.0643	0.7511	0.0213	0.025
H(9A)	0.2899	0.5434	0.1779	0.028
H(9B)	0.3405	0.5464	0.0209	0.028
H(10)	0.6717	0.6645	0.2593	0.029
H(13A)	0.7411	0.3935	0.5112	0.084
H(13B)	0.6999	0.3793	0.6691	0.084
H(13C)	0.7852	0.4791	0.6267	0.084
H(14A)	0.6032	0.5926	0.7106	0.067
H(14B)	0.5092	0.4986	0.7579	0.067
H(14C)	0.4372	0.5824	0.6519	0.067
H(15A)	0.3621	0.4442	0.4832	0.077
H(15B)	0.4443	0.3547	0.5718	0.077
H(15C)	0.4813	0.3774	0.4145	0.077
H(17)	0.2436	0.6845	-0.2808	0.030
H(18)	0.1398	0.6902	-0.5123	0.035
H(19)	-0.1063	0.7185	-0.5596	0.040
H(20)	-0.2486	0.7477	-0.3748	0.042
H(21)	-0.1464	0.7429	-0.1435	0.033
H(23A)	-0.0216	0.5245	0.4004	0.047
H(23B)	-0.0461	0.4086	0.3512	0.047
H(23C)	-0.1546	0.4956	0.2895	0.047
H(25A)	0.0713	0.3533	-0.2262	0.061
H(25B)	0.2148	0.3780	-0.3004	0.061
H(25C)	0.0725	0.4450	-0.3367	0.061

Table 5. Torsion angles [°] for gp7.

C(6)–N(1)–C(1)–C(2)	–64.2(3)	C(7)–N(1)–C(1)–C(2)	169.9(2)
C(6)–N(1)–C(1)–C(9)	174.78(19)	C(7)–N(1)–C(1)–C(9)	48.9(2)
N(1)–C(1)–C(2)–C(10)	–179.0(2)	C(9)–C(1)–C(2)–C(10)	–65.3(3)
N(1)–C(1)–C(2)–C(3)	–1.5(3)	C(9)–C(1)–C(2)–C(3)	112.2(3)
C(10)–C(2)–C(3)–C(4)	–158.3(3)	C(1)–C(2)–C(3)–C(4)	24.2(5)
C(2)–C(3)–C(4)–C(5)	–0.5(5)	C(3)–C(4)–C(5)–C(6)	3.2(5)
C(1)–N(1)–C(6)–C(5)	99.6(2)	C(7)–N(1)–C(6)–C(5)	–138.7(2)
C(4)–C(5)–C(6)–N(1)	–52.2(3)	C(1)–N(1)–C(7)–C(16)	–158.5(2)
C(6)–N(1)–C(7)–C(16)	75.2(3)	C(1)–N(1)–C(7)–C(8)	–33.4(2)
C(6)–N(1)–C(7)–C(8)	–159.73(19)	N(1)–C(7)–C(8)–C(24)	–119.7(2)
C(16)–C(7)–C(8)–C(24)	3.4(3)	N(1)–C(7)–C(8)–C(22)	122.8(2)
C(16)–C(7)–C(8)–C(22)	–114.1(2)	N(1)–C(7)–C(8)–C(9)	4.6(2)
C(16)–C(7)–C(8)–C(9)	127.7(2)	N(1)–C(1)–C(9)–C(8)	–44.0(2)
C(2)–C(1)–C(9)–C(8)	–166.1(2)	C(24)–C(8)–C(9)–C(1)	145.6(2)
C(22)–C(8)–C(9)–C(1)	–94.5(2)	C(7)–C(8)–C(9)–C(1)	23.9(2)
C(3)–C(2)–C(10)–C(11)	177.9(3)	C(1)–C(2)–C(10)–C(11)	–4.5(4)
C(2)–C(10)–C(11)–O(1)	–20.5(5)	C(2)–C(10)–C(11)–O(2)	159.7(3)
O(1)–C(11)–O(2)–C(12)	6.5(4)	C(10)–C(11)–O(2)–C(12)	–173.7(2)
C(11)–O(2)–C(12)–C(15)	59.1(3)	C(11)–O(2)–C(12)–C(13)	176.5(3)
C(11)–O(2)–C(12)–C(14)	–65.8(3)	N(1)–C(7)–C(16)–C(21)	–150.4(2)
C(8)–C(7)–C(16)–C(21)	91.3(3)	N(1)–C(7)–C(16)–C(17)	32.1(3)
C(8)–C(7)–C(16)–C(17)	–86.3(3)	C(21)–C(16)–C(17)–C(18)	–0.2(4)
C(7)–C(16)–C(17)–C(18)	177.4(2)	C(16)–C(17)–C(18)–C(19)	–0.6(4)
C(17)–C(18)–C(19)–C(20)	1.2(4)	C(18)–C(19)–C(20)–C(21)	–1.1(4)
C(19)–C(20)–C(21)–C(16)	0.3(4)	C(17)–C(16)–C(21)–C(20)	0.3(4)
C(7)–C(16)–C(21)–C(20)	–177.3(2)	C(24)–C(8)–C(22)–O(3)	–116.5(3)
C(9)–C(8)–C(22)–O(3)	118.2(3)	C(7)–C(8)–C(22)–O(3)	4.2(3)
C(24)–C(8)–C(22)–O(4)	63.8(2)	C(9)–C(8)–C(22)–O(4)	–61.6(3)
C(7)–C(8)–C(22)–O(4)	–175.6(2)	O(3)–C(22)–O(4)–C(23)	0.0(4)
C(8)–C(22)–O(4)–C(23)	179.8(2)	C(22)–C(8)–C(24)–O(5)	32.7(3)
C(9)–C(8)–C(24)–O(5)	155.0(2)	C(7)–C(8)–C(24)–O(5)	–87.5(3)
C(22)–C(8)–C(24)–O(6)	–149.3(2)	C(9)–C(8)–C(24)–O(6)	–27.0(3)
C(7)–C(8)–C(24)–O(6)	90.4(2)	O(5)–C(24)–O(6)–C(25)	2.8(4)
C(8)–C(24)–O(6)–C(25)	–175.1(2)		

Table 5. Torsion angles [°] for gp7.

C(6)–N(1)–C(1)–C(2)	–64.2(3)	C(7)–N(1)–C(1)–C(2)	169.9(2)
C(6)–N(1)–C(1)–C(9)	174.78(19)	C(7)–N(1)–C(1)–C(9)	48.9(2)
N(1)–C(1)–C(2)–C(10)	–179.0(2)	C(9)–C(1)–C(2)–C(10)	–65.3(3)
N(1)–C(1)–C(2)–C(3)	–1.5(3)	C(9)–C(1)–C(2)–C(3)	112.2(3)
C(10)–C(2)–C(3)–C(4)	–158.3(3)	C(1)–C(2)–C(3)–C(4)	24.2(5)
C(2)–C(3)–C(4)–C(5)	–0.5(5)	C(3)–C(4)–C(5)–C(6)	3.2(5)
C(1)–N(1)–C(6)–C(5)	99.6(2)	C(7)–N(1)–C(6)–C(5)	–138.7(2)
C(4)–C(5)–C(6)–N(1)	–52.2(3)	C(1)–N(1)–C(7)–C(16)	–158.5(2)
C(6)–N(1)–C(7)–C(16)	75.2(3)	C(1)–N(1)–C(7)–C(8)	–33.4(2)
C(6)–N(1)–C(7)–C(8)	–159.73(19)	N(1)–C(7)–C(8)–C(24)	–119.7(2)
C(16)–C(7)–C(8)–C(24)	3.4(3)	N(1)–C(7)–C(8)–C(22)	122.8(2)
C(16)–C(7)–C(8)–C(22)	–114.1(2)	N(1)–C(7)–C(8)–C(9)	4.6(2)
C(16)–C(7)–C(8)–C(9)	127.7(2)	N(1)–C(1)–C(9)–C(8)	–44.0(2)
C(2)–C(1)–C(9)–C(8)	–166.1(2)	C(24)–C(8)–C(9)–C(1)	145.6(2)
C(22)–C(8)–C(9)–C(1)	–94.5(2)	C(7)–C(8)–C(9)–C(1)	23.9(2)
C(3)–C(2)–C(10)–C(11)	177.9(3)	C(1)–C(2)–C(10)–C(11)	–4.5(4)
C(2)–C(10)–C(11)–O(1)	–20.5(5)	C(2)–C(10)–C(11)–O(2)	159.7(3)
O(1)–C(11)–O(2)–C(12)	6.5(4)	C(10)–C(11)–O(2)–C(12)	–173.7(2)
C(11)–O(2)–C(12)–C(15)	59.1(3)	C(11)–O(2)–C(12)–C(13)	176.5(3)
C(11)–O(2)–C(12)–C(14)	–65.8(3)	N(1)–C(7)–C(16)–C(21)	–150.4(2)
C(8)–C(7)–C(16)–C(21)	91.3(3)	N(1)–C(7)–C(16)–C(17)	32.1(3)
C(8)–C(7)–C(16)–C(17)	–86.3(3)	C(21)–C(16)–C(17)–C(18)	–0.2(4)
C(7)–C(16)–C(17)–C(18)	177.4(2)	C(16)–C(17)–C(18)–C(19)	–0.6(4)
C(17)–C(18)–C(19)–C(20)	1.2(4)	C(18)–C(19)–C(20)–C(21)	–1.1(4)
C(19)–C(20)–C(21)–C(16)	0.3(4)	C(17)–C(16)–C(21)–C(20)	0.3(4)
C(7)–C(16)–C(21)–C(20)	–177.3(2)	C(24)–C(8)–C(22)–O(3)	–116.5(3)
C(9)–C(8)–C(22)–O(3)	118.2(3)	C(7)–C(8)–C(22)–O(3)	4.2(3)
C(24)–C(8)–C(22)–O(4)	63.8(2)	C(9)–C(8)–C(22)–O(4)	–61.6(3)
C(7)–C(8)–C(22)–O(4)	–175.6(2)	O(3)–C(22)–O(4)–C(23)	0.0(4)
C(8)–C(22)–O(4)–C(23)	179.8(2)	C(22)–C(8)–C(24)–O(5)	32.7(3)
C(9)–C(8)–C(24)–O(5)	155.0(2)	C(7)–C(8)–C(24)–O(5)	–87.5(3)
C(22)–C(8)–C(24)–O(6)	–149.3(2)	C(9)–C(8)–C(24)–O(6)	–27.0(3)
C(7)–C(8)–C(24)–O(6)	90.4(2)	O(5)–C(24)–O(6)–C(25)	2.8(4)
C(8)–C(24)–O(6)–C(25)	–175.1(2)		

